HETEROCYCLES, Vol. 83, No. 7, 2011, pp. 1435 - 1487. © The Japan Institute of Heterocyclic Chemistry
Received, 21st January, 2011, Accepted, 17th March 2011, Published online, 1st April, 2011
DOI: 10.3987/REV-11-693

N-HYDROXY- AND *N*-AMINOTETRAZOLES AND THEIR DERIVATIVES — SYNTHESIS AND REACTIONS

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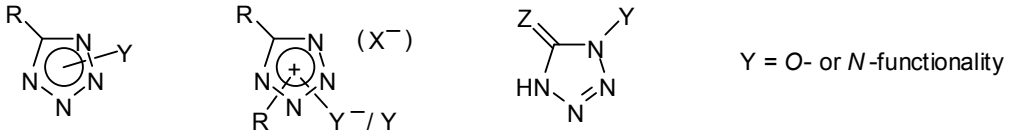
Abstract – This account summarizes the preparative chemistry of the title compounds as it developed from the beginnings a century ago; though detailed, the report is intended to be illustrative rather than encyclopedic.

INTRODUCTION

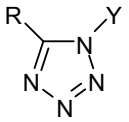
While tetrazole chemistry in all its branches is expanding with breath-taking speed,[1] there is a growing demand for specialized reviews. Regarding surveys on functionalized representatives, the past decade has seen the publication of accounts on (i) 1,3- and 1,4-disubstituted tetrazolium salts,[2] (ii) vinyltetrazoles,[3] (iii) 2-substituted and 2,5-disubstituted tetrazoles,[4] (iv) 1-substituted 5-alkyl(aryl)sulfanyltetrazoles and their derivatives,[5] (v) Fe(II) complexes of 1-alkyltetrazoles,[6] (vi) organometallic tetrazole derivatives,[7] and (vii) metal derivatives of tetrazoles.[8] Whereas the chemistry of *N*-hydroxytetrazoles has not been summarized at all, *N*-aminotetrazoles have been surveyed briefly twenty years ago when the entire family of *N*-aminoazoles was reviewed.[9] The present concept, however, enables the author to provide more details. *N*-Attached *O*- or *N*-functionalities are found with three major categories of tetrazole rings (below).



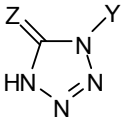
A closer look shows that the left-hand class accommodates the widest variety of such groups [see overleaf Chart 1: Series (**A**), (**C**) and (**B**), (**D**)], whereas with the remaining ring types this diversity is reduced. Arrangement of material is as follows: After a joint retrospect of early findings the title systems are dealt with apart. Separation into sections on 'Synthesis' and 'Reactions' seemed only viable for the types shown in Chart 1/Part I. The first-named section describes those approaches that are generalized in Scheme 1, while transformations of the Y function (including most secondary processes) are found under 'Reactions.'

Chart 1. Overview of title compounds

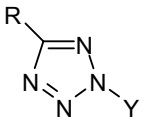
Part I



A, C



A', C'

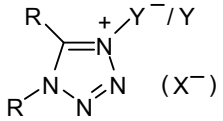


B, D

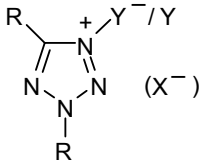
			Y				Y
A1		**B1**	OH	**C8**		**D8**	$N(COR)_2$
A2	**A'2**	**B2**	OR			**D9**	$N(SO_2R)_2$
A3			OCOR	**C10**			NCl_2
A4			OCONHR	**C11**		**D11**	N(R)NO
A5			OSO_2R	**C12**		**D12**	$NHNO_2$
				C13			$NHCH_2NHR$, $NHCH(R)X^2$
C1	**C'1**	**D1**	NH_2	**C14**	**C'14**	**D14**	$N{=}CHR$, $N{=}CR_2$
C2	**C'2**	**D2**	NHR, NR_2	**C15**			$N{=}CHNR_2$, $N{=}C(R)X^3$
C3	**C'3**	**D3**	NHCOR, N(R)COR	**C16**			$N{=}C{=}NR$
	C'4		$NHCO_2R$	**C17**			$NHC(OR){=}NR$
C5		**D5**	NHCONHR, N(R)CONHR			**D18**	$N{=}C(R)OCOR$
C6			$NHCONHNHX^1$	**C19**			$N{=}NR$
C7		**D7**	$NHSO_2R$, $N(R)SO_2R$	**C20**			$N{=}C{:}$

X^1 = H, COR; X^2 = OH, $PO(OR)_2$; X^3 = NH_2, $NHNH_2$, NHOH, N_3, Cl, CN

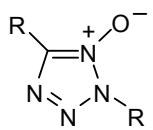
Part II



E, L / O



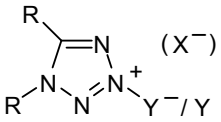
F, M / P



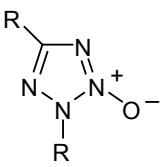
G

			Y^-
E	**F**	**H**	O
		N1	NH
L3	**M3**	**N3**	NCOR
L5	**M5**	**N5**	NCONHR
L7	**M7**	**N7**	NSO_2R

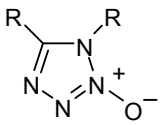
			Y
O1	**P1**	**Q1**	NH_2
O2	**P2**		NHR, NR_2
O3	**P3**	**Q3**	NHCOR,
O3	**P3**	**Q3**	N(R)COR
O5	**P5**	**Q5**	NHCONHR



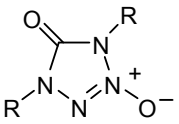
H, N / Q



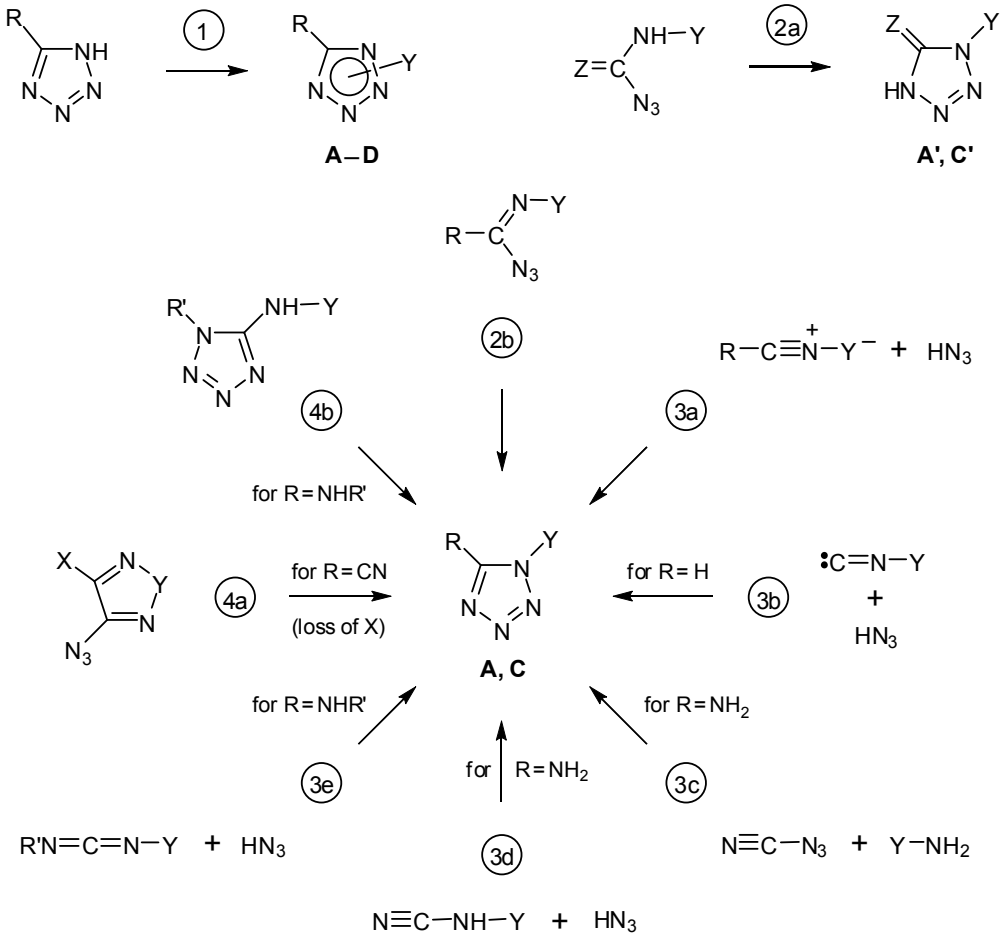
J



K



K'



Route	Applied for
1	**A1, B1, C1, D1**
2a [a]	**A'2, C'1, C'2, C'3, C'4, C'14**
2b [b]	**A1, A2, A3, C1, C2, C3, C7, C14, C15** [c], (**C16**) [d]
3a [a]	**A1**
3b	**A1, C1, C2**
3c	**A2, C1, C2, C3, C5, C6**
3d	**C14**
3e [a]	**C1, C14**
4a	**A1**
4b	**C1**

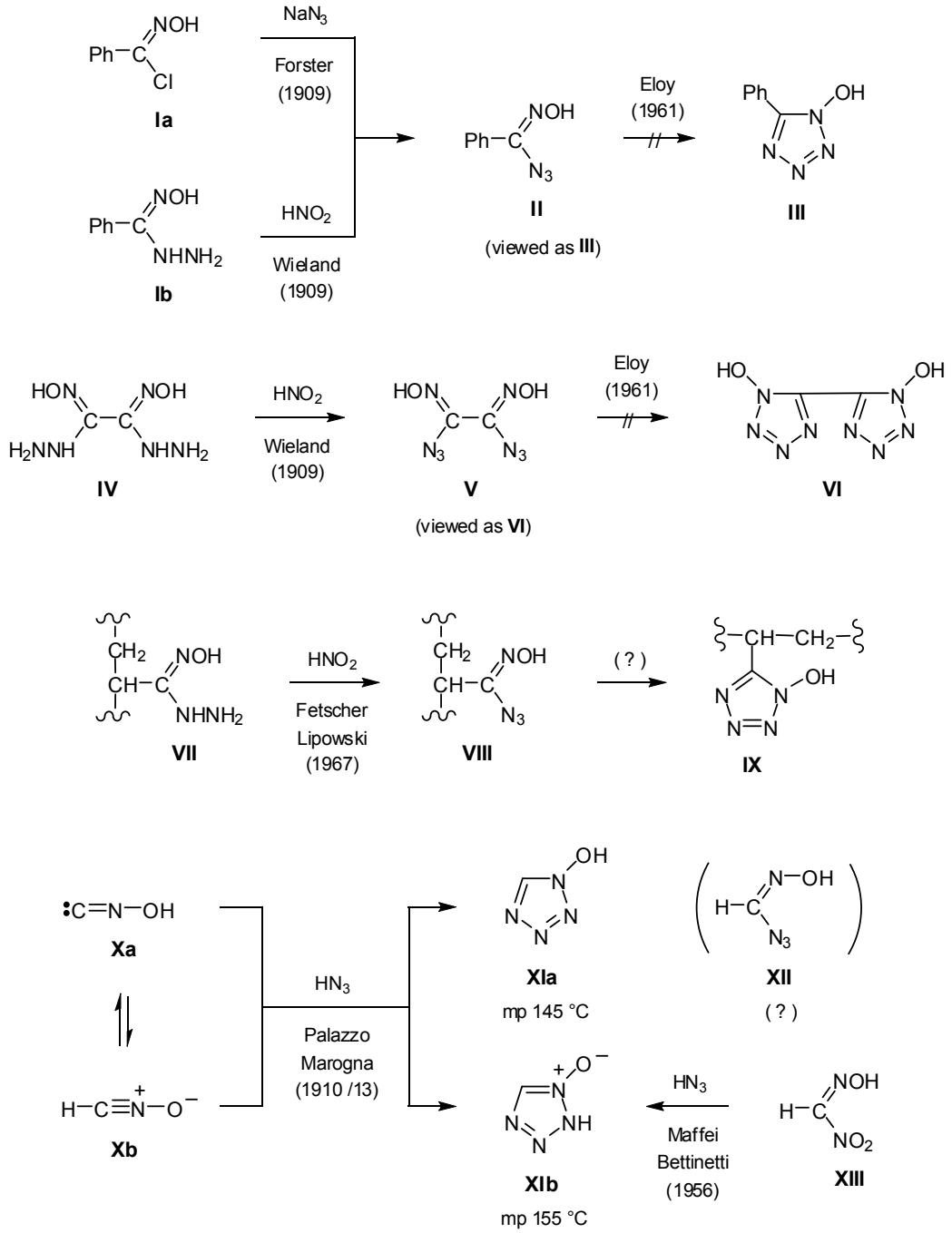
[a] Crucial intermediate shown. [b] Immediate precursor: (*E*)-azide (unisolable).
[c] $X^3 = N_3$, Cl, CN. [d] **C16** directly formed from **C15** ($X^3 = N_3$).

Scheme 1. Access to compounds of series (**A**)– (**D**), (**A'**), and (**C'**)
by ring functionalization (1), cyclization reactions (2, 3), and/or ring transformations (4)

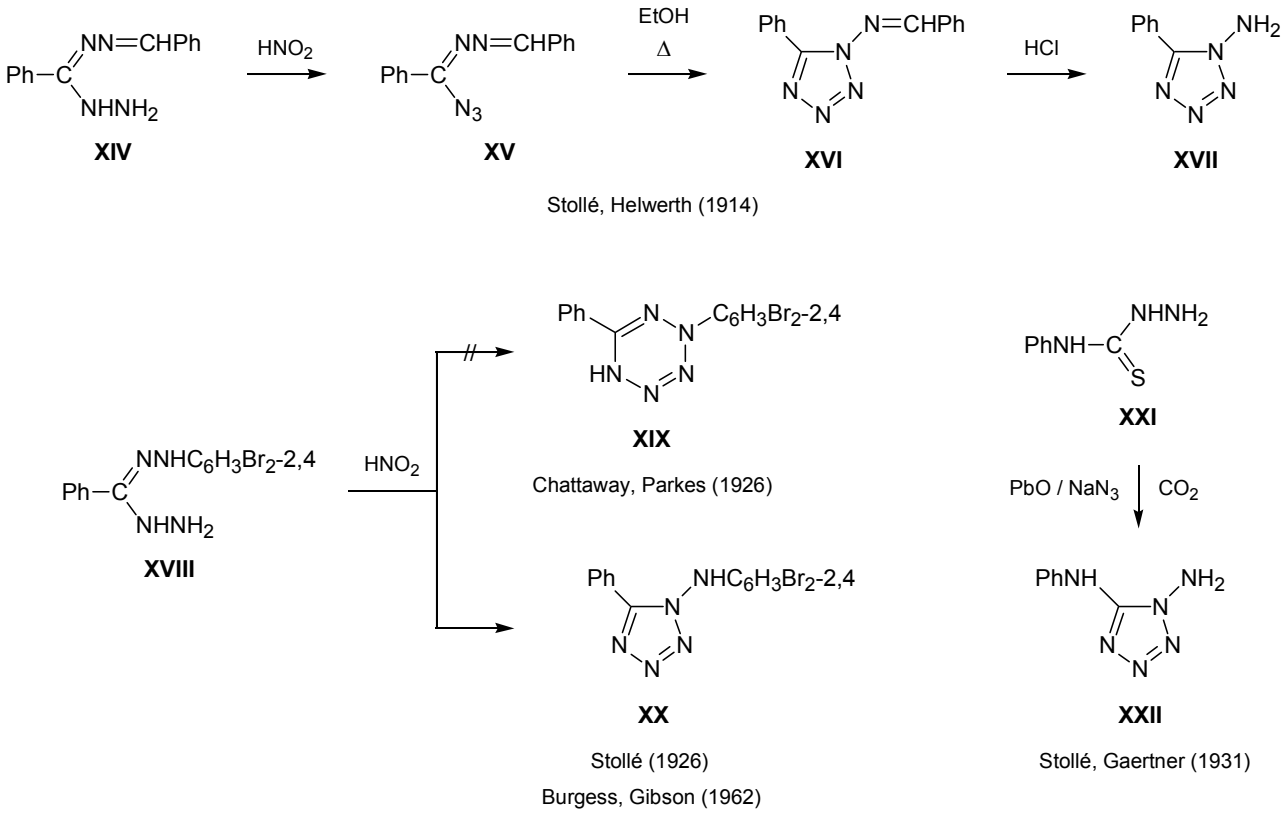
EARLY HISTORY

The first report on *N*-hydroxytetrazoles dates back to 1909 (Scheme 2). At that time the hydroximoyl derivatives (**Ia**) and (**Ib**, **IV**) were treated with sodium azide[10] and nitrous acid,[11] respectively, and the

products isolated were thought to be **III** and **VI**. This view was maintained until the early 1960s, when IR spectroscopy revealed that the former materials were the open-chain azides (**II**) and (**V**) instead[12,13] — members of a new class of compounds[14–16] which proved surprisingly stable and, according to later findings, cyclize only under special conditions.[17] A structure to be established, however, remains that of the product obtained by nitrosation (**VIII**) of the hydroxyamidrazone of polyacrylic acid (**VII**).[18] The authors presented the material as the hydroxytetrazole (**IX**), but did not want to exclude that it existed in



Scheme 2



Scheme 3

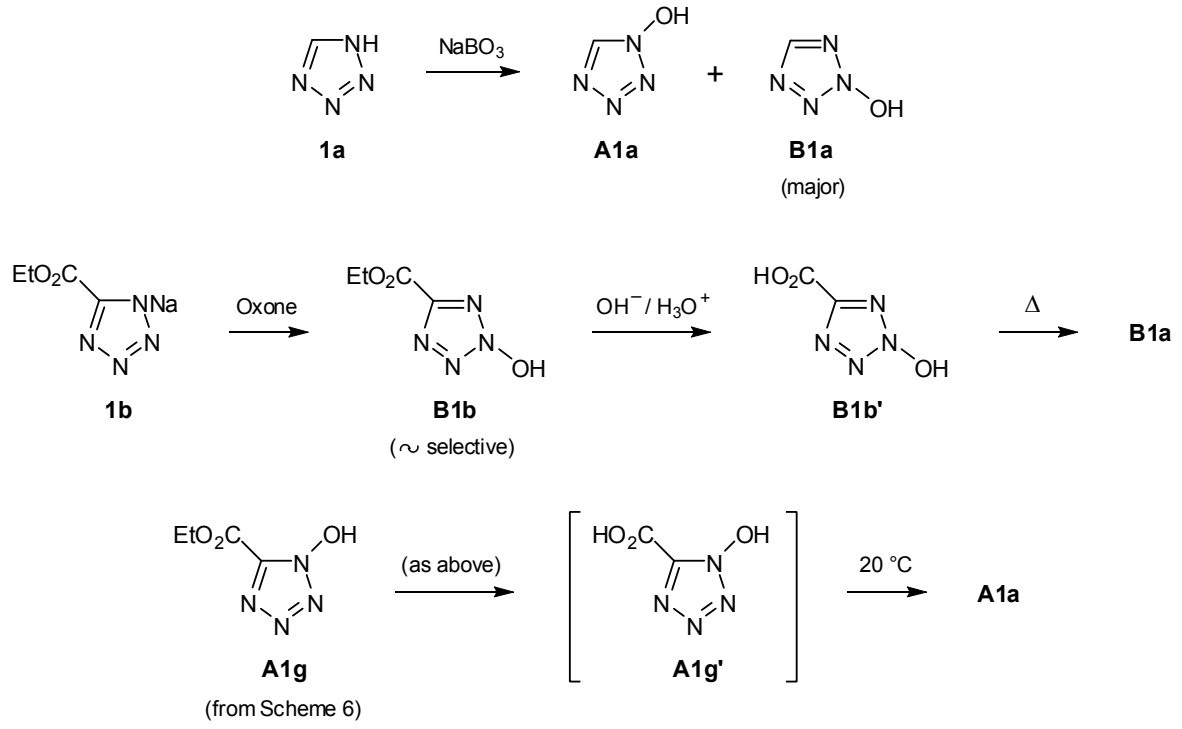
ring-open form (**VIII**). Another early study (1910/13) was directed toward the reaction of fulminic acid with hydrogen azide.[19] Two isomers were obtained and described as the hydroxytetrazole (**XIa**) and its *N*-oxide (**XIb**).[19a,b] While the structure of the first compound (**XIa**) appeared 'reasonable' inasmuch as **Xa** was the accepted constitution of fulminic acid in those days,[20] the authors explaining **XIb** assumed the occurrence of a tautomerism between **Xa** and **Xb**[19c] — a possibility that had just been considered elsewhere.[21] Judging from the melting points, the product (**XIb**) must be identical to the material that was to arise some time later from the nitrolic acid (**XIII**) and hydrogen azide[22] and more recently from *N*-unsubstituted tetrazole and sodium perborate[23a] (see Chapter I/1); hence, its actual formula should be **XIa**. The nature of the lower melting substance, however, awaits clarification (**XII** ?[24]).

The class of *N*-aminotetrazoles was discovered in 1914 (Scheme 3): the benzylidene substituted hydrazonoyl azide (**XV**), prepared from **XIV**, cyclized[25] on being heated to the derivative (**XVI**) which upon hydrolysis gave the representative (**XVII**).[26a] Next, the reaction of the aryl substituted hydrazidine (**XVIII**) with nitrous acid was studied, but the authors believed their product was the dihydropentazine (**XIX**).[27] The prior workers,[26a] in view of the formation of **XVI**, rejected the pentazine structure immediately in favor of the constitution (**XX**)[28] which was to be confirmed later.[29] Moreover, another early approach to *N*-aminotetrazoles (**XXI** → **XXII**)[30] clearly demonstrated that formation of a pentazine ring is disfavored.

I/1) *N*-OXYGEN FUNCTIONALITIES: SERIES (A), (A'), (B)

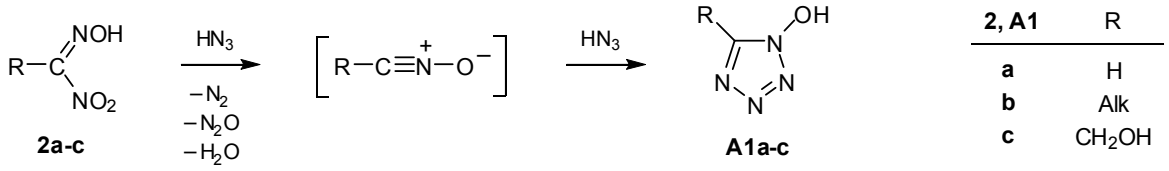
a) Synthesis

Treatment of tetrazole (**1a**) with sodium perborate in an acidic environment affords a 1 : 1.9 mixture of the hydroxytetrazoles (**A1a**) and (**B1a**) in 60% yield (Scheme 4) (*cf.* Scheme 1: Route 1). Separation of the isomers was effected *via* their benzyl ethers (→ Scheme 10) to eventually give 33% and 17% of pure **A1a** and **B1a**.[23a] As for **B1a**, an alternate access consists in oxygenation of the tetrazolide ion of **1b** with oxone, which occurs *quasi* selectively at N(2) affording a ~ 1 : 70 mixture of **A1g** and **B1b** from which the latter component directly crystallized in 80% yield[31a] (*cf.* also ref.[31b]); hydrolysis (→ **B1b'**; 65%) followed by decarboxylation gave 40% of the target compound (**B1a**).[31a, 32] While the overall yield of this sequence is comparable to that observed when starting from **1a**, a major advantage of the procedure is the greater handiness which also allows multi-gram scale operations. As expected, the isomer (**A1a**) is readily available from the ester (**A1g**);[31a] the spontaneous decarboxylation of the product of hydrolysis (**A1g'**) is typical of 1*H*-tetrazole-5-carboxylic acids.



Scheme 4

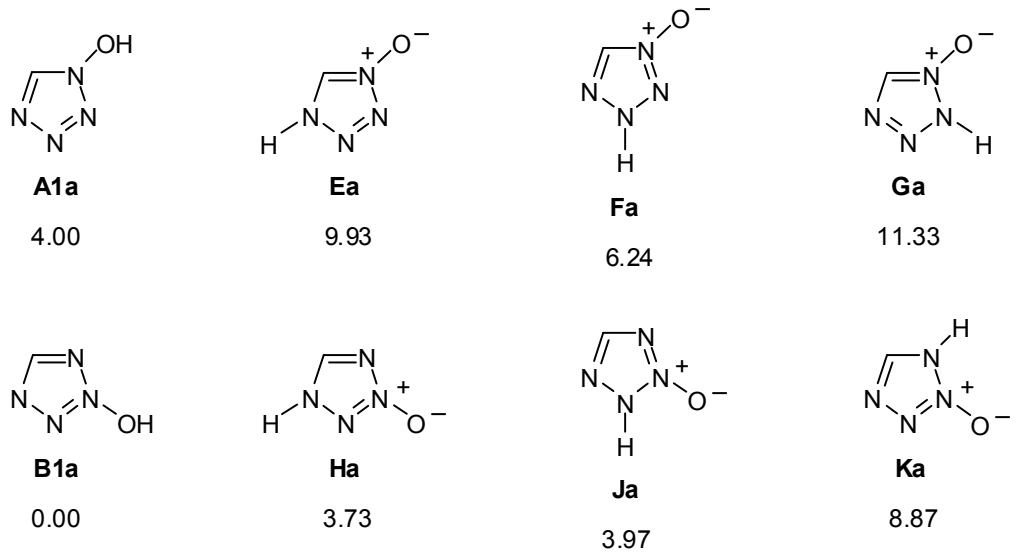
Nitrolic acids such as (**2a-c**) react with hydrogen azide at ambient temperature to give the respective hydroxytetrazoles (**A1a-c**) in yields ranging from 50% (**A1a**)[22] over 81% (**A1c**)[33] to almost quantitative (**A1b**; Alk = Me, Et)[22] (Scheme 5). The prior authors[22] already recognized the reaction as proceeding *via* a nitrile oxide (*cf.* Scheme 1: Route 3a) and, in view of the results with fulminic acid (*cf.* Scheme 2),[19b]



Scheme 5

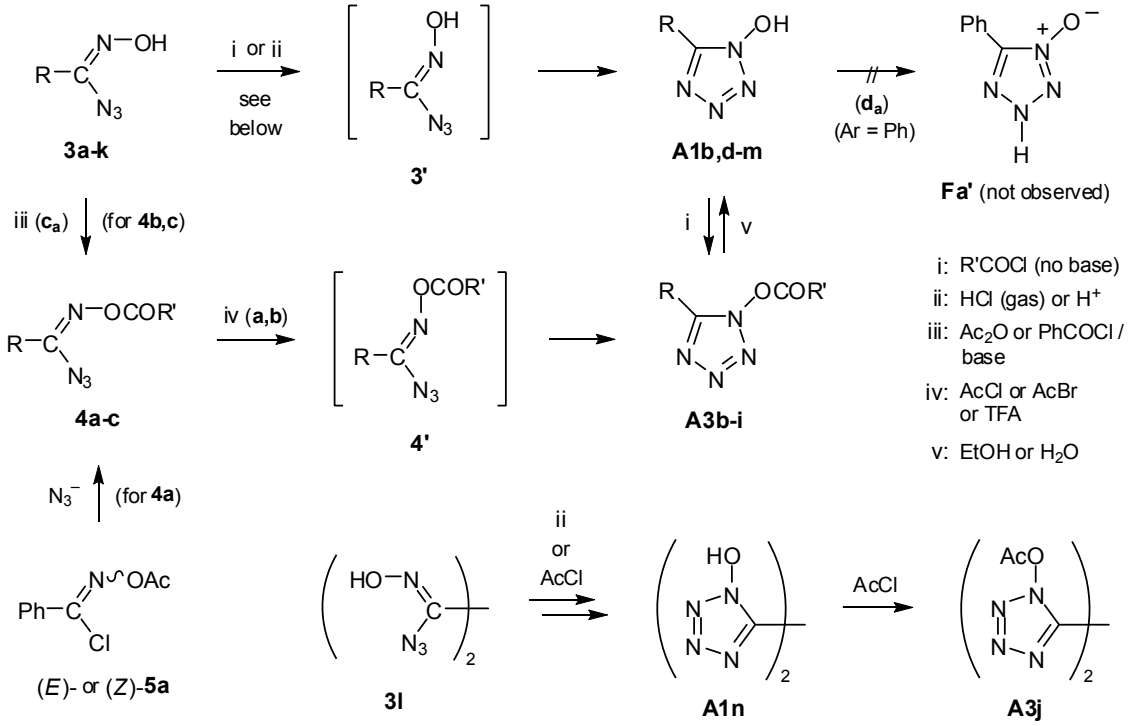
described their products as *N*-oxides of type (**G**; NH in place of NR), believing that the *N*-hydroxy tautomers (**A1**) have formed in negligible amounts at best. A constitution (**G**), however, does not match established tetrazolium structures (*cf.* ref.[34a]). Indeed, a comparison of the energies of the tautomers (**A1a**), (**Ea**), (**Fa**), and (**Ga** ≈ **XIb**) calculated at the B3LYP/6-31G** level shows that the species in question is least favored (Chart 2);[35a] even *N*-oxides with a conventional substitution pattern, *viz.* **Ea** and **Fa**, are higher in energy than the *N*-hydroxy form [a similar relationship is also found with the family (**B1a**/**Ha**/**Ja**/**Ka**)].[35b] Nevertheless, *N*-oxides of that kind, in particular those of the **F**, **H**, and **J** series, might occur under conditions that favor the existence of azolium *N*-oxides in general.[36,37]

Chart 2. Relative energies (kcal/mol) of 5-unsubstituted *N*-hydroxytetrazoles and *N*-oxides [B3LYP/6-31G** (gas phase)]

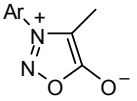


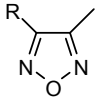
The most important entry to hydroxytetrazoles of class (**A1**) consists in cyclization of hydroximoyl azides (**3**) (Scheme 6; *cf.* Scheme 1: Route 2b). It was in the 1970s that this conversion could be accomplished for the first time.[38a] The authors found that the reaction of **3b** (Ar = Ph) with acetyl or propionyl chloride in cyclohexane at ambient temperature directly yielded the hydroxytetrazole (**A1d**; Ar = Ph). In the case of **3c** (Ar = Ph), propionyl and benzoyl chlorides were used, but here, instead of the respective product (**A1e**), the corresponding acyl derivatives (**A3d**; R" = Et, Ph) were isolated; yet, heating of the propionyl

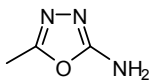
compound in ethanol gave the free hydroxytetrazole very readily. Further examples of **A1d,e** (Ar = subst. Ph),[38b] **A1f**,[38c] and **A3d** (R" = Me, CH_2Cl) [38b] were described in turn. These studies not only confirmed



3	4	R	R'	A1	method	A3 [a]
a		Alk	Me	**b**	i	(**b**)
b		Ar	Alk	**d**	i, ii	(**c**)
	a	Ph	Me			$\mathbf{c_a}$
c		$CHAr_2$	R" [b]	**e**	i	**d**
$\mathbf{c_a}$	**b**	$CHPh_2$	Me	$\mathbf{e_a}$		$\mathbf{d_a}$
$\mathbf{c_a}$	**c**	$CHPh_2$	Ph			
d		COPh	Me	**f**	i	(**e**)
e		CO_2Et	Me	**g**	i	(**f**)
f		CONHPh		**h**	ii	
g		2-pyridyl [c]	Me	**i**	i	(**g**)
h		2-thienyl [d]	Me	**j**	i	(**h**)
i		Het^1	Alk	**k**	i	**i**
j		Het^2		**l**	ii	
k		Het^3		**m**	ii	

Het^1 = 

Het^2 = 

Het^3 = 

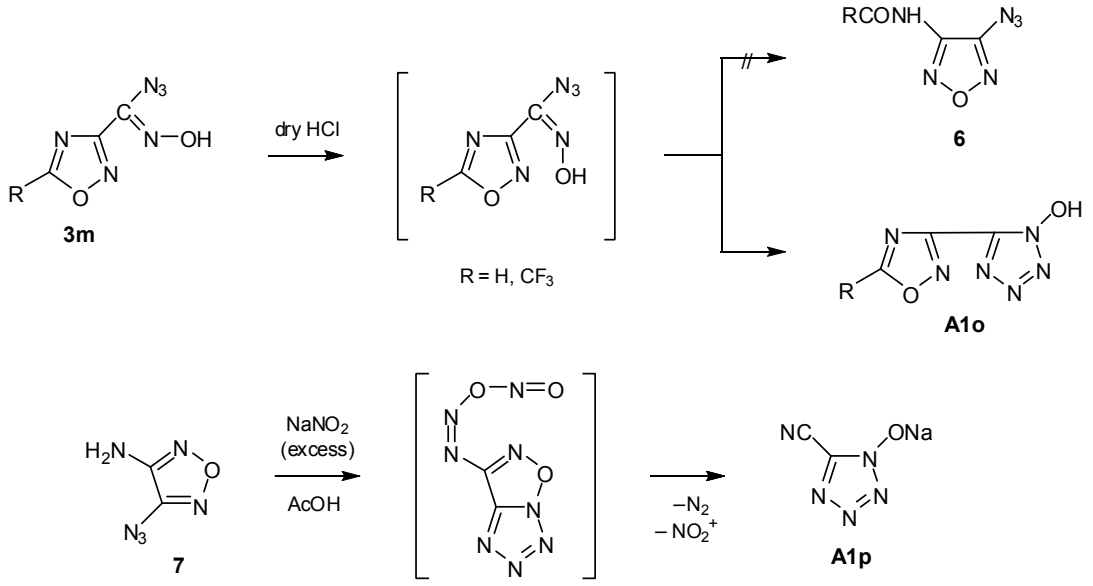
[a] Derivatives in parentheses not isolated. [b] **A3d**: R"= Me, CH_2Cl, Et, Ph (*cf*. text). [c] Selected from a range of examples having for R a variety of (benz)azinyl groups. [d] Selected from a range of examples having for R a variety of (substituted) thienyl, furyl, and (benz)azolyl groups.

Scheme 6

the pronounced sensitivity of **A3c** (Alk = Me, Et) to hydrolysis[38b] (*cf*. above) and showed **A3e** to be labile as well;[38c] especially, they established that acid chlorides in the presence of base (as anticipated[13]) and also acetic anhydride lead to linear systems (like **4b,c**). In acidic media, however, these compounds can

be cyclized too (exemplified for **4b** → **A3d$_a$**/**A1e$_a$**).[38b] To explain this, the authors suggested that N(1) of the azido group is protonated whereby ring closure would be facilitated.[38b] However, more appropriate is a stereoelectronic approach, considering that ring closure requires a *cis* lone pair:[39,40] It was found[39a] that treatment of the (*Z*)- or (*E*)-chloride (**5a**) with sodium azide in aqueous acetone at room temperature uniformly gave the (*Z*)-azide (**4a**). When this material was heated with excess acetyl chloride in benzene, the tetrazole (**A3c$_a$**) was formed, *i.e.* the acid chloride, acting as a Lewis acid (!), acylates the imino nitrogen; this brings about 'C=N' bond rotation followed by dissociation of the acetyl group and cyclization of the (*E*)-isomer (**4'**). The same principle may underlie the ring closure of **3** since the acid chloride primarily causes *Z*/*E* inversion (→ **3'**) rather than acylation of the hydroxy group.[39b] Hence, contrasting with the sequence (**3** → **4** → **A3** → **A1**) put forward in ref.[38b] derivatives of type (**A3**) would constitute secondary products of **A1**. This view gains support by the observation that, on treatment of **3l** with acetyl chloride, the bitetrazole (**A1n**) was formed prior to its acetyl derivative (**A3j**).[41a]

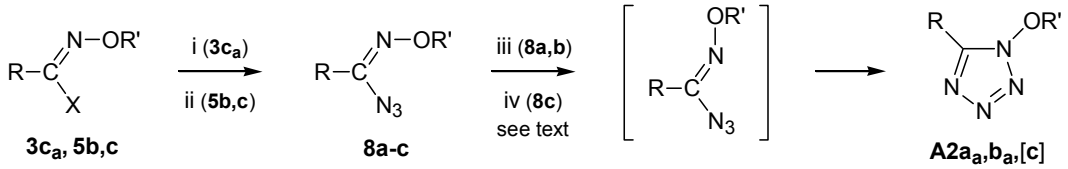
Expectedly, the preceding method for cyclization of **3** with an acid chloride[38] found wide application by other workers. Such ring closures (mostly effected with acetyl chloride) include: **3a** → **A1b** [Alk = *i*-Pr, (α-subst.) CH_2Ph, cyclohex(en)yl];[42a] **3b** → **A1d** [Ar = (subst.) Ph],[42–44] **3b** → **A1d** (Ar = naphthyl),[42a] **3d** → **A1f**,[38c] **3e** → **A1g**,[45] **3g** → **A1i**,[42a] **3h** → **A1j**,[42a] and **3i** → **A1k**.[46] Only in the latter case the corresponding acyl derivatives (**A3i**: Alk = Me, Et) have been isolated and, in analogy to the questionable theory of ref.,[38b] have been viewed as arising from acylated **3i**.[46]



Scheme 7

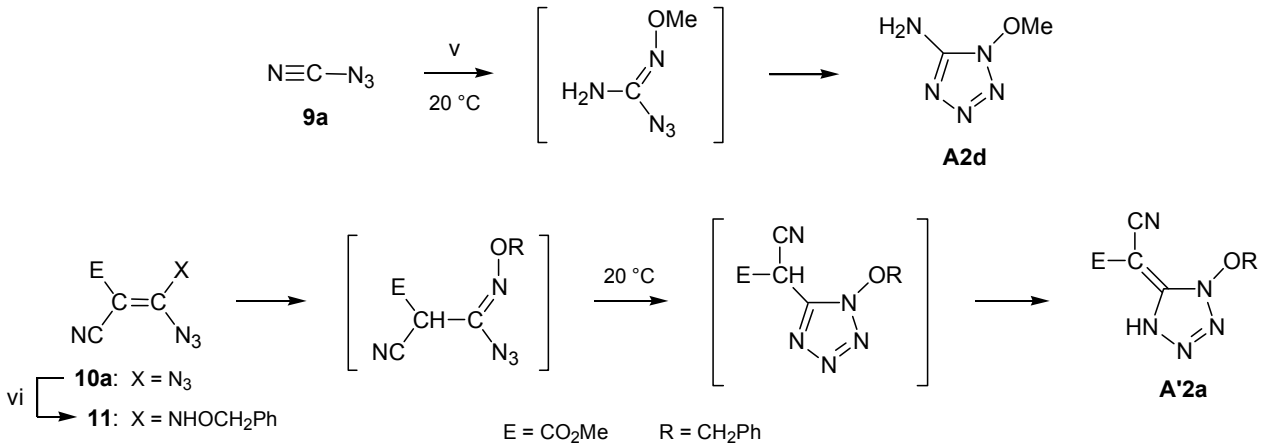
A preparative alternative of more recent date consists in treating **3** with gaseous hydrogen chloride. Pertinent examples include conversions such as **3b** → **A1d** [Ar = (subst.) Ph],[41a] **3f** → **A1h**,[47] **3j** →

A1l,[41b,48,49] **3k** → **A1m**,[50] **3l** → **A1n**,[41a] and **3m** → **A1o**[51] (Scheme 7; note the suppression of the Boulton-Katritzky rearrangement which would lead to **6**). Moreover, even acid impurities can be sufficient to induce ring closure [as observed for **3a** → **A1b** (Alk = Bu)].[41a] As regards the general success of both cyclization methods (**3** → **A1**), in most cases reasonable to excellent yields were observed. Finally, an entry of a different kind constitutes the ring transformation (**7** → **A1p**) (*cf.* Scheme 1: Route 4a). The process is viewed as proceeding through a heteropentalene species which, remarkably, ring-opens between the positions 5 and 6.[52]



	X	R	R'	8	A2
3c$_a$	N_3	$CHPh_2$	H		
		$CHPh_2$	Me	**a**	**b$_a$**
5b	Br	Ph	Me	**b**	**a$_a$**
5c [a]	NO_2	Me	$C(Me)(NO_2)_2$	**c** [a]	**c** [b]

[a] Actual geometry not known. [b] Not formed.



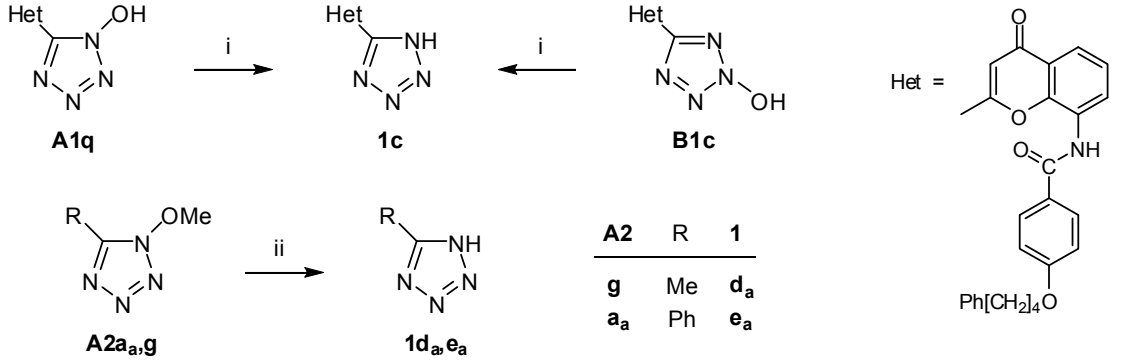
Scheme 8

Entries to the series (**A2**) and (**A'2**) by ring closure have been verified as follows (Scheme 8): (i; *cf.* Scheme 1: Route 2b) The azide (**8a**), obtained from **3c$_a$**, cyclized to **A2b$_a$** on treatment with acetyl chloride.[38b] The conversion occurred *ca.* 8 times more slowly than the cyclization of **3c$_a$**; this is due to the electron-donating ability of the methoxy group which slows down *Z*/*E* inversion of **8a** (*cf.* also later Scheme 19). Similarly, **8b** (obtained from **5b**) could be transformed into **A2a$_a$**, whereas trifluoroacetic

acid mainly led to the corresponding urea.[53] Yet, attempts at ring-closing **8c** (made from **5c**) failed; on treatment with electrophilic reagents there occurred only a change in geometry and the new (more stable) isomer reverted to the original form when irradiated with UV light.[54] (ii; *cf.* Route 3c) Applying the concept for making 1-substituted 5-aminotetrazoles from cyanogen azide (**9a**) and primary amines,[55a] methoxyamine was reacted with **9a** (generated *in situ*) to yield compound (**A2d**; 70%); while the linear intermediate has been presented in the *Z*-form,[55a] the direct precursor should be *E*. (iii; *cf.* Route 2a) Treatment of the geminal diazide (**10a**) with benzyloxyamine gave the tetrazole (**A'2a**; 67%), its dihydro structure is a corollary of the two acceptor groups at C(α); the S_N product (**11**) was not isolated, it underwent a 1,3-*H* shift followed by cyclization.[56a] Monosubstituted hydrazines are capable of converting **10a** in the same manner (see Chapter II/1).[56a]

b) Reactions

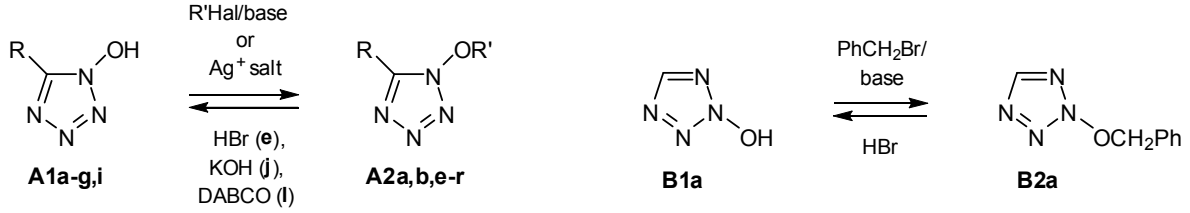
Reduction: Treatment of the hydroxytetrazoles (**A1q**) and (**B1c**) with titanium tetrachloride/lithium aluminium hydride led to the *N*-unsubstituted tetrazole (**1c**), *i.e.* the anti-asthma agent pranlukast (Scheme 9); the derivative (**A1q**) turned out to react more easily.[31b] Reductive removal of the methoxy group from $\mathbf{A2a_a}$[57a] and **A2g**[58] leading to $\mathbf{1e_a}$ and $\mathbf{1d_a}$, respectively, has been effected with hydroiodic acid.



Scheme 9

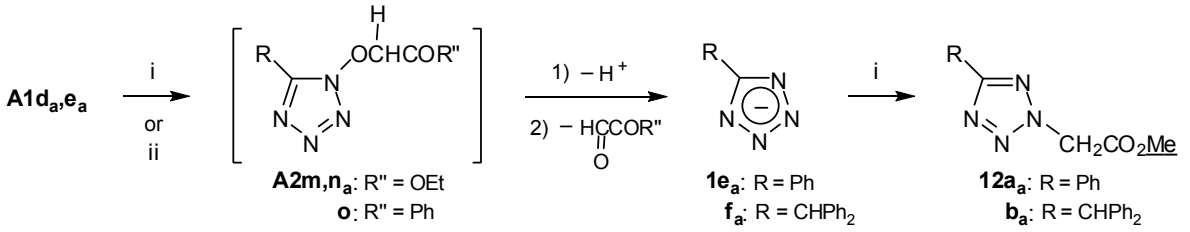
Alkylation: *O*-Substituted derivatives of type (**A2**) have been prepared in great number by treatment of hydroxytetrazoles (**A1**) with alk(en)yl halides in the presence of base (Scheme 10). Also silver salts of **A1** have been reacted [as shown for $\mathbf{A2a_a}$,[58] **A2g**,[58] **A2h**,[33] **A2j**,[59] and **A2q** (Alk = Me, *i*-Pr)[45]]. Contrasting with this plethora, examples of the isomeric series (→ **B2a**[23a]) seem to be rare.[60] The reverse reaction, *i.e.* dealkylation, has been performed with **A2e**/**B2a**,[23a] **A2j**,[59] and **A2l**,[42b] showing that certain R' ligands can be used as protective groups. An unexpected process was encountered when $\mathbf{A1d_a}$ and $\mathbf{A1e_a}$ were heated with a large excess of ethyl bromoacetate in methanol: Instead of the 'regular' products (**A2m**) and ($\mathbf{A2n_a}$)

the 2*H*-tetrazoles (**12a$_a$**) and (**12b$_a$**) were obtained. It was thought that **A2m,n$_a$** underwent deprotonation followed by N–O bond cleavage to give the anions of **1e$_a$** and **1f$_a$** which were in turn alkylated at N(2). Likewise, the intermediate (**A2o**) [formed from **A1e$_a$** and phenacyl bromide (1 eq.) in hot ethanol] lost its side chain.[57b]



A1	R	R'	A2	ref.	A1	R	R'	A2	ref.
a	H	CH_2Ph	**e**	23a	**d$_a$**	Ph	CH_2(9-anthryl)	**l**	42b
b	Alk	$CH_2CONR''_2$	**f** [a]	42a		Ph	CH_2CO_2Et	**m** [d]	57b
b$_a$	Me	Me	**g**	58	**e$_a$**	$CHPh_2$	Alk	**b**	57b,c
c	CH_2OH	Me	**h**	33		$CHPh_2$	$[CH_2]_nCO_2Et$	**n** [e]	57b
d	Ar	Alk, Alkenyl	**a**	57,58		$CHPh_2$	CH_2COPh	**o** [d]	57b
	Ar	$CH_2CONR''_2$	**i** [b,c]	42a	**f**	COPh	Me	**p**	38c
d$_a$	Ph	$[CH_2]_2OH$	**j**	59	**g**	CO_2Et	Alk	**q**	45
	Ph	CH_2Ph	**k**	57c	**i**	2-pyridyl	$CH_2CONR''_2$	**r** [f,g]	42a

[a] NR''_2 = piperidino. [b] NR''_2 = pyrrolidin-1-yl, (substituted) piperidino, $NAlk_2$, N(Alk)Ar. [c] An X-ray analysis has been performed in the case Ar = 2-ClC_6H_4 and NR''_2 = piperidino.[42c] [d] Not isolated (see below). [e] n = 1, 2. [f] NR''_2 = (substituted) piperidino. [g] Analogous products were also obtained from **A1j** and congeners: NR''_2 = (substituted) piperidino, $NAlk_2$, N(Alk)Ar.[42a]

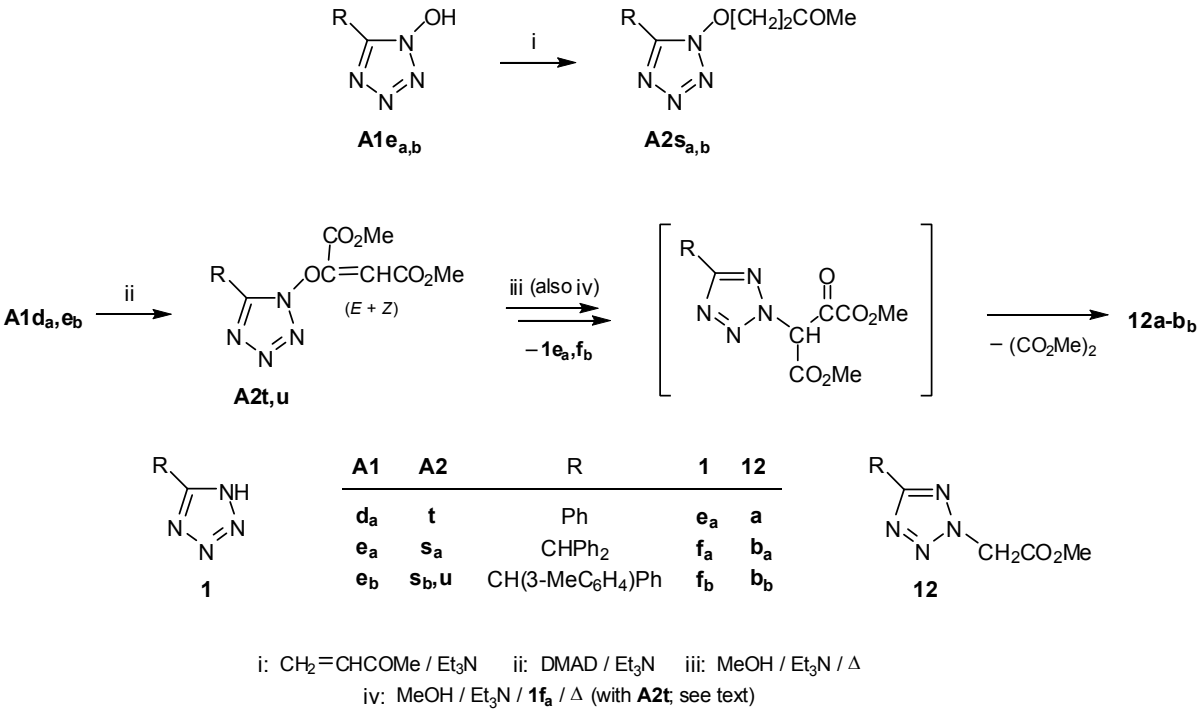


i: $BrCH_2CO_2Et$ (excess)/K_2CO_3/MeOH/Δ ii: $BrCH_2COPh$ (1 eq.) /K_2CO_3 /EtOH/Δ

Scheme 10

Further *O*-alk(en)yl derivatives (**A2**) were prepared *via* Michael type additions (Scheme 11).[61] Thus, the 1-hydroxytetrazoles (**A1e$_{a,b}$**) reacted with methyl vinyl ketone to readily give **A2s$_{a,b}$**. Extending this study to dimethyl butynedioate (DMAD), educts like **A1d$_a$** and **A1e$_b$** not only led to the anticipated Michael compounds (**A2t,u**) but, surprisingly, also to the *N*-unsubstituted and 2-substituted tetrazoles (**1e$_a$,f$_b$**) and (**12a,b$_b$**), respectively. The formation of these by-products was rationalized assuming a complex sequence of addition/elimination steps; separate experiments revealed that when **A2t,u** were refluxed in methanol/ triethylamine the formation of those materials occurred too, whereas heating **A2t** in the presence of **1f$_a$**

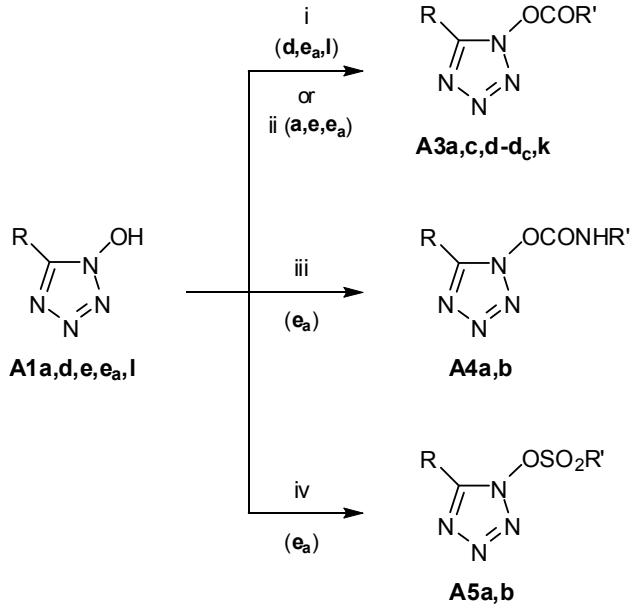
not only produced the mixture of **1e$_a$** and **12a** but also gave rise to **12b$_a$**.[61]



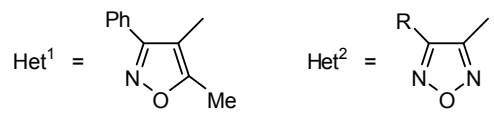
A1	A2	R	1	12
d$_a$	t	Ph	e$_a$	a
e$_a$	s$_a$	CHPh$_2$	f$_a$	b$_a$
e$_b$	s$_b$,u	CH(3-MeC$_6$H$_4$)Ph	f$_b$	b$_b$

Scheme 11

Acylation: An early, rather isolated example constitutes the reaction of the sodium salt of **A1a** with benzoyl chloride to give the compound (**A3a**) (Scheme 12).[19b] However, the product was not described as such, but viewed as an *N*-benzoyl derivative, as the authors believed the substrate was the *N*-oxide



A1	R	R'	A3	A4	A5
a	H	Ph	a		
d	Ar	Me	c		
e	CHAr$_2$	Alk	d		
e$_a$	CHPh$_2$	Me	d$_a$	a	a
	CHPh$_2$	Ph	d$_b$	b	
	CHPh$_2$	Het^1	d$_c$		
	CHPh$_2$	4-MeC$_6$H$_4$			b
l	Het^2	Me	k		



i: (MeCO)$_2$O ii: R'COCl iii: R'NCO iv: R'SO$_2$Cl

Scheme 12

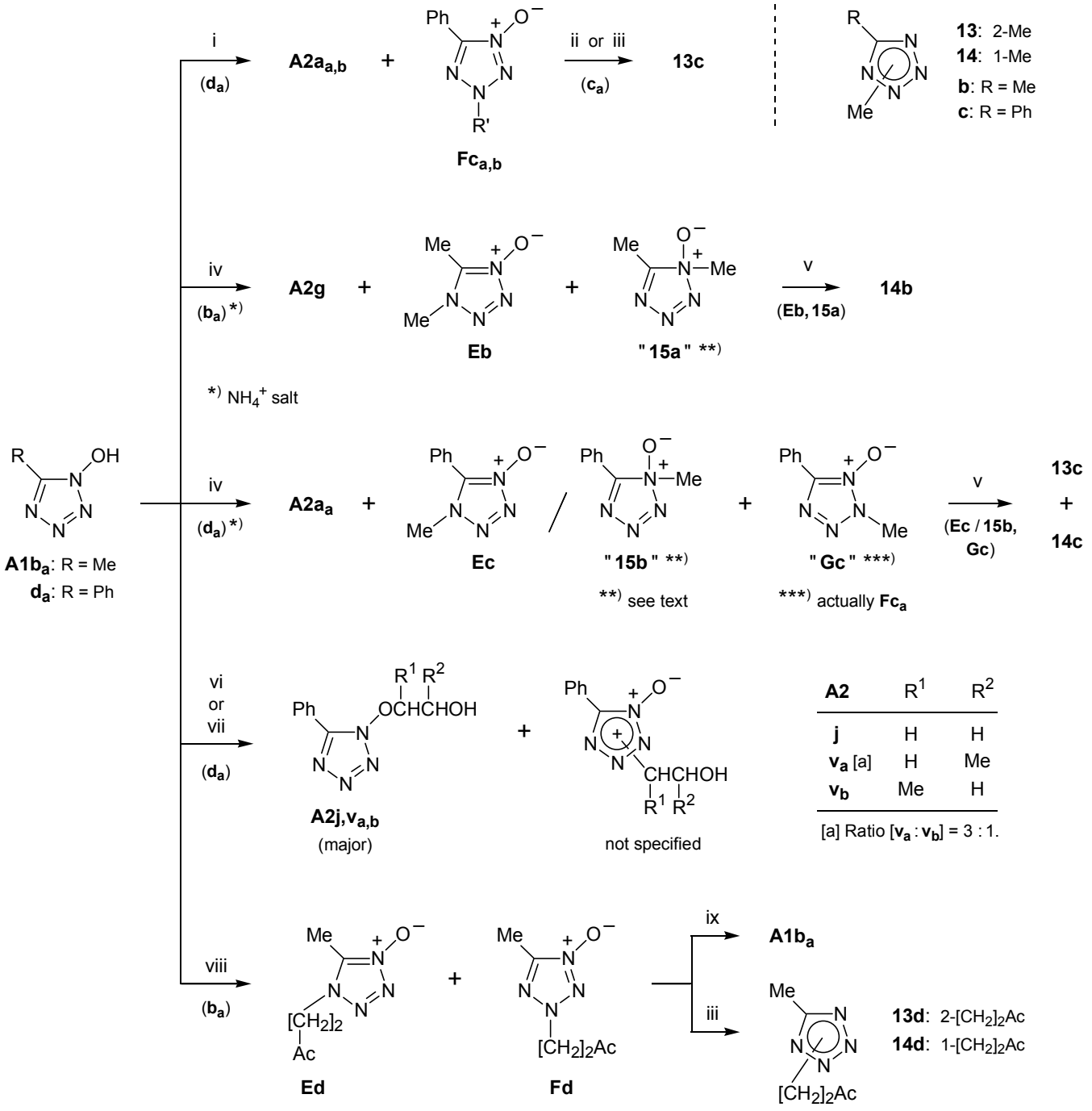
(**XIb**) (*cf.* Scheme 2). After the discovery[38a] how the hydroximoyl azides (**3**) could be cyclized the number of *O*-acyl derivatives of **A1** increased: With acid chlorides compounds like **A3d** [Ar = (subst.) Ph; Alk = Me, CH_2Cl, Et],[38a,b] **A3d$_a$**,[38b,57b] **A3d$_b$**,[38a,b,57b] and **A3d$_c$**[57b] were made; usage of acetic anhydride led to derivatives such as **A3c** [Ar = (subst.) Ph][41a] and **A3k**[41b] including **A3d$_a$**.[57b] Isocyanates smoothly gave carbamoyl compounds such as **A4a,b**,[57b] while sulfonyl derivatives like **A5a,b** were readily prepared from the sodium salt of **A1e$_a$**.[57b] — In conjunction with the processes leading to **A3** and **A5** mention should be made of the efficacy of **A1a**/**B1a**[23b] and **A1d** (Ar = Ph, 3-$NO_2C_6H_4$)[43] as acylation catalysts in peptide and oligonucleotide synthesis, respectively.

I/2) *N*-OXYGEN FUNCTIONALITIES: SERIES (E) – (K')

Synthesis and Reactions

The discovery of tetrazolium *N*-oxides is associated with alkylation reactions of **A1**. Since the substrates, especially their anions,[62a] exhibit ambident character, alkylation can affect the ring atoms (Scheme 13). This was first observed when preparing the *O*-alkyl derivatives (**A2a$_a$**) and (**A2a$_b$**): While these materials were obtained in 76 and 89% yield, isomeric *N*-oxides like **Fc$_a$** and **Fc$_b$** were isolated as side products (1 and 4%, respectively); their structures were inferred from deoxygenation of **Fc$_a$** to 2-methyl-5-phenyl-tetrazole (**13c**).[57a] The *N*-oxides (**Fc$_{a,b}$**) also arose (53 and 30% yield) when **A2a$_{a,b}$** were briefly heated to 190–210°C (see later). A study especially concerned with methylation of the hydroxytetrazoles (**A1b$_a$**) and (**A1d$_a$**) disclosed more details:[58] The authors observed that *N*-methylation was insignificant when the silver or triethylammonium salts of **A1b$_a$** and **A1d$_a$** were treated with methyl iodide or dimethyl sulfate, but action of diazomethane on the free hydroxytetrazoles led to a methylation ratio of N : O = 1 : 5–6.[62b] A substantial increase in *N*-methylation resulted on employment of trimethyloxonium tetrafluoroborate: Treatment of the ammonium salt of **A1b$_a$** with this reagent caused 41% ring methylation (two *N*-oxides observed) and gave only 57% **A2g**. Based on ^{1}H NMR and MS data including reduction to 1,5-dimethyl-tetrazole (**14b**), the *N*-oxides were viewed as **Eb** (27%) and **15a** (14%).[58] However, a structure like **15** is untenable on energetic grounds; possibly migration of oxygen had occurred leading to **Kb** (or **Hb** which is still lower in energy; *cf.* Chart 3).[63]

Passing to the reaction of **A1d$_a$** (*ammonium salt*) with trimethyloxonium tetrafluoroborate,[58] the procedure, apart from giving 34% **A2a$_a$**, afforded 42% of a mixture containing the phenyl analogue (**Ec**) [or (**15b**) (no decision)] and a new type viewed as **Gc**; the presence of these components was deduced from deoxygenation giving a 2 : 1 mixture of **13c** and **14c**. The reaction of *free* **A1d$_a$**, however, yielded a total of 85% of *N*- and *O*-methyl derivatives (10 : 1 mixture) from which the alleged oxide (**Gc**) could be isolated.[58] While the authors recognized this material as identical to the previously made compound (**Fc$_a$**),[57a] they

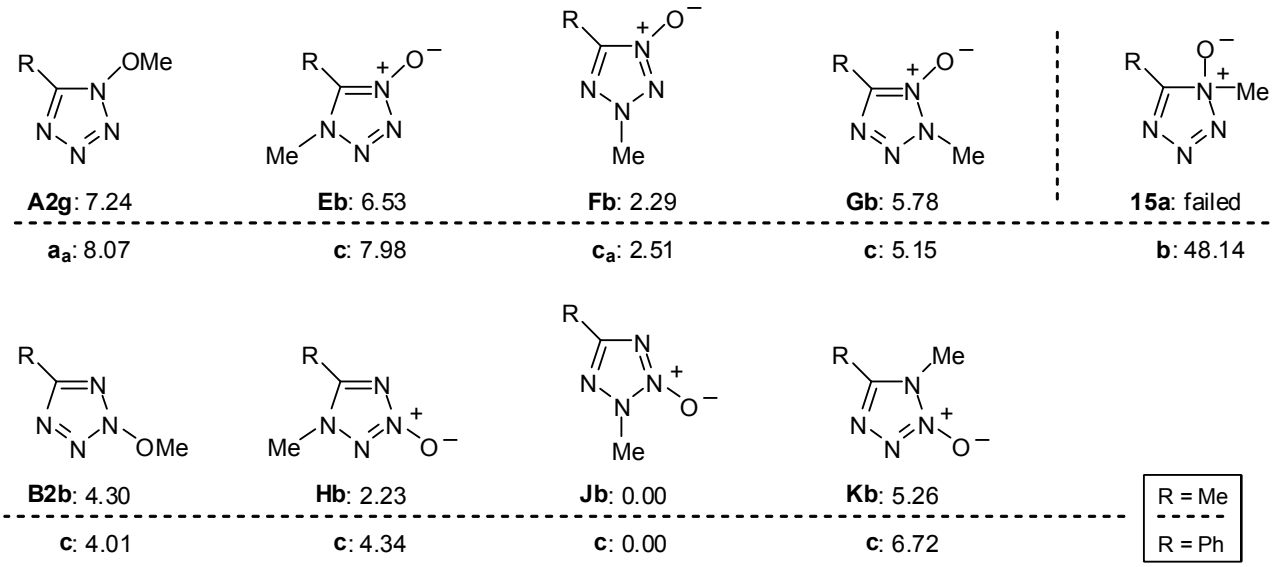


Scheme 13

adhered to their structure for spectroscopic reasons[58] – a view that, expectedly, proved to be erroneous soon (see below).

Concomitant *O*- and *N*-alkylation also occurred on reacting 1-hydroxy-5-phenyltetrazole (**A1d$_a$**) with oxirane; here a 2 : 1 mixture of **A2j** and an unspecified *N*-oxide was obtained. The same O : N proportion

Chart 3. Relative energies (kcal/mol) of 5-substituted *N*-methoxytetrazoles and *N*-oxides derived therefrom [B3LYP/6-31G** (gas phase)]

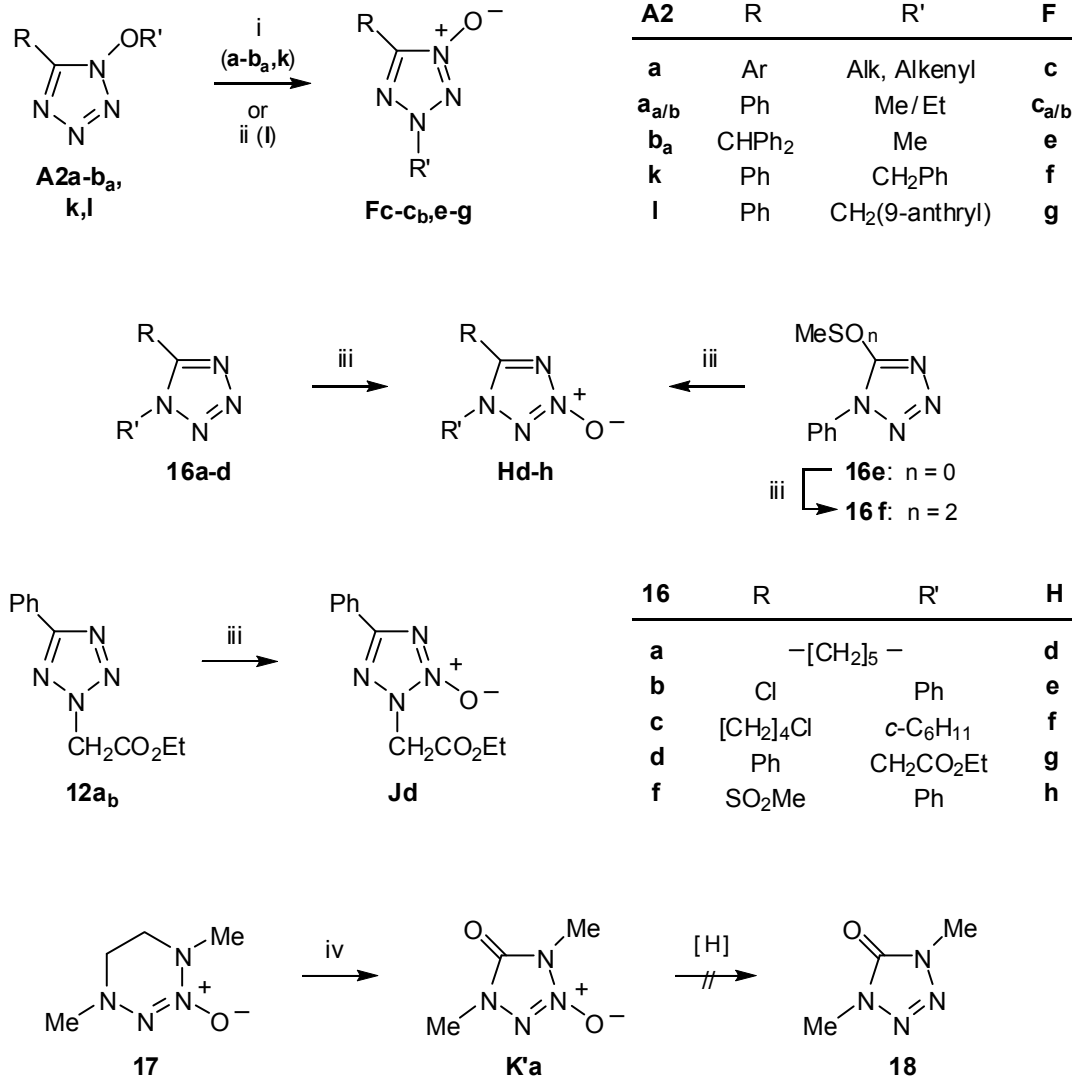


was observed using methyloxirane, but the products were doubled in each class, with the derivatives where R^1 = H/R^2 = Me (*e.g.* **A2v$_a$**) predominating.[59]

Contrasting with the foregoing (and also with the findings outlined in Scheme 11), Michael addition of 1-hydroxy-5-methyltetrazole (**A1b$_a$**) led exclusively to *N*-oxides like **Ed** and **Fd** (ratio 3 : 1). While treatment with phosphorus trichloride afforded the respective deoxygenation products (**13d**) and (**14d**), alkali hydroxide caused retro addition to yield the starting tetrazole (**A1b$_a$**).[64]

An efficient entry to *N*-oxides of type (**F**) constitutes brief heating of *O*-substituted derivatives (**A2**)[57a,c] (Scheme 14). The rearrangement has been shown to proceed intermolecularly; and, regarding the above controversy (**Gc** *vs.* **Fc$_a$**),[58] an X-ray analysis confirmed **Fc$_a$** to be correct.[57c,65] This finding is also in line with the calculated energies of the *N*-oxides 'derived' from **A2a$_a$** (Chart 3).[63] The wide scope of the reaction has found a preparative complement since, with certain substituents, also trifluoroacetic acid is capable of inducing this rearrangement (*e.g.* **A2l** → **Fg**).[42b]

Authentic examples of type (**H**) have recently become available by direct functionalization: treatment of the 1,5-disubstituted tetrazoles (**16a-d,f**) with the hypofluorous acid · acetonitrile complex gave the derivatives (**Hd-h**) in high yields; also a representative of type (**J**), *viz.* **Jd**, could be obtained in this manner.[66] Compounds of type (**K**) are unknown, except for a dihydro congener like **K'a**; this material arose in low yield by oxidative ring contraction of **17** but withstood attempts of deoxygenation to give the known 1,4-dimethyltetrazolinone (**18**).[67]



A2	R	R'	F
a	Ar	Alk, Alkenyl	c
a$_{a/b}$	Ph	Me / Et	c$_{a/b}$
b$_a$	$CHPh_2$	Me	e
k	Ph	CH_2Ph	f
l	Ph	CH_2(9-anthryl)	g

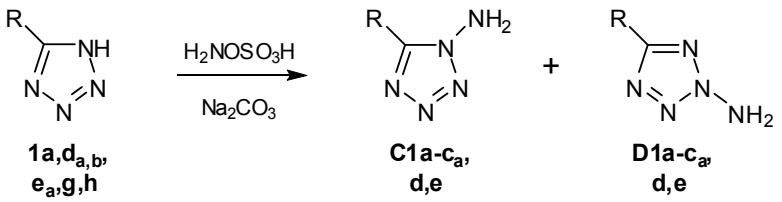
16	R	R'	H
a	$-[CH_2]_5-$		d
b	Cl	Ph	e
c	$[CH_2]_4Cl$	*c*-C_6H_{11}	f
d	Ph	CH_2CO_2Et	g
f	SO_2Me	Ph	h

Scheme 14

II/1) *N*-NITROGEN FUNCTIONALITIES: SERIES (C), (C'), (D)

a) Synthesis

Direct amination of *N*-unsubstituted tetrazoles (**1**) has been accomplished with hydroxylamine-*O*-sulfonic acid in the presence of an inorganic base (Scheme 15) (*cf.* Scheme 1: Route 1). The procedure leads to a mixture of 1- and 2-aminotetrazoles (**C1**/**D1**) with **C1** predominating (except for **C1c$_a$**).[34a,68,69] As the reagent is prone to hydrolysis the overall yields of the products are relatively low. Hence, working in an aprotic medium with a phase-transfer catalyst might constitute a general improvement (as exemplified for the preparation of **C1e** and **D1e**[70]).

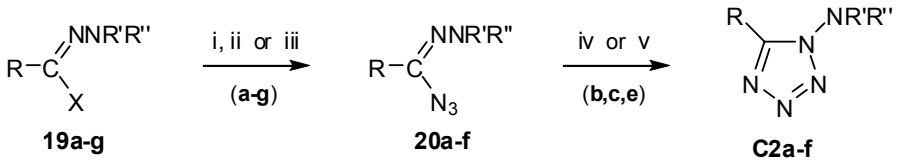


1	R	C1 / D1	Yield (%)
a	H	**a**	25 / 13
$\mathbf{d_a}$	Me	$\mathbf{b_a}$	41 / 27
$\mathbf{d_b}$	Pr	$\mathbf{b_b}$	35 / 26
$\mathbf{e_a}$	Ph	$\mathbf{c_a}$	13-15 / 32
g	2-furyl	**d**	28 / 21
h	NH_2	**e**	8.5 / 4.5 [a]

[a] Yield 64 / 19 (!) under phase-transfer catalysis (**1g**, K^+ salt; dicyclohexano-18-crown-6).

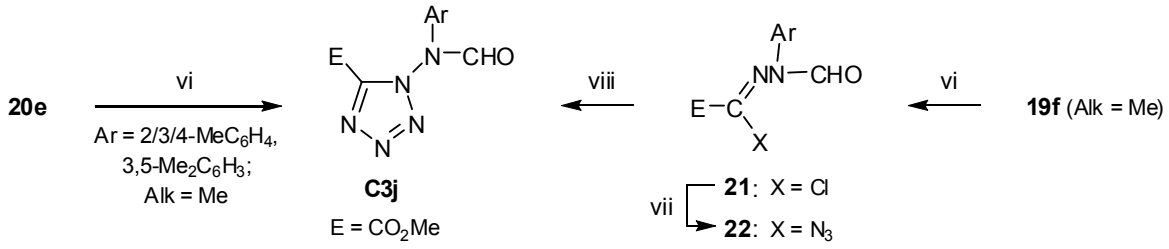
Scheme 15

Very important are cyclization reactions, although they only provide an entry to series (**C**). Nevertheless, there is a wide variety of routes and here, not unlike the methodology for 1-hydroxytetrazoles, cyclization of hydrazonoyl azides and their derivatives reigns supreme. Compounds of type (**C2**) have been prepared as detailed below (Scheme 16) (*cf.* Scheme 1: Route 2b): (i) **C2a** [Ar = (subst.) Ph][29,71a] and **C2c**[72] were obtained directly by treatment of the respective hydrazidines (**19**) with nitrous acid, the intermediary azides (**20**) being unisolable;[71b] (ii) also directly accessible were **C2d** (Ar = 2-Cl/$MeOC_6H_4$)[73] and **C2f**,[74]



19	20 / C2	X	R	R'	R"	Reagent(s)	20 isolated
a	**a**	$NHNH_2$	Ar	H	Ar	i	no
b	**b**	Br	Ar	H	4-$NO_2C_6H_4$	ii; iv	yes
c	**c**	$NHNH_2$	*t*-Bu	H	2-Br-4-$NO_2C_6H_3$	i	no
d	**c**	Br	*t*-Bu	H	2-Br-4-$NO_2C_6H_3$	ii; iv	yes
e	**d**	Cl	Het [a]	H	Ar	ii	no
f	**e**	Cl	CO_2Alk	H	Ar	ii; v [b]	yes
g	**f**	OMe	CH_2CO_2Me	Me	Me	iii	no

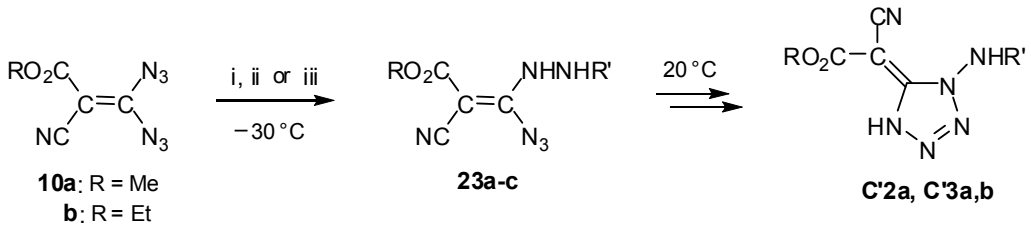
[a] Het = 5-Ph-1,3,4-oxadiazol-2-yl. [b] Also effective: $AlCl_3$, BF_3, MeCOCl / pyridine (as shown for Alk = Me / Ar = Ph), and $POCl_3$ (example not specified).



i: HNO_2 ii: NaN_3 iii: HN_3 iv: MeCOCl or EtCOCl v: $SOCl_2$ vi: $POCl_3$ / DMF vii: NaN_3 viii: $POCl_3$

Scheme 16

viz. by action of sodium (or hydrogen) azide on **19e** and **19g**; (iii) contrasting with the foregoing, azides prepared from **19b,d** [Ar = (subst.) Ph][72] and **19f** [Ar = (subst.) Ph][75a] have been isolated and, in analogy to the process (**3** → **A1**) (*cf.* Scheme 6), could be cyclized with acid chlorides giving **C2b,c** [yields higher than *via* nitrosation of **19** (X = $NHNH_2$)][72] and **C2e**;[75a] the applied reagents might act as a Lewis acid attacking the hydrazinic N(1) of **20** [rather than N(2) as shown in ref.[72]]. Interestingly, the reaction (**20e** → **C2e**) will terminate in a modified product when certain azides of this kind were cyclized under Vilsmeier conditions:[75b,c] While representatives with Ar = Ph (or an electronegatively substituted phenyl group) gave the 'regular' tetrazoles (**C2e**), those bearing electron-donating groups yielded the *N*-formyl derivatives (**C3j**). Since **C2e** turned out to be inert toward Vilsmeier reagent (as exemplified with Alk = Me/Ar = 2-MeC_6H_4), formylation was considered to precede cyclization. This assumption could be confirmed by a model study using **19f** (Ar = 2-MeC_6H_4) which was converted into the respective tetrazole (**C3j**) *via* **21** and **22**. It should be noted that **22** eluded isolation when **C3j** was prepared from **20e**.



10a: R = Me
b: R = Et

23a-c

C'2a, C'3a,b

23	R	R'	**C'2**	**C'3**	Reagent	**23** isolated
a [a]	Alk	Ph	**a** [a]		i	yes [b]
b	Me	COMe		**a**	ii	yes
c [a]	Alk	COPh		**b** [a]	iii	no

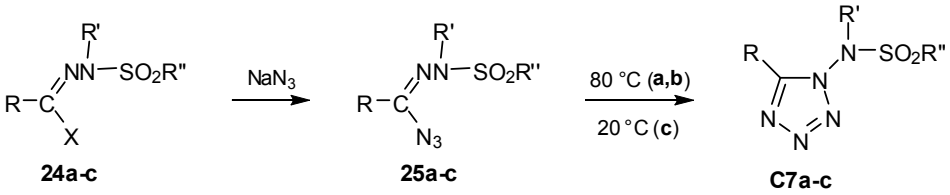
[a] R = Me, Et. [b] R = Me

i: $PhNHNH_2$ ii: $MeCONHNH_2$ iii: $PhCONHNH_2$

Scheme 17

Applying the principle that above gave **A'2a** (*cf.* Scheme 8), the reaction of the geminal diazides (**10a,b**) with appropriate hydrazine derivatives afforded dihydrotetrazoles like **C'2a** and **C'3a,b** in *ca.* 80% yield (Scheme 17) (*cf.* Scheme 1: Route 2a). Isolation of the S_N products (**23**) was not possible in all cases.[56a,b]

Cyclization to *N*-sulfonamidotetrazoles like **C7a,b** was observed when the respective hydrazonoyl azides (**25a,b**) [Ar = (subst.) Ph] were refluxed in benzene (Scheme 18) (*cf.* Scheme 1: Route 2b). The yields, however, are low, since loss of molecular nitrogen from **25** competes with the ring closure so as to give rise to sulfonylsemicarbazides and nitriles as major products.[76] When starting from **24c**, an azide was formed that spontaneously cyclized even at room temperature to afford the tetrazole (**C7c**) in 63% yield.[77]



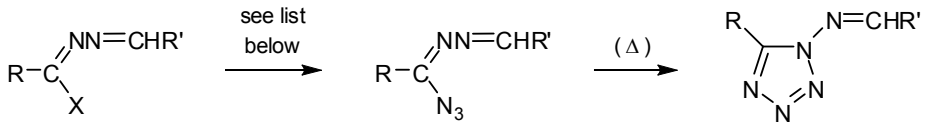
24a-c **25a-c** **C7a-c**

24, 25	X	R	R'	R"	**25** isolated	**C7**
a	Cl	Ar [b]	H	Ph	yes	**a** [c]
b	Cl	Ar [b]	Me	Ph	yes	**b** [c]
c	Py^+Cl^- [a]	NMe_2	H	4-MeC_6H_4	no	**c**

[a] Py = Pyridinio. [b] Save 4-$MeOC_6H_4$. [c] Besides the respective semicarbazide and nitrile.

Scheme 18

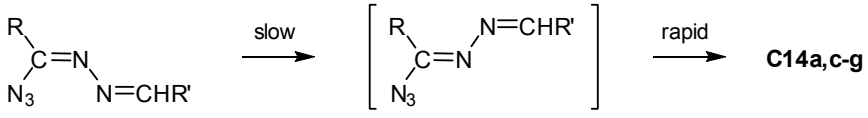
Contrasting with hydrazonoyl azides (**20**), congeners having a second C=N substructure like **27** are prone to ring closure on being heated (Scheme 19) (*cf.* Scheme 1: Route 2b). The earliest example constitutes the reaction (**27a** → **C14a** ≈ **XV** → **XVI**; *cf.* Scheme 3) which in hot ethanol proceeds within 10–20 min.[26a]



26a-k **27a-j$_a$** **C14a-j$_a$**

26	X	R	R'	Reagent [a]	**27, C14**	**27** isolated
a	$NHNH_2$	Ph	Ph	i	**a**	yes
b	Cl / NO_2	Ph	Ph	ii or iii / ii	**a**	yes [b] / no
c	Cl / NO_2	Ar	Ar	ii	**b**	yes [b] / no
d	Cl	Ph	4-ClC_6H_4	ii	**c**	yes
e	Cl	Ph	4-$NO_2C_6H_4$	ii	**d**	yes
f	Cl	Ph	4-$MeOC_6H_4$	ii	**e**	yes
g	Cl	4-MeC_6H_4	Ph	ii	**f**	yes
h	Cl	3-$NO_2C_6H_4$	Ph	ii	**g**	yes
i	Br	(4-ClC_6H_4)S	4-$NO_2C_6H_4$	ii	**h**	no
j	OEt	H	Ph	iv	**i$_a$**	no
k	OEt	Me	Ph	iv	**j$_a$**	no

[a] i = HNO_2, ii = NaN_3, iii = $[(Me_2N)_2C{=}NH_2]\,N_3$, iv = NaN_3 / AcOH. [b] See text.

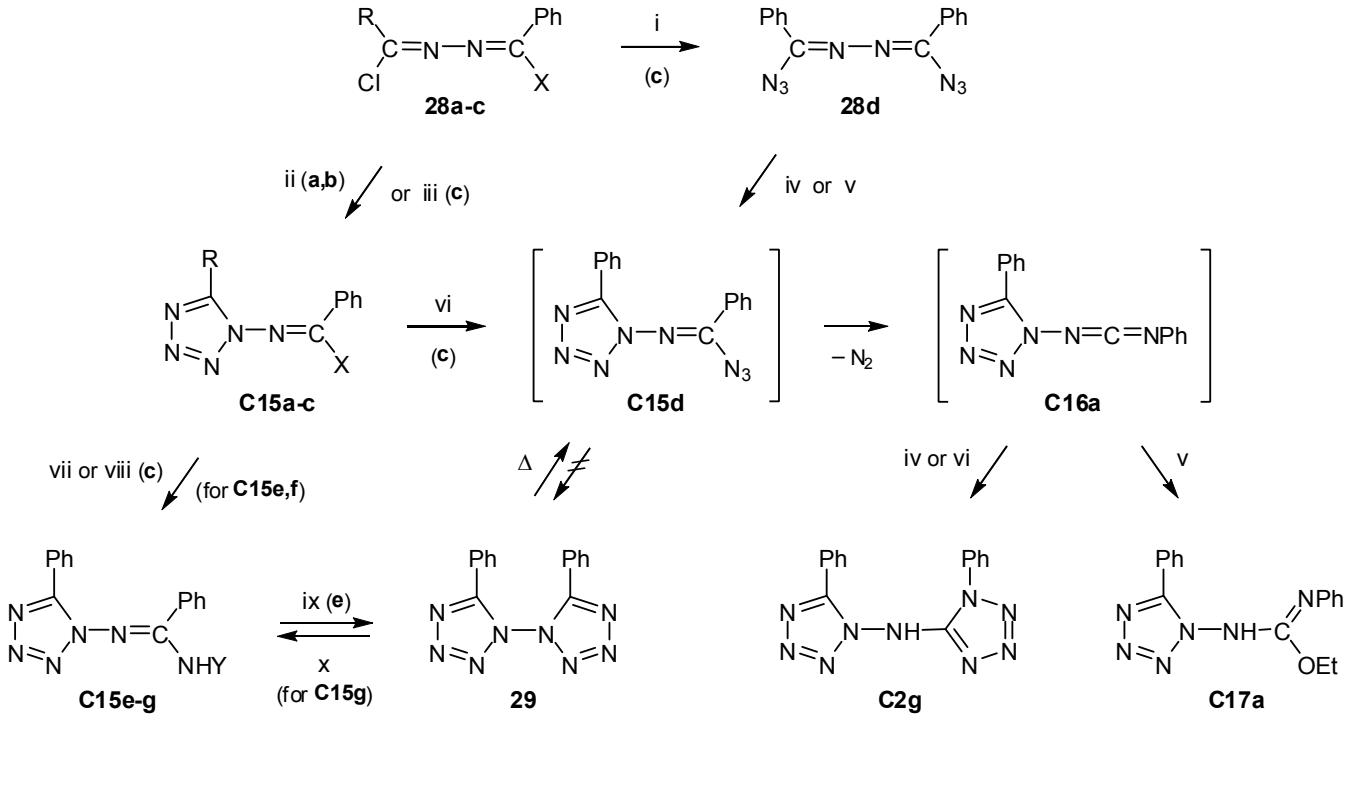


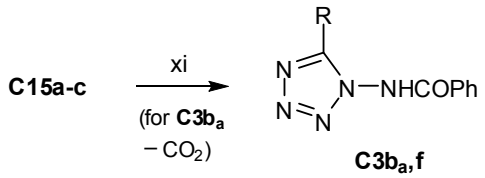
27a,c-g **27'**

$k_{rel\,[27\,\rightarrow C14]}$: 1 (**a**); 1.8 (**c**); 10.9 (**d**); 0.32 (**e**); 1.28 (**f**); 0.69 (**g**)

Scheme 19

Hence, the tetrazole (**C14a**) was obtained directly when the chloride (**26b**; X = Cl) was treated for some hours with the reagent (ii) in refluxing ethanol (or methanol)[26b] or with (iii) in hot acetonitrile;[78] however, in the first case the process could be held at the azide stage when heating was limited to one hour.[26c] On application of relatively mild conditions also azides such as **27b** (Ar = 3-/4-$NO_2C_6H_4$)[26c] and **27c-g**[79a,b] have been isolated and cyclized separately (see below), whereas **C14a** [from **26b** (X = NO_2)],[80] **C14b** (Ar = 4-$MeOC_6H_4$) [from **26c** (X = NO_2)],[80] **C14h**,[81] **C14i$_a$**,[82] and **C14j$_a$**[78] were made in one step, either at elevated or even ambient temperature (as applies to the latter two products). It should be mentioned that it was *via* **C14i$_a$** that the parent (**C1a**) had been obtained for the first time (see below Scheme 29).[82] Later, **C14i$_a$** was prepared by a convenient one-pot procedure using benzaldehyde hydrazone, ethyl orthoformate, and sodium azide.[83] Kinetic studies,[79] performed with **27c-g** in toluene at 70 °C, have disclosed that the (*Z*)-azides (which resulted from synthesis) underwent – in a rate determining step –





28	C3	R	X	C15	Y
a	**f**	Ph	CN	**a e**	NH_2
b		CO_2Et	CN	**b f**	OH
c		Ph	Cl	**c g**	H
	b$_a$	H			

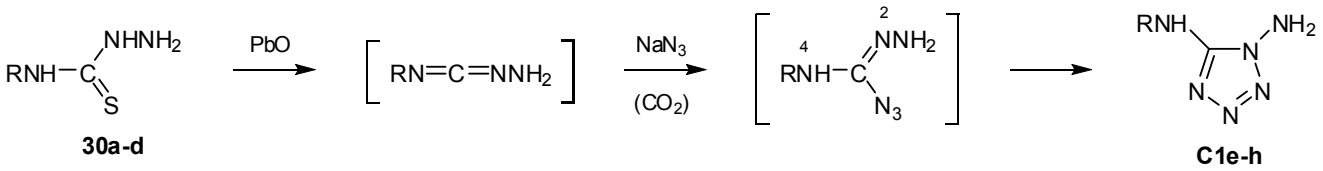
Scheme 20

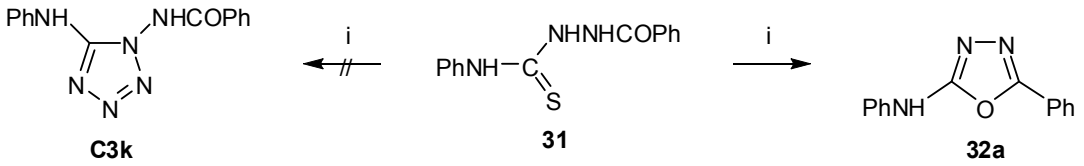
nitrogen inversion to give **27'** which cyclizes immediately. This was deduced from the observation that the process not only showed a low sensitivity to solvents but also a characteristic dependence on substituents: ligands at the remote phenyl group had a more pronounced effect on the rate.

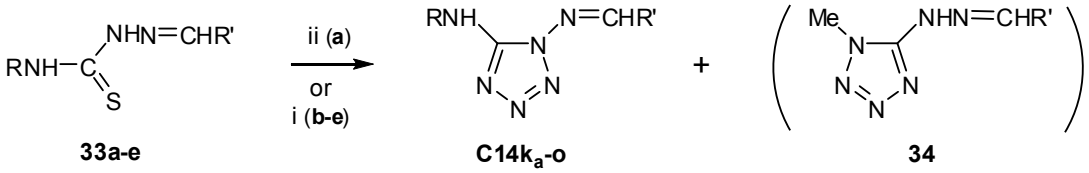
Derivatives of type (**C15**) having an imidoyl cyanide group as in **C15a,b** were obtained on gentle heating of the respective chlorides (**28a,b**) with sodium azide in DMF (Scheme 20) (*cf.* Scheme 1: Route 2b).[84] Although the presence of the open-chain isomers (**28a,b**; N_3 for Cl) was not excluded by IR spectroscopy, the authors were sure to view their products as tetrazoles since the materials were colorless and treatment with alkali hydroxide and acid gave the benzamido derivatives (**C3f**) and (**C3b$_a$**), respectively; **C3f** was then hydrolyzed to the free aminotetrazole (**C1c$_a$**) using hydrobromic acid. The related imidoyl chloride (**C15c**) was made and identified analogously.[85a] It gained importance as an intermediate for constructing the bitetrazole (**29**), after attempts to approach this compound *via* **28d** had met with failure.[26b,85a] While one imidoyl azide 'subfunction' of **28d** cyclized smoothly (→ **C15d**) (*cf.* **28c** → **C15c**), the other group lost molecular nitrogen to form a carbodiimide (**C16a**) which was intercepted by azide ion (→ **C2g**)[26b,85a] or ethanol (→ **C17a**).[26b] As this degradation also occurred when **C15c** was used as precursor,[85a] the latter had to be converted into the amidrazone (**C15e**)[85b] which on treatment with nitrous acid gave the target compound (**29**) very readily. Thermolysis of this material caused ring opening of one of the tetrazole nuclei giving rise to **C16a** (trapped as **C17a**; *cf.* above), whereas hydrogenation led to the amidine (**C15g**).[85a]

A classical entry to 1-aminotetrazoles (**C1**) and derivatives (**C14**) bearing a nitrogen function also at C(5) consists in joint action of lead(II) oxide and sodium azide on thiosemicarbazides (**30**) and -carbazones (**33**), respectively (Scheme 21) (*cf.* also 'Early History:' **XXI** → **XXII**).[30] The reaction was viewed as proceeding *via* the carbodiimide stage (*cf.* Scheme 1: Route 3e; here shown for **30** → **C1**) and was advantageously carried out in a CO_2 atmosphere. However, the procedure did not work with **33a** since benzylidene semicarbazide was formed rather than the tetrazole (**C14k$_a$**); only lead(II) azide proved successful (low yield). An attempt to follow this route also for the synthesis of **C3k** failed since the substrate (**31**) was converted into the 1,3,4-oxadiazole (**32a**).[30] Interestingly, with thiosemicarbazones such as **33b** cyclization of the intermediary amidrazono azide not only affected N(2) but also N(4) to give, besides **C14l**, traces of the isomers (**34**).[86] This competing course is a consequence of the electron-donating influence of the methyl group at that nitrogen (see also later Scheme 32: Dimroth rearrangement).

Regarding the above synthesis of diaminotetrazole (**C1e**) from **30a**, improvements have been made: (i) by replacing carbon dioxide with ammonium chloride and by using dimethylformamide instead of ethanol (yield 59%),[87] (ii) by replacing sodium azide – ammonium chloride with trimethylsilyl azide (79%)[88a,b] (see ref.[88a] also for an X-ray analysis of **C1e**). Avoiding lead containing reagents, **C1e** has been prepared: in 58% yield from diaminoguanidinium chloride (**35a**; X = Cl) *via* **35b** (*cf.* Scheme 1: Route 2b)[89a–c] or

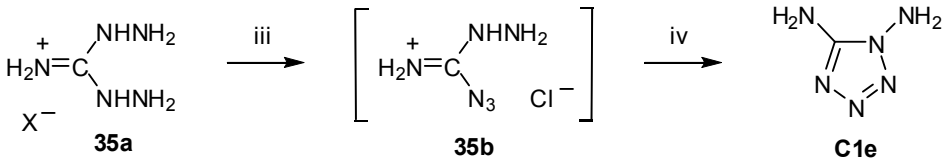




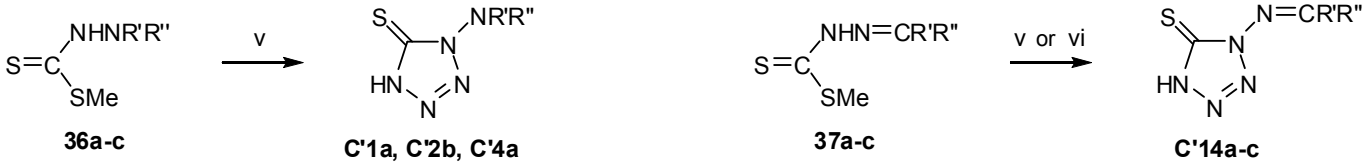


30	33	R	R'	C1	C14
a	**a**	H	Ph	**e**	$\mathbf{k_a}$
	b	Me	Ar		**l** [a]
b	**c**	$CH_2CH=CH_2$	Ph	**f**	**m**
c	**d**	Ph	Ph	$\mathbf{g_a}$	**n**
d		NH_2	Ph	**h**	
	e	PhCH=N	Ph		**o**

[a] Also traces of **34** (R'= Ph, 4-ClC_6H_4, 4-MeC_6H_4).



i: PbO / NaN_3 / CO_2 ii: $Pb(N_3)_2$ iii: $NaNO_2$ (1 eq.) / HCl iv: Na_2CO_3 / 40 °C



36	R'	R''	C'1	C'2	C'4
a	H	H	**a**		
b	Me	Me		**b**	
c	H	CO_2Bu-t			**a**

v: NaN_3

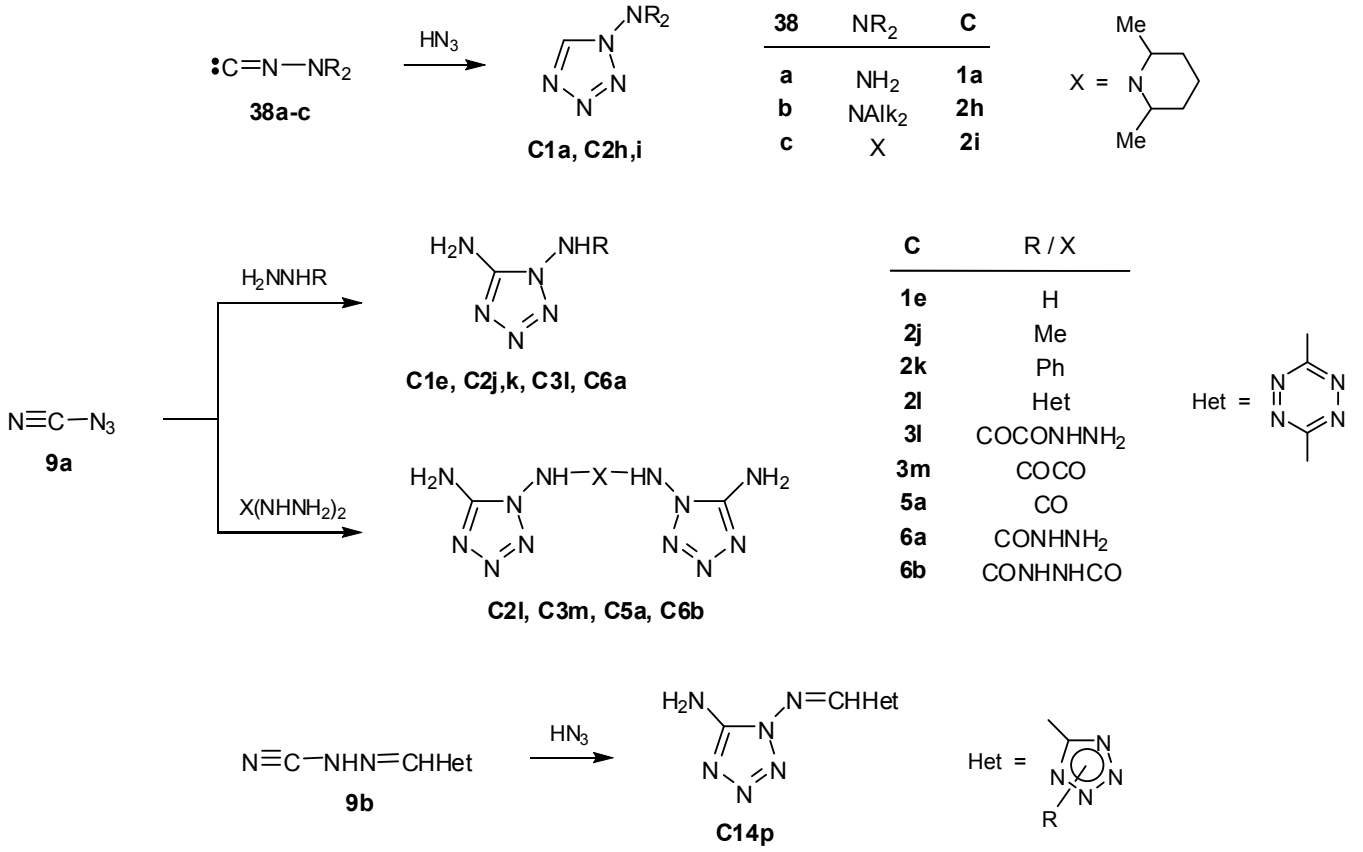
vi: $[(Me_2N)_2C=NH_2]\,N_3$

R'	37, C'14	R''
H	**a**	Ph
Me	**b**	Me
Me	**c**	Ph

Scheme 21

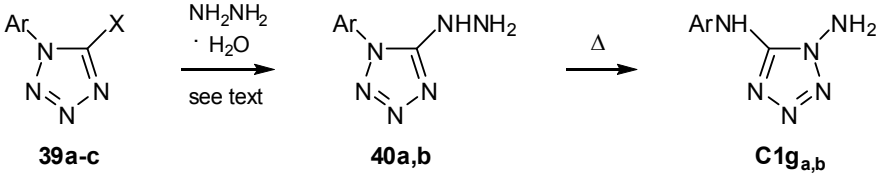
– applying the principle that above gave **A2d** (Scheme 8)[55a] – from cyanogen azide (**9a**) and hydrazine in 79% yield (Scheme 22) (*cf.* Scheme 1: Route 3c).[55b]

4,5-Dihydro-1*H*-tetrazoles like **C'1a**, **C'2b**, **C'4a**, and **C'14a-c** having a thioxo group at C(5) are readily available by reacting appropriate dithiocarbazates (**36**) and (**37**) with an azide salt in ethanol (Scheme 21) (*cf.* Scheme 1: Route 2a).[90a–c] Studies in this field aimed at providing special ligands for a range of β-lactam antibiotics.[91]



Scheme 22

An approach that recalls the historical process (**Xa** → **XIa**) (Scheme 2) consists in adding hydrogen azide onto the amide of isofulminic acid (**38a**) to give the parent (**C1a**) in low yield (Scheme 22) (*cf.* Scheme 1: Route 3b).[92] Alkyl derivatives such as **C2h** (Alk = Et, *i*-Pr, Bu) and **C2i** are available in like manner (yields 54–79 and 24%, respectively).[93] Substrates having a cyano function lead to the class of diamino-tetrazoles (*cf.* Scheme 1: Routes 3c,d). Thus, hydrogen azide adds smoothly to cyanohydrazones like **9b** (R in Het = 1-Alk, 1-Ph; 2-Alk) to afford the respective derivatives (**C14p**) in high yield.[94] As shown recently, this entry can be performed 'inversely,' *i.e.* by reacting cyanogen azide (**9a**) with a hydrazine component. Depending on its substituent (R) and (X), respectively, not only **C1e** (as mentioned above) but also derivatives of the series (**C2**), (**C3**), (**C5**), and (**C6**) have been obtained in reasonable yield.[55b]



39a-c **40a,b** **C1g$_{a,b}$**

39	Ar	X	**40**	(isolated)	**C1**
a	Ph	SO_2Me	**a**	(yes)	**g$_a$**
b	Ph	Cl	**a**	(no)	**g$_a$**
c	4-MeC_6H_4	Cl	**b**	(no)	**g$_b$**

Scheme 23

As a different route to diaminotetrazoles the Dimroth rearrangement has been followed (Scheme 23) (*cf.* Scheme 1: Route 4b). When the 5-sulfonyltetrazole (**39a**) was refluxed with hydrazine hydrate for 2–3 min the 5-hydrazinotetrazole (**40a**) could be isolated; however, heating the latter in boiling xylene, morpholine or benzylamine gave the rearranged tetrazole (**C1g$_a$**) very rapidly.[95] Accordingly, prolonged treatment of the 5-chlorotetrazoles (**39b,c**) with hydrazine hydrate in boiling ethanol led directly to the derivatives (**C1g$_a$**) and (**C1g$_b$**).[96] Conceivably, this applies also to an experiment in which **39b** was refluxed for 24 hours with hydrazine hydrate: the product, contrary to the authors' belief of having prepared **40a**,[97] proved to be pure **C1g$_a$**.[98]

b) Reactions

A theoretical study (INDO level) on the structure of all parent *N*-aminoazoles accompanied by selected experimental work has established that the amino group is sp^3 configurated and prefers a configuration that avoids (or minimizes) lone pair–lone pair repulsions[99a] (*cf.* also ref.[100]). With monocycles, the most stable configuration shows the lone pair in the ring plane ('parallel' orientation) and the hydrogens on opposite sides. Thus, one α-nitrogen implies *ap* conformation, but with two α-nitrogens the 'perpendicular' orientation becomes important.[99a] As for the tetrazoles (**C1a**) and (**D1a**), this has in part been confirmed at the MP2/6-31G* level.[101a] In pursuit of this, B3LYP/6-31** calculations were carried out on **C1a**/**D1a** including **C1e**/**D1e** (Figure 1).[101b] For **C1a** they showed that the *ap* conformation is favored over *sp*[99b] by 4.30 kcal; in the case of **D1a**, 'parallel' (*sp*) and 'perpendicular' (*ac*) conformers were found that are almost identical in energy, the geometry of the latter corresponds to that reported in ref.[101a] Regarding **C1e**/**D1e**, the spatial arrangement of the *N*-amino groups parallels that of **C1a**/**D1a**, while the *C*-amino groups are conjugated with the π-system. For **C1e** (*ap* conformer) this difference was earlier demonstrated by an X-ray analysis.[88a] As a consequence the *N*-attached amino group is more nucleophilic; quite a number of reactions of **C1e** described below will illustrate this.

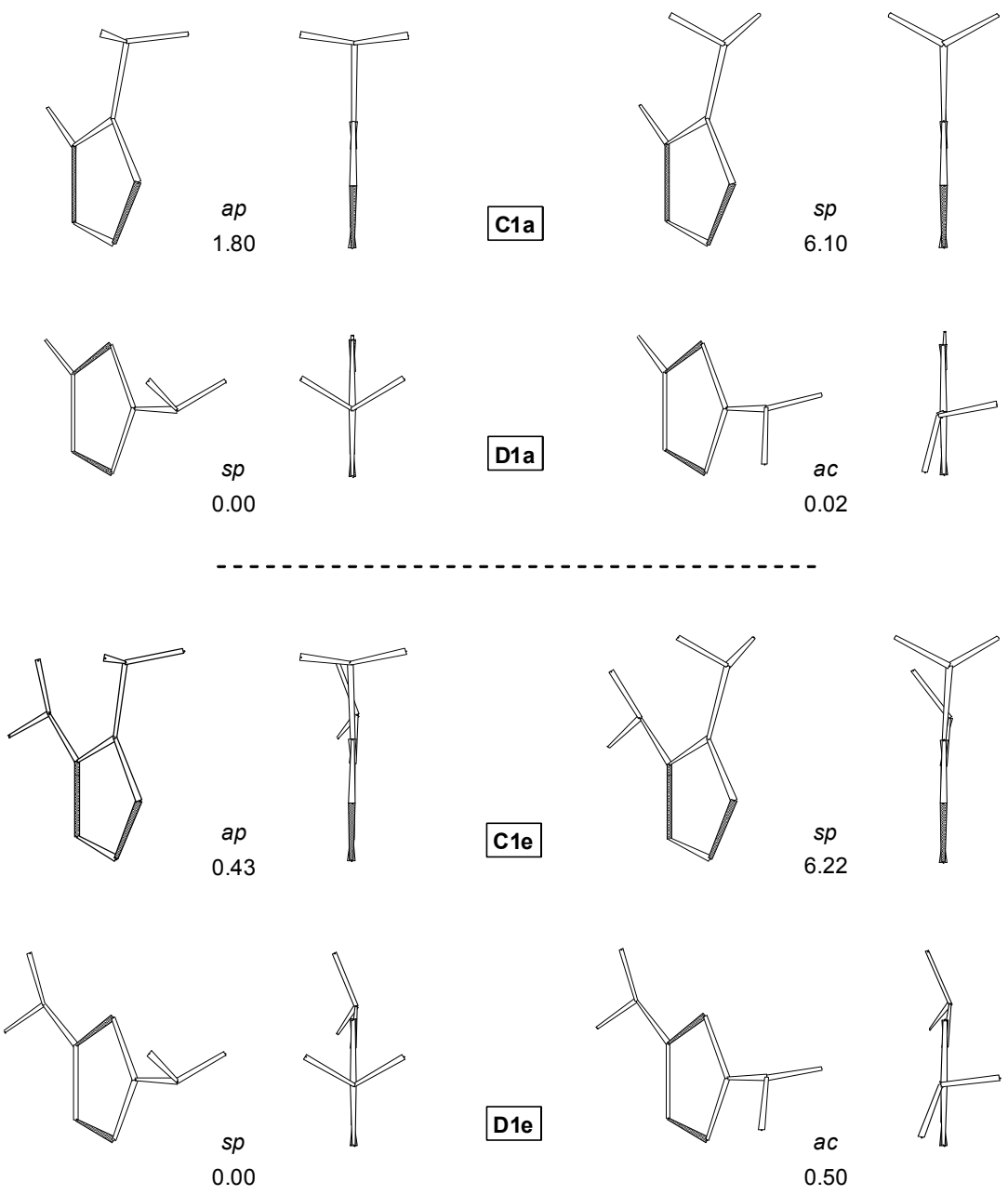
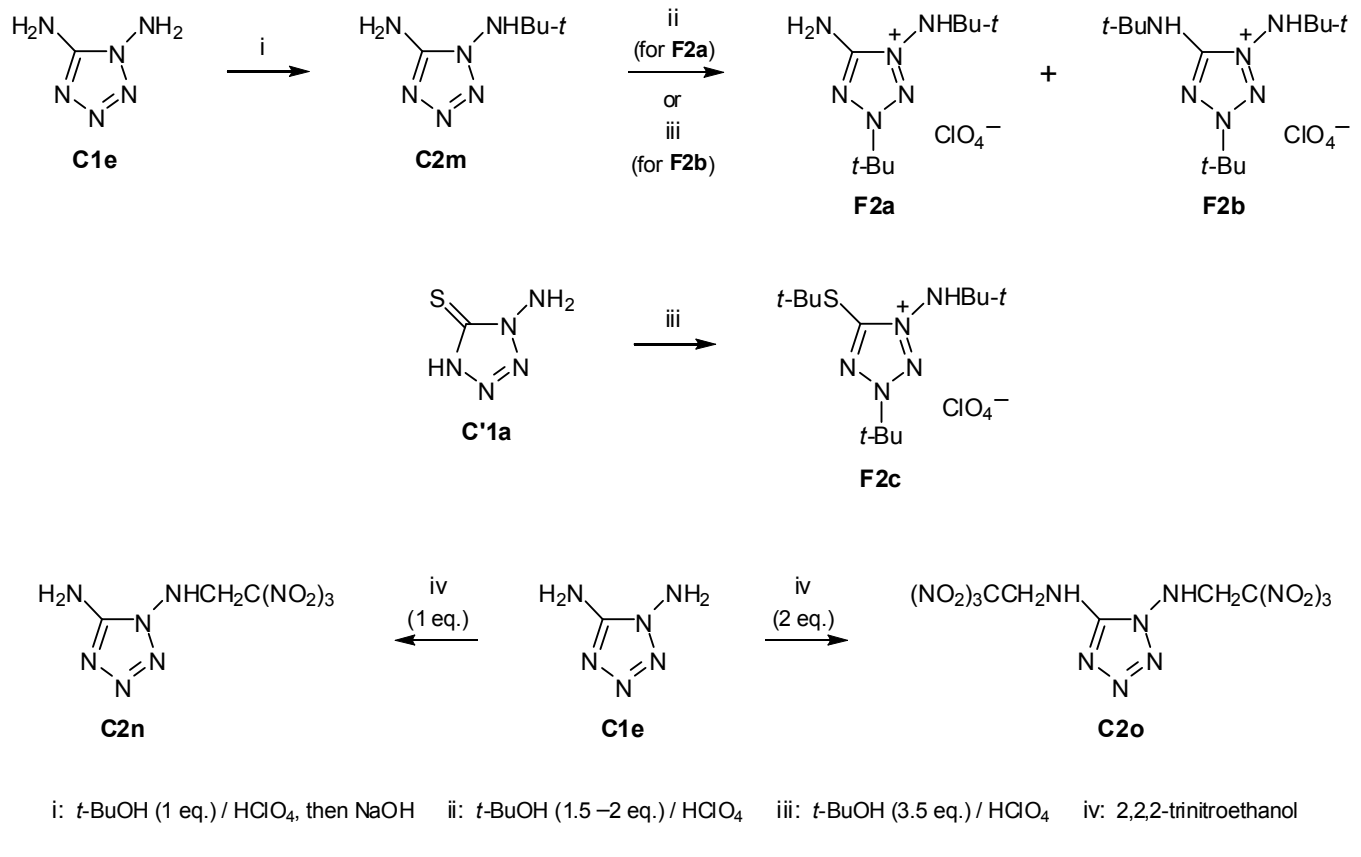


Figure 1. Conformers of *N*-aminotetrazoles according to B3LYP/6-31G** (gas phase); relative energies (kcal/mol) shown

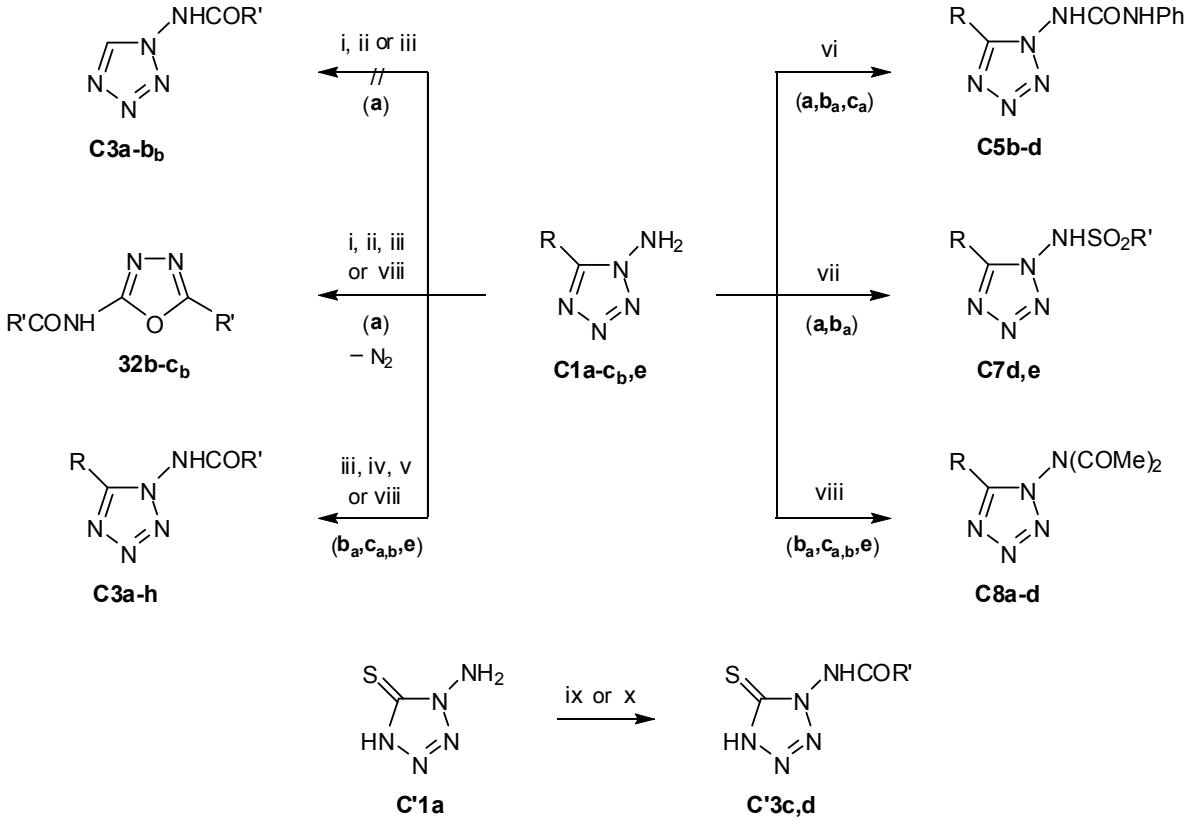
Alkylation: Unlike alkylations of the *N*-hydroxy function, corresponding reactions at the amino counterpart are rare. When **C1e** was treated with 1 eq. of *tert*-butyl alcohol in perchloric acid, work-up at pH 8–9 gave the derivative (**C2m**) in 28% yield (Scheme 24).[102] The stoichiometry must be obeyed rigorously since 1.5–2 eq. of the reagent affected also the ring (→ **F2a**; 25–30%) and 3.5 eq. alkylated the *C*-amino group in addition (→ **F2b**; 68%). The thioxo substrate (**C'1a**) likewise underwent threefold alkylation (→ **F2c**; 75%).[102] Moreover, in conjunction with the development of new energetic materials (*cf.* also Chapter II / 2), compounds like **C2n** and **C2o** have been prepared.[103] Because of the electron-



Scheme 24

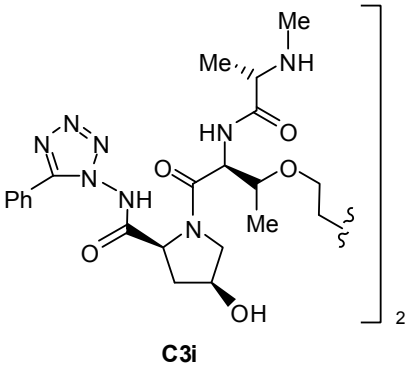
withdrawing influence exerted by the tetrazole ring (*cf.* ref.[104]) the C–C bond of the side chain is stabilized; as observed above,[102] the *N*-amino group of **C1e** reacted more readily.

Acylation: First experiments in the field pertain to **C1c$_{a,b}$** (Scheme 25): the materials were heated with excess acetic anhydride which, because of the forcing conditions, caused exhaustive acetylation (→ **C8b,c**); a mono derivative (**C3g**) was detected as side product.[26c] Preparation of **C8b** was duplicated later[34b,68] and analogues like **C8a**[34b] and **C8d**[68,87] were made too. The structure of the latter – at one time deduced from the known failure of 5-aminotetrazoles to afford diacetylamino derivatives under these conditions[68] – was recently confirmed by an X-ray analysis.[105a] The formation of compound (**C8d**) like that of **C3h**[105b] illustrates the enhanced reactivity of the 1-amino group over the 5-amino group. Interestingly, the 5-unsubstituted educt (**C1a**) failed to yield a compound of type (**C8**; R = H), nor did products of monoacylaion (**C3**) occur: reactions with several carboxylic acid chlorides and anhydrides gave, even under mild conditions, oxadiazoles (**32b-c$_b$**) rather than **C3a-b$_b$**.[82b] The surprising result was rationalized assuming a tetrazolium intermediate (**O3f**);[82b] this species having an extremely labile hydrogen at C(5) underwent proton loss and release of molecular nitrogen.[106] Regarding the spectacular acyl derivative (**C3i**) which belongs to a family of dimeric IAP inhibitors, this material has presumedly been made using an appropriate hydroxyproline synthon.[107] Acylations of the amino group of the



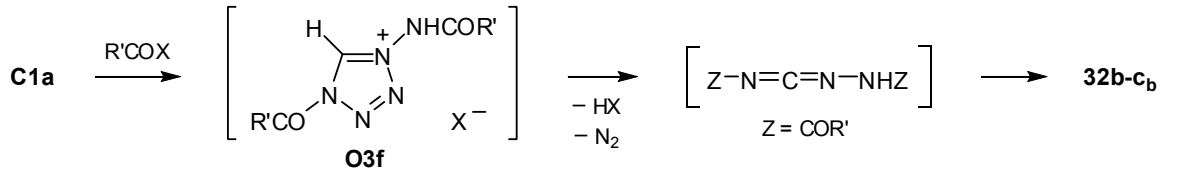
i: MeCOCl ii: $(ArCO)_2O$ (neat) / Δ iii: ArCOCl / pyridine iv: $(MeCO)_2O$ (1.2 eq.) / $MeCO_2H$ / Δ v: HCO_2H / HCO_2Na / Δ
vi: PhNCO vii: $R'SO_2Cl$ / base viii: $(MeCO)_2O$ (neat) / Δ ix: HCO_2H / $(MeCO)_2O$ x: $(MeCO)_2O$ / THF / Δ

C1	R	R'	32	C3	C'3	C5	C7	C8
		H			**c**			
a	H	Me	**b**	**a**	**d**	**b**		
	H	Ph	**c$_a$**	**b$_a$**				
	H	3,5-$(NO_2)_2C_6H_3$	**c$_b$**	**b$_b$**				
	H	4-MeC_6H_4					**d**	
b$_a$	Me	Me		**c**		**c**		**a**
	Me	Ph		**d**			**e**	
c$_a$	Ph	Me		**e**		**d**		**b**
	Ph	Ph		**f**				
c$_b$	2-ClC_6H_4	Me		**g** [b]				**c**
e	NH_2	H		**h**				
	NHR" [a]							**d**



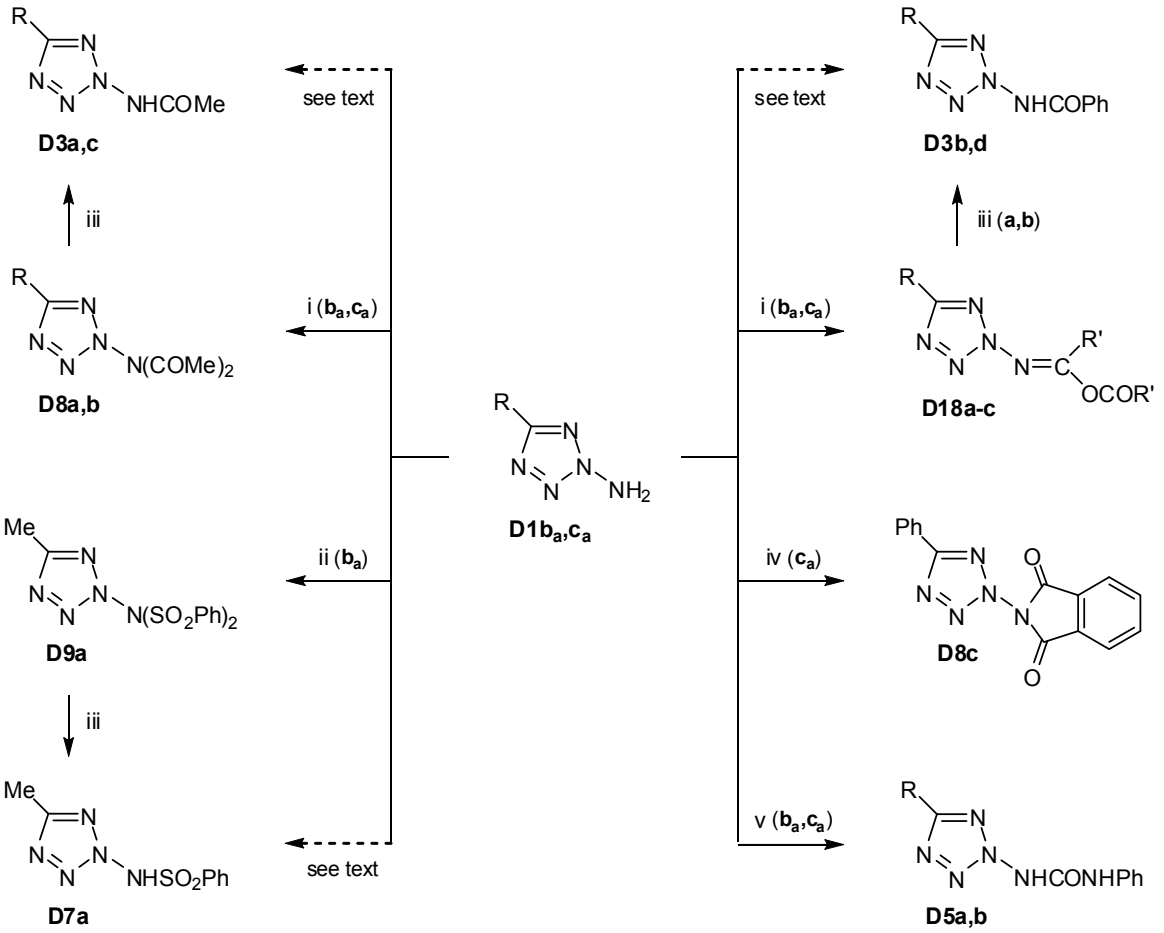
C3i

[a] R" = H (**C1e**), COMe (**C8d**). [b] Detected as side product of **C8c**.



Scheme 25

dihydrotetrazole (**C'1a**) with various anhydrides proceeded smoothly too (→ **C'3c,d**).[90a,b] The same applies to carbamoylation and sulfonylation of substrates (**C1**): not only could products like **C5c,d**[34b] and **C7e**[34c] be prepared, in this case it was also possible to obtain 5-unsubstituted derivatives such as **C5b** and **C7d**.[82b]



i: MeCOCl or R'COCl (2 eq.)/Et_3N ii: $PhSO_2Cl$ (2 eq.)/Et_3N iii: 2 N KOH/Δ iv: 1,2-$(COCl)_2C_6H_4$ / Et_3N v: PhNCO/pyridine

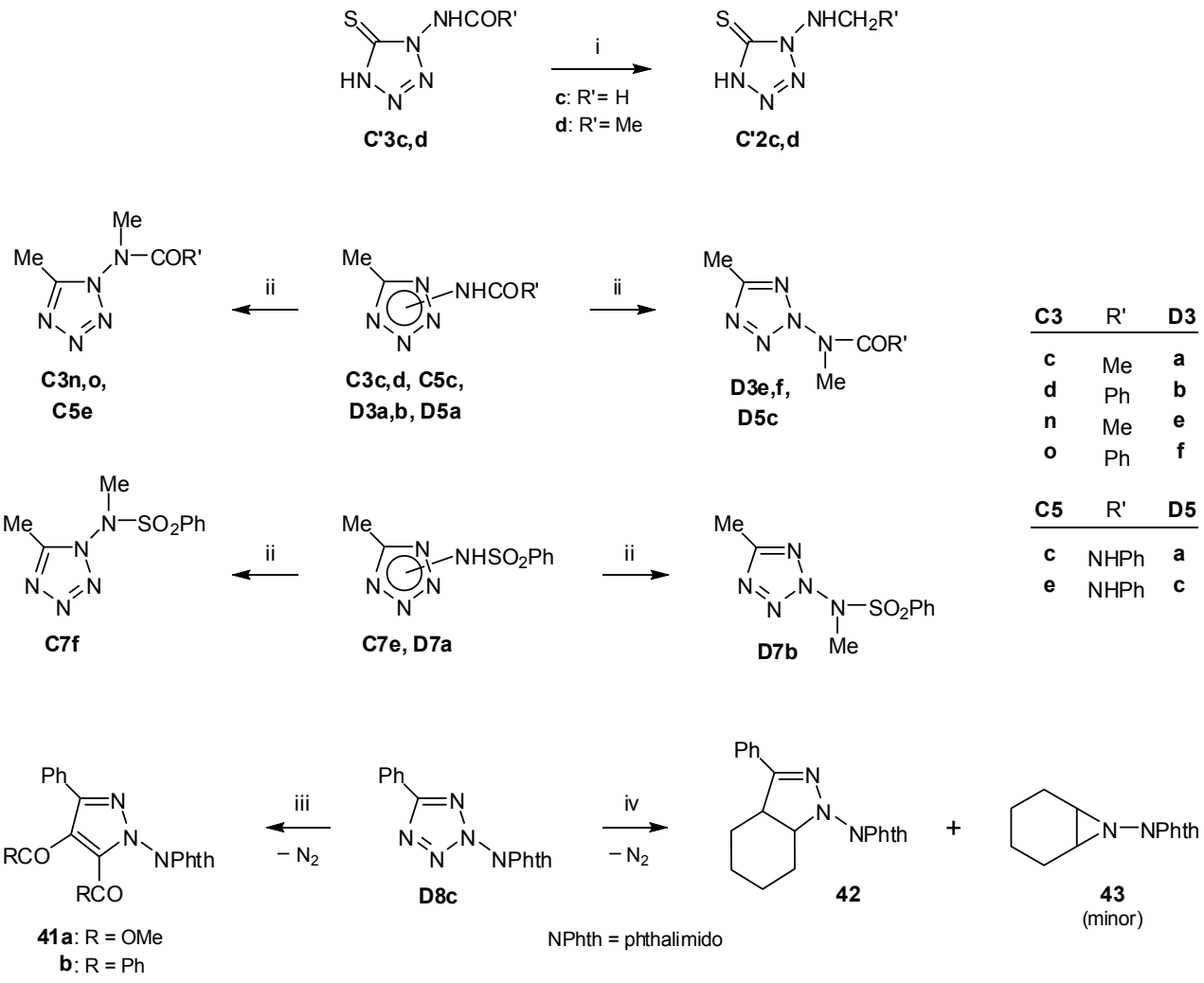
D1	R	R'	D3	D5	D8	D18
$\mathbf{b_a}$	Me	Ph	**a**	**a**	**a**	**a**
	Me		**b**			
$\mathbf{c_a}$	Ph	Ph	**c**	**b**	**b**	**b**
	Ph		**d**			
	Ph	4-MeC_6H_4				**c**

Scheme 26

As a consequence of the stronger electron-withdrawing influence exerted by the tetrazol-2-yl system[104] aminotetrazoles (**D1**) are less nucleophilic. Thus, on submission of $\mathbf{D1b_a}$ and $\mathbf{D1c_a}$ to the conditions suitable for making **C3c-f** the substrates turned out to be fully inert.[34b] Only working with triethylamine,

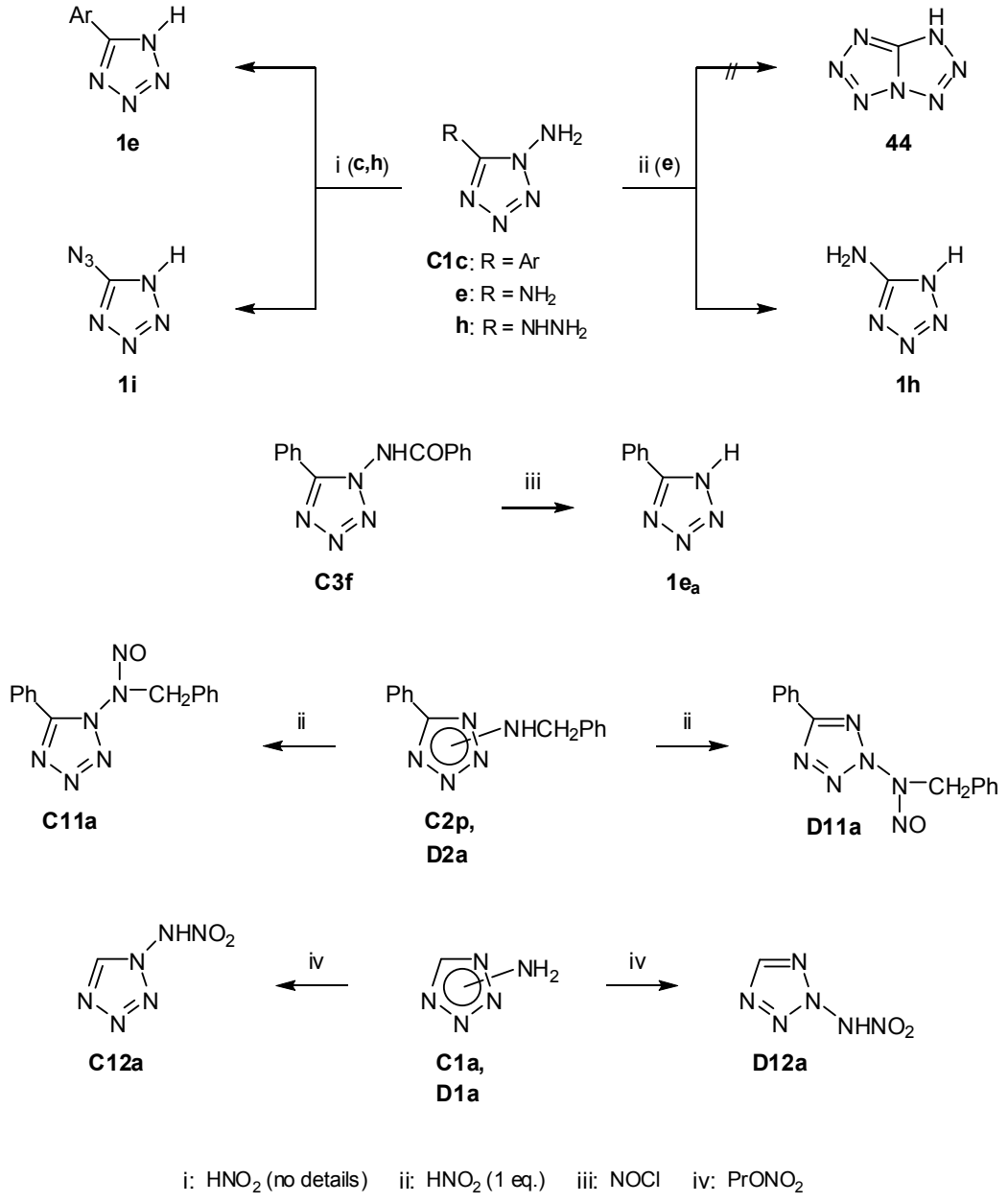
in analogy to the process (**D1c$_a$** → **D8c**),[69] caused the reaction to occur (Scheme 26). But since usage of just 1 eq. of the acylating agent resulted in twofold functionalization – to give inseparable mixtures of the target derivatives (**D3a-d**) and unwanted diamides (**D8a,b**) or isoimides (**D18a,b**)[34d] –, preparation of **D3a-d** had to be performed stepwise: exhaustive acylation of the amino group followed by partial hydrolysis.[34b] The same procedure was required for a sulfonamide (**D9a** → **D7a**).[34c] The ureas (**D5a,b**) were accessible directly, but also here employment of a base was compulsory.[34b]

Reactions of acyl derivatives (beyond those shown above) are detailed below (Scheme 27). Side chain transformations include: (i) reduction of the amide functions in **C'3c,d** to secondary amino groups (→ **C'2c,d**);[90a,b] (ii) methylation of the amide functions in **C3c,d** and **D3a,b** as well as of the ureido groups in **C5c** and **D5a** to yield the derivatives (**C3n,o**), (**C5e**), (**D3e,f**), and (**D5c**), respectively;[34b] (iii) methylation of the sulfonamide functions in **C7e** and **D7a** to afford the derivatives (**C7f**) and (**D7b**).[34c] Ring opening



Scheme 27

with evolution of nitrogen has been reported for the phthalimide derivative (**D8c**); the resultant nitrilimine was trapped as **41a,b** and **42**, while part of it decomposed into benzonitrile and phthalimidonitrene as evidenced by the adduct (**43**).[69] It is worth noticing that, because of the electronegative substituent at N(2), cleavage of **D8c** occurs at much lower temperature than with 2,5-diaryltetrazoles. Also, comparing the behavior of 2-amino-5-phenyltetrazole (**D1c$_a$**) and its 2-methyl congener (**13c**) in hot nitrobenzene (180–190 °C), the former compound has been found to ring open about 100 times faster.[108]



Scheme 28

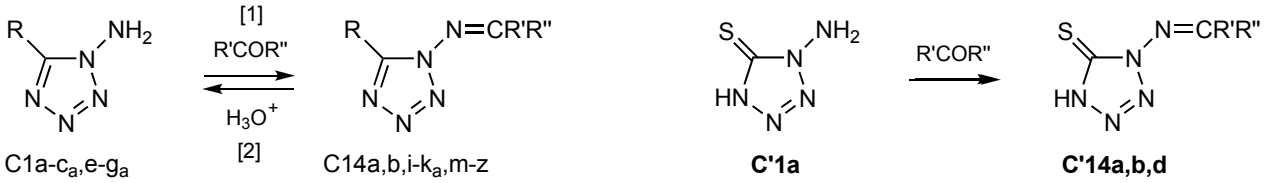
Nitrosation, Nitration: Typical of *N*-aminoazoles,[9] compounds such as **C1c** (Ar = 2-Cl/4-$NO_2C_6H_4$) underwent deamination (→ **1e**) when treated with nitrous acid[26c] (Scheme 28); in the case of **C1h**,

apparently the explosive azide (**1i**) arose.[30] Accordingly, 1,5-diaminotetrazole (**C1e**) was defunctionalized to **1h** (evidenced by the melting point) rather than cyclized to **44** as has been claimed.[109] Treatment of the benzamide (**C3f**) with nitrosyl chloride also resulted in complete defunctionalization (→ **1e$_a$**).[85a] The recent technique of deaminating *N*-aminoheterocycles using a heteropoly acid (Preyssler's anion) has not been extended to tetrazoles (**C1**) or (**D1**).[110] In conjunction with studies on the conformational mobility of certain (*N*-benzyl-*N*-nitrosoamino)azoles the derivatives (**C11a**) and (**D11a**) have been prepared (low yield; *E*/*Z*-isomerism not observable because of broadened signals).[111a] The novel reagent bismuth chloride–sodium nitrite, while in use for nitrosating *sec.* amines, amides, and even *N*-unsubstituted tetrazoles,[111b] has not been applied to the types (**C2**) and (**D2**).

Two isomeric (*N*-nitramino)tetrazoles (**C12a**) and (**D12a**) have been prepared by reacting the potassium salts of (**C1a**) and (**D1a**) with propyl nitrate. The products were converted into the ammonium and silver salts which were studied in detail as to their combustive behavior.[112]

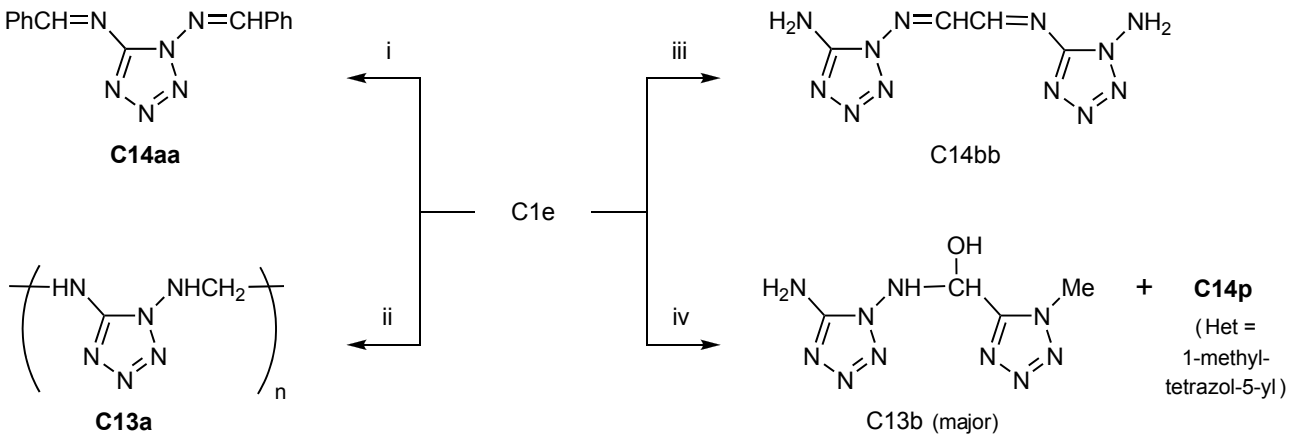
Aldehydes, Ketones: Condensation of 1-aminotetrazoles (**C1**) with carbonyl compounds to give products of type (**C14**) constitutes the reaction most frequently performed, leaving a plethora of derivatives; also the tetrazolinethione (**C'1a**) has been transformed in that way (→ **C'14**) (Scheme 29). Often catalytic amounts of a strong acid have been employed.[68,87,94,113,114] Regarding the behavior of **C1e**, the amino group at N(1) reacted in preference to that at C(5). This is evidenced by the derivatives (**C14k,k$_a$,p,w-y**) including the hemiaminal (**C13b**); the latter resulted as the major product (60%) from 1-methyltetrazole-5-carbaldehyde.[94,119] Nevertheless, condensation reactions are possible at both amino groups: Apart from cyclic systems (see Scheme 33), this is shown by the derivatives (**C14aa**)[116b] and (**C13a**);[87] also compound (**C14bb**) – remarkable for its unsymmetrical structure – belongs to this category.[120] As listed in Scheme 29, acid hydrolysis of **C14** (reaction [2]) has been reported for several examples; in addition, there exist some cases of hydrazinolysis. — Imines of type (**D14**) have been prepared too, albeit in relatively low number (Scheme 30).

Reactions occurring at the double bond of the aforementioned derivatives are shown in Scheme 31. Hydrogenation of **C14a** and **D14f** using sodium borohydride gave the (benzylamino)tetrazoles (**C2p**) and (**D2a**), respectively,[111a] in the same way the derivative (**C'14b**) was converted into **C'2c**.[90a,b] Treatment of the imines (**C14u**) and (**D14h**) with sodium borohydride or lithium aluminium hydride afforded the (propargylamino)tetrazoles (**C2q**) and (**D2b**), whereas action of Grignard reagent led to the derivatives (**C2r**) and (**D2c**).[114] Joint action of 4-fluorobenzaldehyde and dibutyl phosphonate on diaminotetrazole (**C1e**) gave the aminophoshonate (**C13c**) (Kabachnik-Fields reaction).[116a] One-pot phosphonoalkylation of both amino groups (→ **C13d**) was possible in the presence of sulfuric acid; however, for higher yields the separately prepared bis-imine (**C14aa**) had to be submitted.[116b]



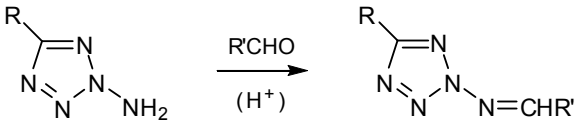
C1	R	R'	R''	C14	Reaction	ref.	C'14	ref.
a	H	Ar	H	**i**	[1]	82b [f], 92		
	H	Ph	H	**i_a**	[1] // [2]	82b, 92 // 82 [g], 83b	**a**	90a
	H	Het	H	**q** [b]	[1]	68	**d** [l]	90b
	H	Me	Me	**r**	[1]	82b	**b**	90a,b,c
b_a	Me	Ar	H	**j**	[1]	113 [h]		
	Me	Ph	H	**j_a** [c]	[2]	78		
b_b	Pr	Ar	H	**s**	[1]	68		
	Pr	Het	H	**t** [b]	[1]	68		
c	Ar	Ar	H	**b**	[1] // [2]	26c // 26c		
c_a	Ph	Ph	H	**a**	[1] // [2]	111a // 26a, 78 [i]		
	Ph	C≡CR"	H	**u**	[1]	114		
	Ph	Me	Me	**v**	[1]	26c		
e	NH_2	Ar	H	**k**	[1]	68, 94, 113 [h], 115, 116a		
	NH_2	Ph	H	**k_a**	[1] // [2]	30, 68 // 30 [k], 117 [i]		
	NH_2	Het	H	**p** [d]	[1] // [2]	68, 94 // 118		
	NH_2	C≡CR"	H	**w**	[1]	114		
	NH_2	ferrocenyl	H	**x**	[1]	87		
	NH_2	Me	Me	**y**	[1]	87		
f	XNH [a]	Ph	H	**m**	[1] // [2]	30 // 30		
g_a	PhNH	Ph	H	**n**	[1] // [2]	30 // 30		
	PhNH	Me	Me	**z**	[1] // [2]	30 // 30		
⁄	PhCH=NNH	Ph	H	**o** [e]	[2]	30		

[a] X = $CH_2CH = CH_2$. [b] Het = 5-nitro-2-furyl. [c] From **26k** only (Scheme 19). [d] Het = 5-nitro-2-furyl, 1/2-substituted tetrazol-5-yl. [e] From **33e** only (Scheme 21); hydrolysis leads to **C1h** (R = $NHNH_2$). [f] Ar also 2,5-$(MeO)_2C_6H_2$ of sym. bis-imine. [g] Hydrolysis of **C14i$_a$** once obtained from **26j** (Scheme 19) gave the parent (**C1a**) for the first time; cleavage also with phenylhydrazine / AcOH. [h] Ar = 4,4'-$(OH)_2$-3,3'-(4-$XC_6H_4CH)(C_6H_3)_2$ (substituent of sym. bis-imine). [i] Cleavage with anhydrous hydrazine. [k] Cleavage also with NaOH. [l] Het = 2-furyl.



i: $PhCHO/H_2SO_4$ ii: CH_2O/HCl iii: OCHCHO (0.5 eq.)/HCl iv: 1-methyltetrazole-5-carbaldehyde/TosOH

Scheme 29

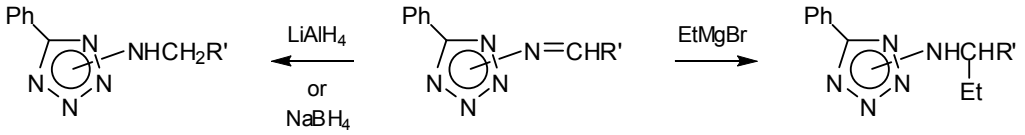


D1a-c$_a$,e **D14a-k**

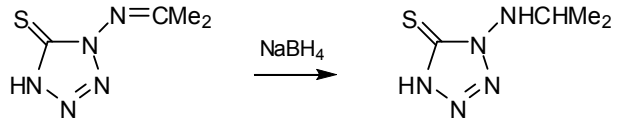
D1	R	R'	**D14**	ref.	**D1**	R	R'	**D14**	ref.
a	H	Ar	**a**	68	**c$_a$**	Ph	Ar	**g**	68
	H	Het	**b** [a]	68		Ph	C≡CR''	**h**	114
b$_a$	Me	Ph	**c**	68	**e**	NH_2	Ph	**i**	68
b$_b$	Pr	Ar	**d**	68		NH_2	Ar	**j**	68, 113 [b]
	Pr	Het	**e** [a]	68		NH_2	Het	**k** [a]	68
c$_a$	Ph	Ph	**f**	111a					

[a] Het = 5-nitro-2-furyl. [b] Ar = 4,4'-$(OH)_2$-3,3'-(4-$XC_6H_4CH)(C_6H_3)_2$ (substituent of sym. bis-imine).

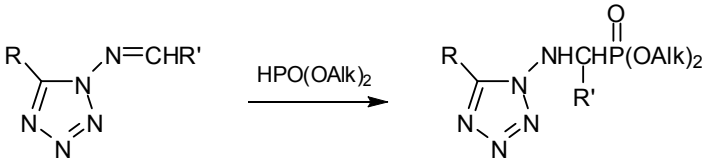
Scheme 30



C2p,q, D2a,b **C14a,u, D14f,h** **C2r, D2c**



C'14b **C'2c**

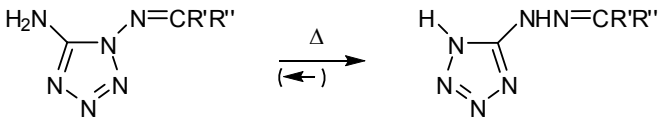


C14k$_b$,aa **C13c,d**

C14	**D14**	R	R'	Alk	**C2**	**D2**	**C13**
a	**f**		Ph		**p**	**a**	
u	**h**		C≡CR''		**q**	**b**	
			C≡CR''		**r**	**c**	
k$_b$		NH_2	4-FC_6H_4	Bu			**c** [a]
aa		PhCH=N	Ph				
		$NHCH(Ph)PO(OMe)_2$	Ph	Me			**d** [b]

[a] By one-pot reaction of 1,5-diaminotetrazole (**C1e**) with 4-FC_6H_4CHO and $HPO(OBu)_2$.
[b] Also by one-pot reaction of **C1e** with PhCHO and $HPO(OMe)_2$ in the presence of H_2SO_4.

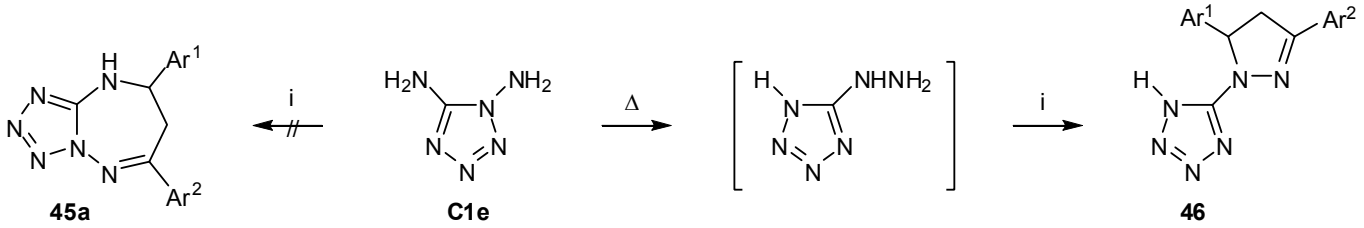
Scheme 31



C14k,p,y **34a-g**

C14	R'	R''	34	$t_{1/2}$ [min] / °C [a]
$\mathbf{k_a}$	Ph	H	**a**	
$\mathbf{k_c}$	4-ClC_6H_4	H	**b**	⩽10 / 140
$\mathbf{k_d}$	4-$MeOC_6H_4$	H	**c**	⩾15 / 140
$\mathbf{p_a}$	Het [b]	H	**d**	⩽10 / 120
$\mathbf{p_b}$	Het [c]	H	**e**	10 / 100
$\mathbf{p_c}$	Het [d]	H	**f**	30 / 100
y	Me	Me	**g**	20 / 140

[a] **C14** → **34**. [b] Het = 5-nitro-2-furyl. [c] Het = 1-cyclohexyl-tetrazol-5-yl. [d] Het = 2-cyclohexyltetrazol-5-yl.



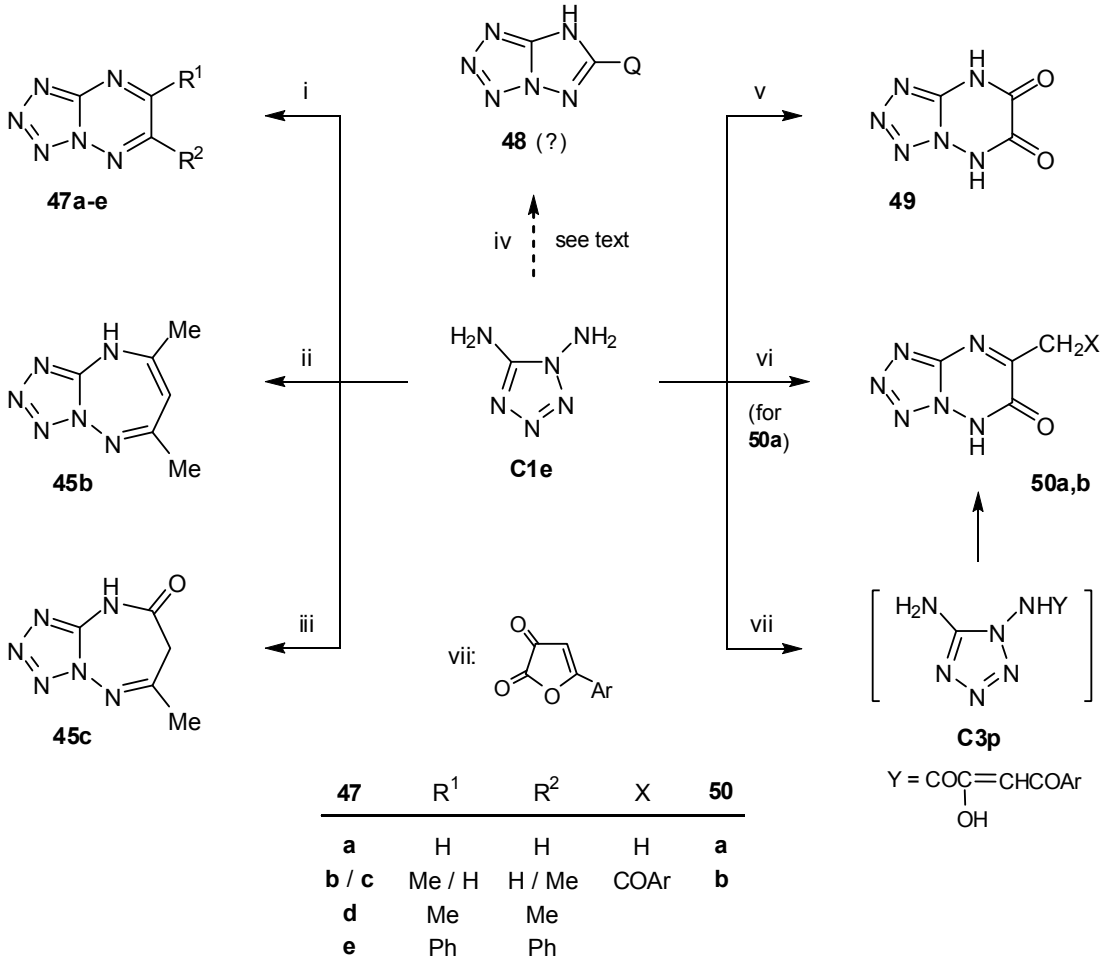
45a **C1e** **46**

i: $Ar^1CH{=}CHCOAr^2$

Scheme 32

An important feature of compounds of type (**C14**) having a free amino group at C(5) constitutes their propensity to undergo the Dimroth rearrangement (Scheme 32): on being heated, the listed derivatives were converted into the hydrazones (**34**).[94] Expectedly, electronegative groups at the imine carbon support this process as evidenced by comparing the half-lives of $\mathbf{C14k_c}$ *vs.* $\mathbf{C14k_d}$ and $\mathbf{C14p_b}$ *vs.* $\mathbf{C14p_c}$. However, the reaction does not attain completion when the overall acceptor force of the imine function is too weak [as shown by the presence of $\mathbf{C14k_{a,c}}$ (6%), **C14y** (9%), and $\mathbf{C14k_d}$ (13%) in the final mixtures]. Also the parent amine (**C1e**) is capable of undergoing the Dimroth rearrangement: It has been found that heating of **C1e** with chalcones gave rise to tetrazolyl substituted dihydropyrazoles (**46**)[121a,b] [rather than to dihydrotetrazolotriazepines of type (**45a**) as was originally thought[115]].

Cyclization: As touched upon just before, substrates bearing an additional function at C(5) *quasi* invite to cyclization reactions. While the process (**C1e** → **45a**), however, failed to materialize, a tetrazolotriazepine (**45b**) did arise in high yield when **C1e** was treated with acetylacetone (Scheme 33);[87] also, a congener such as **45c** could be prepared with ethyl acetoacetate.[109] 1,2-Dicarbonyl compounds led to the tetrazolotriazines (**47a-d**)[120, 122] and (**47e**),[109] whereas diethyl oxalate and pyruvic acid yielded the derivatives (**49**) and (**50a**), respectively.[109] In line with this, the reaction of **C1e** with various 5-aryl-2,3-



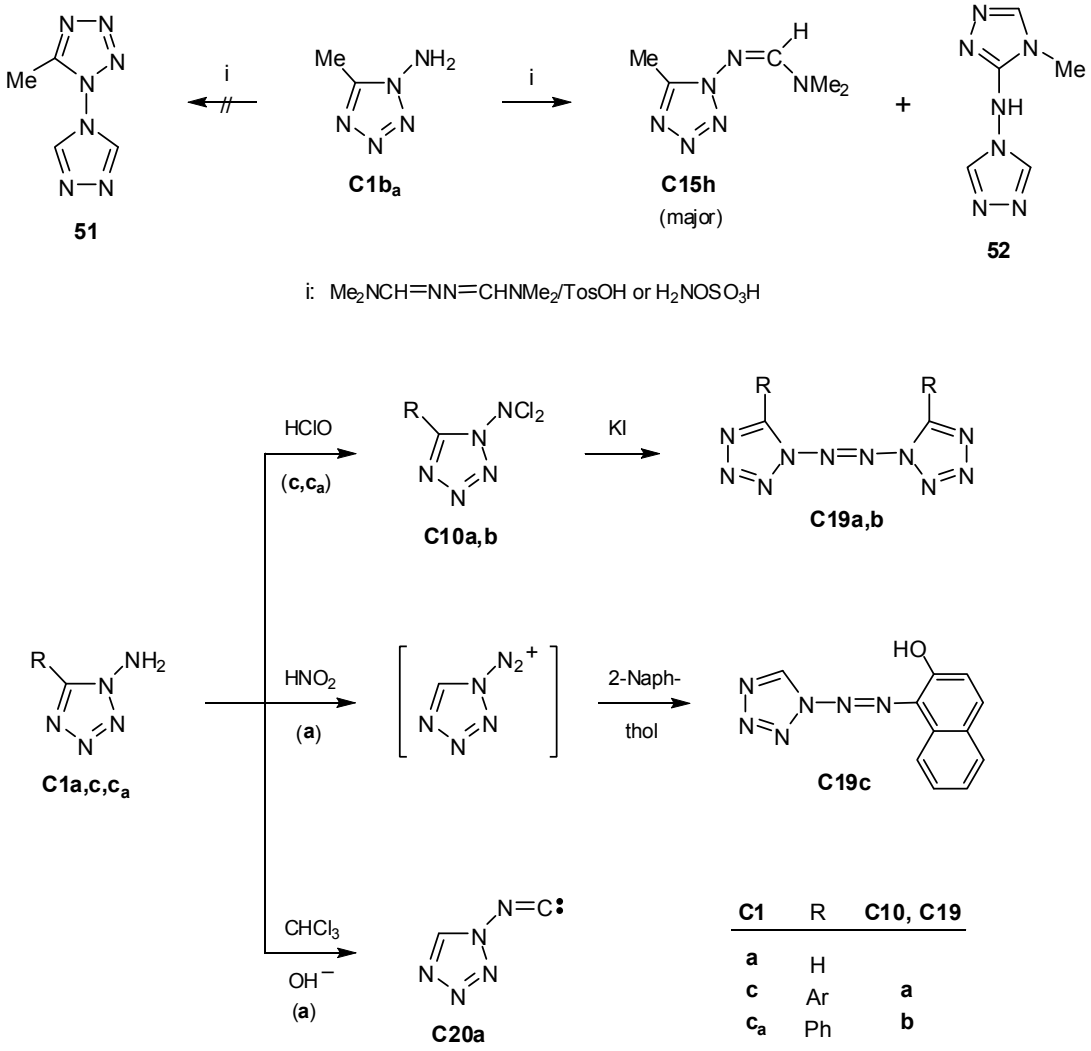
47	R^1	R^2	X	50
a	H	H	H	**a**
b / c	Me / H	H / Me	COAr	**b**
d	Me	Me		
e	Ph	Ph		

i: R^1COCOR^2 (1 eq.)/HCl ii: $(MeCO)_2CH_2$/HCl iii: $MeCOCH_2CO_2Et$ iv: $R'CO_2H$ or CS_2/Δ v: $(CO_2Et)_2$ vi: $MeCOCO_2H$

Scheme 33

dihydrofuran-2,3-diones produced the 7-aroyl substituted analogues (**50b**) [the intermediates (**C3p**) being unisolable].[123] Yet, compounds like **50** (Q = R', SH), claimed as arising from **C1e** and carboxylic acids or carbon disulfide,[109] should be regarded with doubt for two reasons: (i) In an attempt at duplicating the reaction (**C1e** → **48**; Q = Me), *i.e.* by heating **C1e** in boiling acetic acid, the starting material was recovered unchanged;[124] (ii) even though ring closures of that kind would occur, one should realize that fully conjugated azolotetrazoles having an NH ring group (any position) exist as monocyclic azidoazoles.[125] This would also apply to the claimed[109] tetrazolotetrazole (**44**) (*cf.* Scheme 28). — Cyclizations with **C'** are apparently unknown.

Miscellaneous: The amidine (**C15h**) and the ditriazolylamine (**52**) were obtained instead of the desired biazole (**51**) when the aminotetrazole (**C1b$_a$**) reacted with "*N*,*N*-dimethylformamide azine" in the presence of an acid catalyst (Scheme 34). While **C15h** was viewed as arising from **C1b$_a$** and dimethylformamide (supposedly formed by hydrolysis of the "azine" reagent), the pathway leading to **52**



Scheme 34

was not completely understood.[126] Treatment of the aminotetrazoles (**C1c,c$_a$**) with hypochlorous acid led to explosive (dichloroamino)tetrazoles (**C10a,b**); action of potassium iodide (or even storage) converted these materials into azo compounds (**C19a,b**).[26c] Another azo derivative (**C19c**) has been mentioned (but without characterization data) in conjunction with studies on the parent aminotetrazole (**C1a**);[82b] the authors also reported on the isocyanide (**C20a**) which was formed on treating **C1a** with chloroform and alkali.[82a,b]

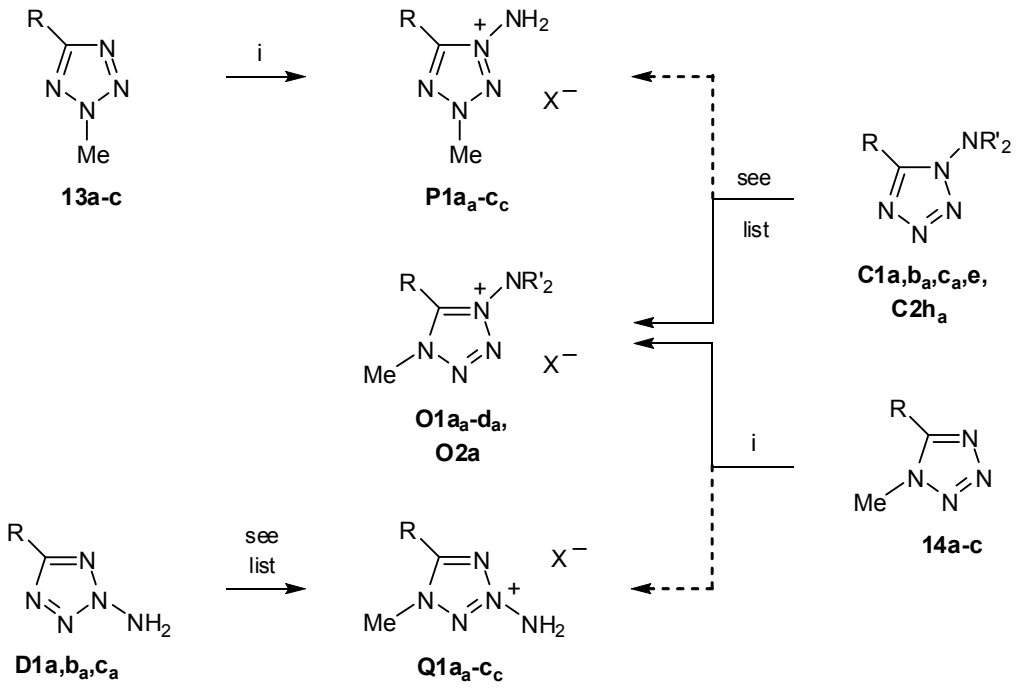
Finally, degradation reactions of **C1**/**D1** are briefly referred to: Action of lead tetraacetate on **C1c$_a$** generated a tetrazolylnitrene which, in analogy to the cleavage of triazolylnitrenes,[9] decomposed into molecular nitrogen and benzonitrile.[78] Detailed studies, in part theoretical ones, exist on the thermolysis of **C1a**,[127a] **C1c$_a$**/**D1c$_a$**[108] (*cf.* also '*Acylation*'), **C1e**,[127b–d] and **D1e**.[127a] With **C1a,e** and **D1e**, two competing reaction modes giving complex mixtures were distinguished; the results of **C1e** were discussed in the light of an amino/imino tautomerism and compared to the thermal decomposition of certain other 5-aminotetrazoles.

II/2) *N*-NITROGEN FUNCTIONALITIES: SERIES (L) – (Q)

Synthesis and Reactions

In principle, aminotetrazolium salts (**O1**), (**P1**), and (**Q1**) are accessible by electrophilic amination as are the amines (**C1**) and (**D1**). But since the starting substrates, *i.e.* (5-substituted) 1-/2-alkyl(aryl)tetrazoles, are distinctly weaker nucleophiles than tetrazolide ions used for **C1** and **D1** (*cf.* Scheme 15), the process, apart from being extremely slow, does not attain completion. Thus, on treatment of **14a-c** with *O*-mesitylsulfonylhydroxylamine the extent of conversion did not exceed 30, 66, and 36%,[34a,c] respectively, and with the less nucleophilic 2*H*-tetrazoles (**13a-c**) a mere 15, 43, and 13%[34a] were observed. From these six experiments could be secured only: (i) the salts (**O1a$_a$**) and (**O1b$_a$**) [the minor components (**Q1**) eluded isolation] and (ii) the salt (**P1b$_a$**) (Scheme 35). Hence, representatives unavailable by amination had to be made by quaternization of the appropriate aminotetrazoles (**C1**)[34a,89a,128] and (**D1**);[34a,128a] this is especially true of the salts (**Q1**) which from the latter were obtained very readily. The substrate (**C1**), because of its ambident character, gave mixtures of **O1** and **P1**, but only in the case of **C1c$_a$** the proportion allowed isolation of both **O1c$_c$** and **P1c$_c$**. Access to **O1d$_a$**[89a] and **O2a**[106b] by methylation of **C1e** and **C2h$_a$** proceeded equally well; the latter salt, in line with the behavior of 1,4-disubstituted tetrazoliums having a free 5-position, decomposed immediately into molecular nitrogen and a carbodiimide on addition of base (analogous to the cleavage of **O3f** in Scheme 25). This degradation can also be caused by anion exchange resin: thus, the liquid salt (**O1a$_a$**) which was formed from **14a** as the predominant isomer (80%) could not be transformed into a crystalline iodide or bromide derivative (X = I / Br in place of $MeOSO_3$).[34a]

Aminotetrazoliums of class (**O1**) and (**Q1**) having NH for NR should arise on treatment of **C1** and **D1** with strong acids, *i.e.* according to the observation that, under these conditions, *N*-amino- and *N*-methylazoles gave the same type of cation.[99c,d] While experimental evidence for the process [**D1** → **Q1** (NH for NR)] is still lacking, the respective behavior of **C1** is well documented (Scheme 36): Diaminotetrazole (**C1e**) has been converted into a variety of salts such as: (i) nitrate (**O1e$_a$**),[89a] (ii) perchlorate (**O1e$_b$**),[89a,129] (iii) picrate (**O1e$_c$**),[130] (iv) trinitrophloroglucinolate (**O1e$_d$**),[131] (v) ethylene- or propylene-bis[(5-nitroimino)-4,5-dihydro-1*H*-tetrazolide] (**O1e$_e$**),[132] and, finally, (vi) 5-nitrotetrazolide,[133] 2,4,5-trinitroimidazolide,[133b] and 3,5-dinitro-1,2,4-triazolide (**O1e$_f$**).[133b] X-Ray analyses were performed with **O1e$_a$**,[89a] **O1e$_b$**,[129] **O1e$_c$**,[130a] **O1e$_d$**,[131] and **O1e$_f$** (Z = 5-nitrotetrazolide),[133b] uniformly showing that protonation had occurred at N(4). This is consistent with computational studies which, in addition, confirmed that the amino groups of **C1e** are least favored for proton uptake.[88b,129,130a] Hence, the (5-aminotetrazol-1-yl)ammonium ion featured in ref.[134] is a misleading description. Nevertheless, when reacting with metal ions, the 1-amino group may be engaged too; a prominent example is the derivative (**53**) whose structure has been verified by X-ray diffraction.[88b]

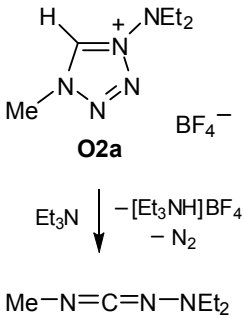


i: 2,4,6-$Me_3C_6H_2SO_2ONH_2$ ii: $(MeO)_2SO_2$ iii: $(MeO)_2SO_2$, then KI iv: $(MeO)_2SO_2$, then NaBr
v: MeI / Δ vi: $[Me_3O]BF_4$

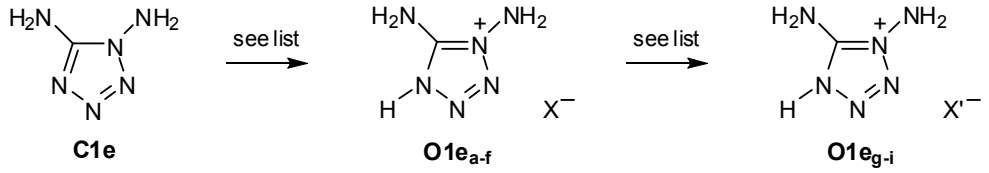
O	(from)	P1	(from)	Q1	(from)	R	R'	X	Reagent used with 14 // 13 resp. C1 // D1	Ratio O1 : P1	Ratio O1 : Q1
1a$_a$	(**14a**)	**a$_a$** [a]	(**13a**)	**a$_a$** [a]	(**14a**)	H	H	MSTS [d]	i // i		6 : 1
1a$_b$ [a]	(**C1a**)	**a$_b$** [a]	(**C1a**)	**a$_b$**	(**D1a**)	H	H	$MeOSO_3$	ii // ii	4 : 1	
1b$_a$	(**14b**)	**b$_a$**	(**13b**)	**b$_a$** [a]	(**14b**)	Me	H	MSTS [d]	i // i		12 : 1
1b$_b$ [a]	(**C1b$_a$**)	**b$_b$** [a]	(**C1b$_a$**)	**b$_b$** [a]	(**D1b$_a$**)	Me	H	$MeOSO_3$	ii // ii	5 : 1	
1b$_{c,d}$	(**C1b$_a$**)	**b$_{c,d}$** [a]	(**C1b$_a$**)	**b$_{c,d}$**	(**D1b$_a$**)	Me	H	[e]	iii, iv or v // iv or v		
1c$_a$ [a]	(**14c**)	**c$_a$** [a]	(**13c**)	**c$_a$** [a]	(**14c**)	Ph	H	MSTS [d]	i // i		36 : 1
1c$_b$ [a]	(**C1c$_a$**)	**c$_b$** [a]	(**C1c$_a$**)	**c$_b$** [a]	(**D1c$_a$**)	Ph	H	$MeOSO_3$	ii // ii	4 : 3	
1c$_c$	(**C1c$_a$**)	**c$_c$**	(**C1c$_a$**)	**c$_c$**	(**D1c$_a$**)	Ph	H	Br	iv // iv		
1d$_a$	(**C1e**)	[b]				NH_2	H	I	v // –		
2a	(**C2h$_a$**)	[c]				H	Et	BF_4	vi // –		

[a] Species not isolated. [b] Isomer (**P1**) not mentioned. [c] Isomer (**P1**) not observed. [d] MSTS = mesitylenesulfonate. [e] **O1b$_c$**, **P1b$_c$**, **Q1b$_c$**: X = I; **O1b$_d$**, **P1b$_d$**, **Q1b$_d$**: X = Br.

	Yield (%)	ref.		Yield (%)	ref.
O1a$_a$	20	34a	**P1b$_a$**	24	34a
1b$_a$	24	34a	**c$_c$**	28	34a
1b$_c$	60 / 76	34a / 127			
1b$_d$	54	34a	**Q1a$_b$**	93	34a
1c$_c$	29	34a	**b$_c$**	50	127a
1d$_a$	86	89a	**b$_d$**	69	34a
2a	87	106b	**c$_c$**	43	34a

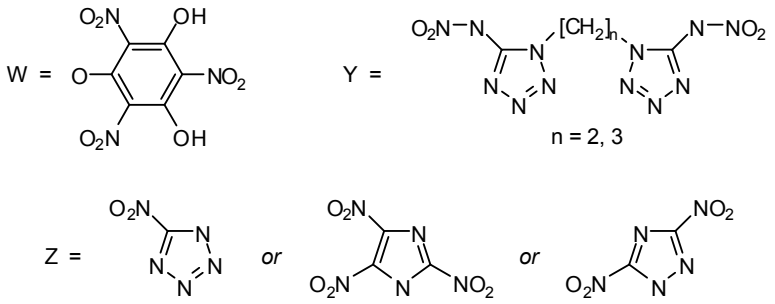


Scheme 35



C1e **O1e$_{a-f}$** **O1e$_{g-i}$**

Reagent	O1	X	Reagent	O1	X'	(from)
i	$\mathbf{e_a}$	NO_3	vii	$\mathbf{e_g}$	1/3 $[La(NO_3)_6]$	(**O1e$_a$**)
ii	$\mathbf{e_b}$	ClO_4	viii	$\mathbf{e_h}$	1/3 $[Ce(NO_3)_6]$	(**O1e$_a$**)
iii	$\mathbf{e_c}$	picrate	ix	$\mathbf{e_i}$	$N(NO_2)_2$	(**O1e$_b$**)
iv	$\mathbf{e_d}$	W				
v	$\mathbf{e_e}$	1/2 Y				
vi	$\mathbf{e_f}$	Z				

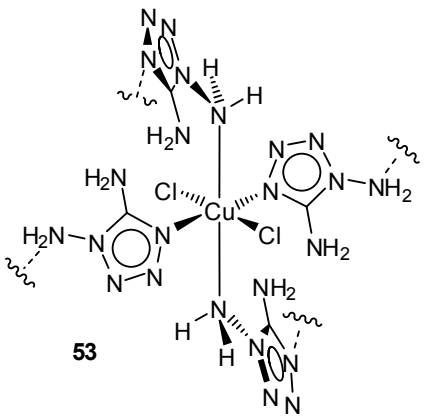


O1b$_c$: R = Me
d$_a$: R = NH_2

O1b$_{d,e}$,d$_{b-h}$ **Q1b$_c$** **Q1b$_{e,f}$**

Reagent	O1	R	X'	Q1
x	$\mathbf{b_d}$	Me	NO_3	$\mathbf{b_e}$
xi	$\mathbf{b_e}$	Me	ClO_4	$\mathbf{b_f}$
iii	$\mathbf{d_b}$	NH_2	picrate	
vii	$\mathbf{d_c}$	NH_2	1/3 $[La(NO_3)_6]$	
viii [a]	$\mathbf{d_d}$	NH_2	1/3 $[Ce(NO_3)_6]$	
x	$\mathbf{d_e}$	NH_2	NO_3	
xii	$\mathbf{d_f}$	NH_2	$N(NO_2)_2$	
xiii	$\mathbf{d_g}$	NH_2	N_3	
xiv	$\mathbf{d_h}$	NH_2	[b]	

[a] In addition $AgNO_3$. [b] 5-Aminotetrazolide.



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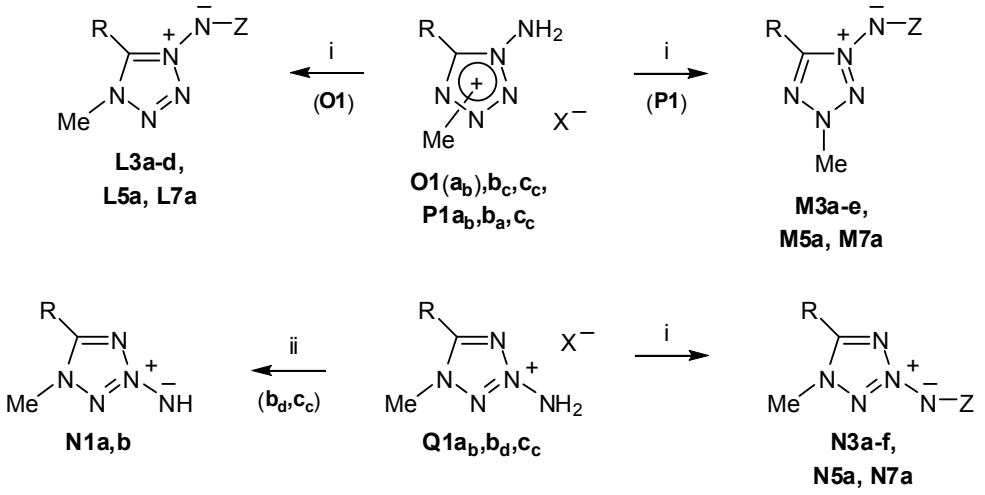
i: HNO_3 ii: $HClO_4$ iii: picric acid iv: trinitrophloroglucinol v: 2,4,5-trinitroimidazole, 3,5-dinitro-1,2,4-triazole or 5-nitrotetrazole vi: 4,4'-ethylene- or 4,4'-propylenebis-[5-(nitroimino)-4,5-dihydro-1*H*-tetrazole] vii: $La(NO_3)_3 \cdot 6H_2O$ viii: $Ce(NO_3)_3 \cdot 6H_2O$ ix: $K[N(NO_2)_2]$ x: $AgNO_3$ xi: $AgClO_4$ xii: $Ag[N(NO_2)_2]$ xiii: AgN_3 xiv: 5-aminotetrazole, Ag^+ salt

Scheme 36

Compounds like **O1b$_{d,e}$,d$_{b-h}$**, **O1e$_{g-i}$**, and **Q1b$_{e,f}$** resulted in good to excellent yields from metathetical reactions. Thus, the tetrazolium iodide (**O1b$_c$**) served to provide the corresponding nitrate (**O1b$_d$**)[89a,128] and perchlorate (**O1b$_e$**),[128] while from the isomeric iodide (**Q1b$_c$**) the respective salts (**Q1b$_e$**) and (**Q1b$_f$**) were obtained.[128a] Diaminotetrazoliums were sought for in higher number: Starting from the perchlorate salt (**O1e$_b$**), the dinitramide (**O1e$_i$**) was made;[135] using the iodide (**O1d$_a$**), salts like the nitrate (**O1d$_e$**),[89a] dinitramide (**O1d$_f$**),[89a,136] azide (**O1d$_g$**),[89a] and 5-aminotetrazolide (**O1d$_h$**)[137] were prepared. From the iodide (**O1d$_a$**) and the nitrate (**O1e$_a$**) derivatives containing hexanitratolanthanate(III) and -cerate(III) ions arose (→ **O1d$_{c,d}$** and **O1e$_{g,h}$**, respectively).[138] All of the ionic compounds of Scheme 36 were synthesized in search for new energetic materials;[139] their physical properties underwent in-depth studies of great number (experimental[140,141] and theoretical ones[142]). The attractive topic, a rapidly developing field, cannot be covered here adequately.

Betainic structures such as **L**, **M**, and **N**, *i.e.* tetrazolium *N*-aminides, have been obtained by deprotonation of the corresponding cations in **O**, **P**, and **Q** (Scheme 37).[34a–c] Direct introduction of the Y$^-$ function,



i: MeCOCl, PhNCO / Et_3N or PhCOCl, $PhSO_2Cl$ / K_2CO_3 ii: K_2CO_3

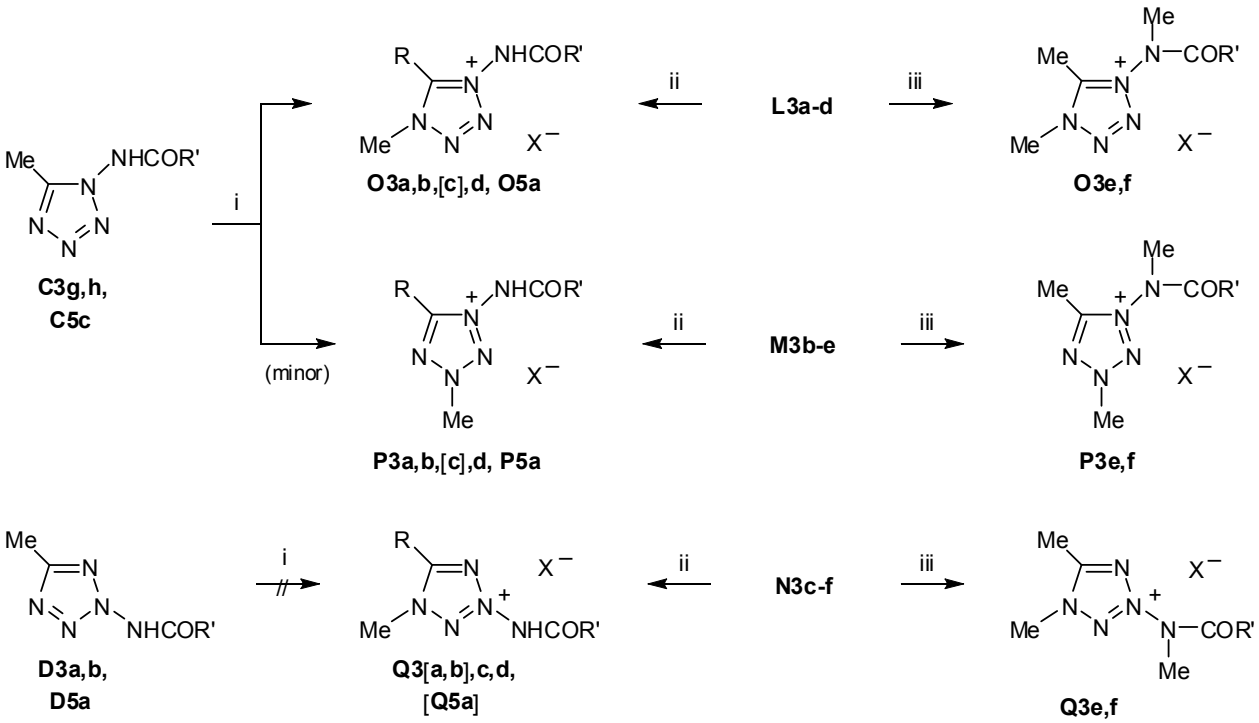
N1	O1	P1	Q1	R	X	R	Z	L	(from)	M	(from)	N	(from)
						H	COMe					**3a**	(**Q1a$_b$**)
	a$_b$	**a$_b$**	**a$_b$**	H	$MeOSO_3$	H	COPh			**3a**	[b]	**3b**	(**Q1a$_b$**)
		b$_a$		Me	MSTS [a]	Me	COMe	**3a**	(**O1b$_c$**)	**3b**	(**P1b$_a$**)	**3c**	(**Q1b$_d$**)
	b$_c$			Me	I	Me	COPh	**3b**	(**O1b$_c$**)	**3c**	(**P1b$_a$**)	**3d**	(**Q1b$_d$**)
			b$_d$	Me	Br	Ph	COMe	**3c**	(**O1c$_c$**)	**3d**	(**P1c$_c$**)	**3e**	(**Q1c$_c$**)
	c$_c$	**c$_c$**	**c$_c$**	Ph	Br	Ph	COPh	**3d**	(**O1c$_c$**)	**3e**	(**P1c$_c$**)	**3f**	(**Q1c$_c$**)
a				Me		Me	CONHPh	**5a**	(**O1b$_c$**)	**5a**	(**P1b$_a$**)	**5a**	(**Q1b$_d$**)
b				Ph		Me	SO_2Ph	**7a**	(**O1b$_c$**)	**7a**	(**P1b$_a$**)	**7a**	(**Q1b$_d$**)

[a] MSTS = mesitylenesulfonate. [b] From the mixture of **O1a$_b$** and **P1a$_b$** (*cf*. Scheme 35), the former component being destroyed with base (*cf*. *ibid*. **O2a**).

Scheme 37

as shown with certain oxygen analogues (Chapter I/2), has not been described till now. For stabilization all aminides of the **L** and **M** type need electronegative substituents (Z) at the side chain; practically, they were inserted by joint treatment of the salts (**O1**) and (**P1**) with an acylating agent and a base. The same technique applied to **Q1** gave the respective derivatives of the isomeric **N** series. But here, because of the enhanced electron-withdrawal of the 1*H*-tetrazolium-3-yl system (*cf.* ref.[143a]), also *N*-unsubstituted aminides proved sufficiently stable to be isolated (→ **N1a,b**).[34b]

Since salts like **O3**/**P3**/**Q3** and **O5**/**P5**/**Q5** are the immediate aminide precursors, an alternate access constitutes quaternization of **C3**/**C5** and **D3**/**D5** (Scheme 38). However, owing to the extremely low nucleophilicity of the respective 2*H*-tetrazoles (*cf.* Scheme 35: **13** → **P1**) the concept works with **C3** and **C5** only, and, in addition, is limited to 5-methyl derivatives. Competing side-chain methylation giving



i: $(MeO)_2SO_2$ ii: HBr iii: MeI

C	D	L	M	N	R	R'	X	O	(from)	P	(from)	Q	(from)	Ratio [O : P]
3g	**3a**				Me	Me	$MeOSO_3$	**3a**	(**C3g**)	**3a**	(**C3g**)	[**3a**	(**D3a**)]	4 : 1 [a]
3h	**3b**				Me	Ph	$MeOSO_3$	**3b**	(**C3h**)	**3b**	(**C3h**)	[**3b**	(**D3b**)]	11 : 2 [a,b]
		3c	**3d**	**3e**	Ph	Me	Br	[**3c**	(**L3c**)]	[**3c**	(**M3d**)]	**3c**	(**N3e**)	
		3d	**3e**	**3f**	Ph	Ph	Br	**3d**	(**L3d**)	**3d**	(**M3e**)	**3d**	(**N3f**)	
		3a	**3b**	**3c**	Me	Me	I	**3e**	(**L3a**)	**3e**	(**M3b**)	**3e**	(**N3c**)	
		3b	**3c**	**3d**	Me	Ph	I	**3f**	(**L3b**)	**3f**	(**M3c**)	**3f**	(**N3d**)	
5c	**5a**				Me	NHPh	$MeOSO_3$	**5a**	(**C5c**)	**5a**	(**C5c**)	[**5a**	(**D5a**)]	11 : 2 [a,b]

[a] Compounds not isolated. [b] Values from ref.[34c]

Scheme 38

C3n,o and **C5e** (*cf.* Scheme 27) can be avoided by strictly adhering to the reaction conditions.[34b] Reprotonation of **L3**, **M3**, and **N3** took place readily with hydrobromic acid (**O3d**, **P3d**, and **Q3d** showed $pk_a \approx 3$), but isolation of acetamide derivatives such as **O3c** and **P3c** (R' = Me for Ph) was vitiated because of hydrolysis.[34b] Methylation of **L3**, **M3**, and **N3** occurred equally well to give **O3d,e**, **P3d,e**, and **Q3e,f**, respectively; in the case of **N3** the enhanced electron-withdrawal of the tetrazolium ring required prolonged action of the reagent.[34b] Unlike tetrazolium *N*-phenacylides,[143a,b] aminides of the **L** and **M** series (*i.e.* even the more reactive ones) have been found to be inert toward phenyl isocyanate.[34c,e]

CONCLUSION

The present overview has traced the considerable progress in preparative chemistry of the title systems since they came into focus around 1910. Yet, while work on *N*-aminotetrazoles is well advanced, gaps show up with the *N*-hydroxy counterparts: 2*H*-isomers (**B**) have barely been studied till now; the old entry to **A1a** using fulminic acid has not been clarified in full, and certain ring alkylations of **A1** are dubious. Future research should allow for this and, maybe, extend its interest to comparative investigations between 1*H*- and 2*H*-isomers (**A** / **B**) as studies of that kind exist only in the class of *N*-aminotetrazoles (**C** / **D**).

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63. Total energies (absolute minima) of **A2g**/**Eb**/**Fb**/**Gb**/**B2b**/**Hb**/**Jb**/**Kb** and **A2a$_a$**/**Ec**/**Fc$_a$**/**Gc**/**15b**/**B2c**/**Hc**/**Jc**/**Kc** (absolute minima): –412.05050/.05163/.05839/.05283/.05518/. 05848/.06204/.05365

and –603.79274/.79289/.80160/.79739/.72888/.79921/.79869/.80560/.79489 a.u. — Calculations at HF/6-31G** level showed the methoxy derivatives (**A2g**) and (**A2a$_a$**) to be lowest in energy, whereas the values of **15a** and **15b** were higher by 47.14 and 46.41 kcal/mol, respectively (all values: D. Moderhack, unpublished results).

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