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TETRAZOLECARBALDEHYDES AND THEIR DERIVATIVES

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Abstract – This article summarizes the preparative chemistry of the three classes of tetrazolecarbaldehydes (**A–C**) including derivatives. Certain comparisons between **A–C** and their closest analogues, the 1,2,4-triazolecarbaldehydes (**D–F**), are drawn.

INTRODUCTION

The chemistry of functional groups attached to the tetrazole ring (C and/or N atoms) is steadily dealt with in the general reviews on that heterocycle,[1] but the sheer mass of material prevents from an in-depth treatment. As a consequence, a growing number of specialized accounts were produced to flank those major works, as exemplified by reviews on vinyltetrazoles,[2a] 1-substituted 5-alkyl(aryl)sulfanyltetrazoles and derivatives,[2b] *N*-hydroxy- and *N*-aminotetrazoles,[2c] metal species of various types,[2d-f] and functionalities attached to tetrazolium rings.[2g,h] The present article focusses on the formyl group as in compounds (**A–C**) (Chart1). These materials have been studied extensively in this laboratory, with a side glance at the closest congeners: the 1,2,4-triazolecarbaldehydes (**D–F**). Apart from providing building blocks for constructing or modifying

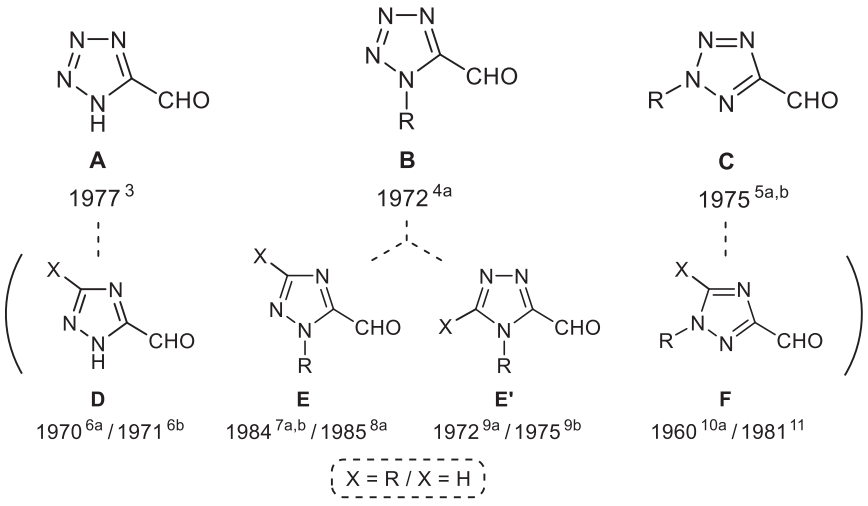
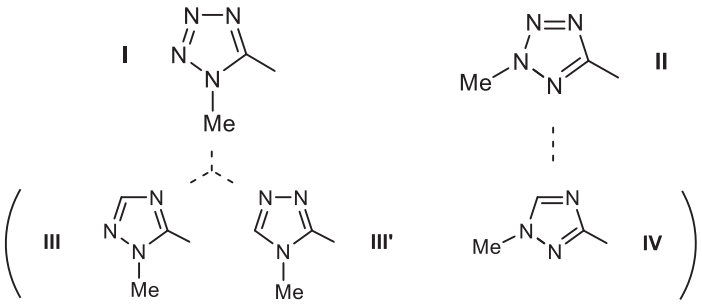


Chart 1. Title aldehydes (**A – C**) and 1,2,4-triazole congeners (**D – F**) with year of first record

bioactive molecules,[12] the title aldehydes attract attention for their chemical behaviour. This is especially true of **B** and **C**, since here – as with tetrazoles bearing other functionalities[13] – numerous reactions illustrate the different influence of the two ring scaffolds, which originates in the fact that an azolic ring carbon located α to the pyrrole-type nitrogen (as in **B**) is more electron-withdrawing than a carbon located β (as in **C**).[14] This effect is not only reflected by calculated charges of C(5) of 1*H*- and 2*H*-tetrazoles (which are more positive with the former),[15] but also by experimental σ constants of the respective tetrazolyl moieties (**I**) and (**II**) (Chart 2).[13b, 14b, 17] The corresponding triazolyl groups (**III**), (**III'**), and (**IV**), however, have smaller values,[18] since the number of (electronegative) heteroatoms is crucial as well.[14]



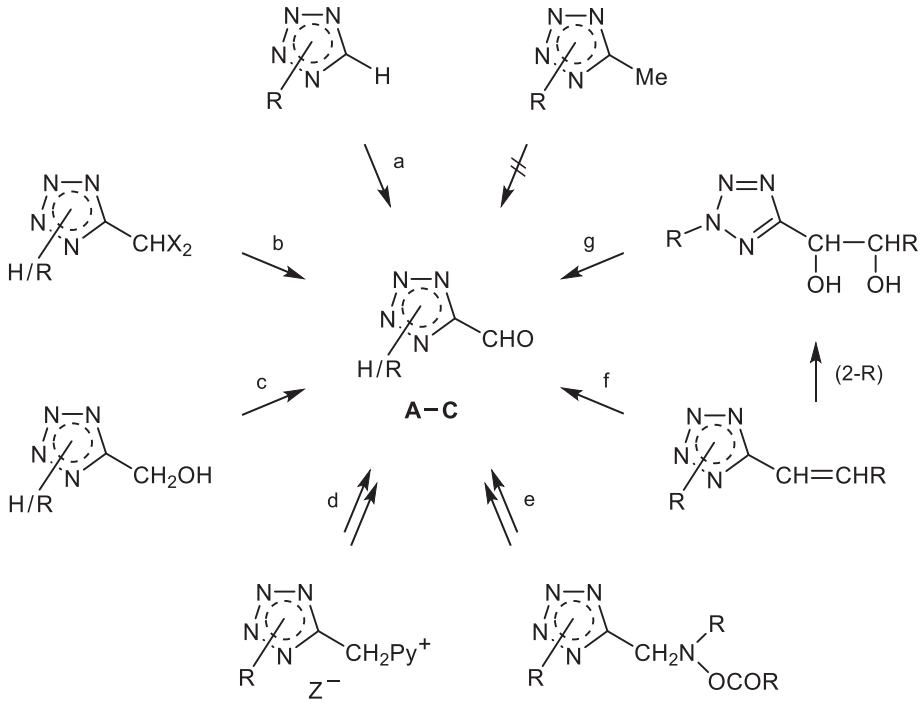
azolyl	σ_I	σ_p	σ_R
I [a]	0.48 [b]		
I	0.34 [c], 0.38 [d]	0.42 [c], 0.46 [d]	0.08 [c], 0.08 [d]
II	0.32 [b]		
II	0.24 [c], 0.22 [d]	0.30 [c], 0.27 [d]	0.06 [c], 0.07 [d]
III	0.24$_2$ [e]	0.28 [e]	0.04 [e]
III'	0.23$_9$ [e]	0.27 [e]	0.03 [e]
IV	0.11$_8$ [e]	0.12$_2$ [e]	0.00$_4$ [e]

[a] σ_I Constants of *N*-unsubstituted analogue: (i) 0.41 (calculated from pK_a of respective tetrazol-5-acetic acid);[16a] (ii) 0.49 [from pK_a of (tetrazol-5-yl)guanidine];[16b] values pointing to 1*H* tautomer as major component. [b] Ref.[17]; method as in [a (i)]. [c] Ref.[13b]; from δ_F of respective 5-(fluorophenyl)tetrazole. [d] Ref.[14b]; method as in [c]. [e] Ref.[18]; as in [c].

Chart 2. Experimental σ constants of *N*-substituted tetrazol-5-yl and 1,2,4-triazol-3/5-yl groups

GENERAL

Regarding access to the title aldehydes, an overview is provided by Scheme 1, showing that most syntheses consist in transformation of suitable side chains of preformed tetrazoles. Two methods were applied for the *N*-unsubstituted aldehyde (**A**), while for the 1- and 2-substituted classes (**B**) and (**C**) six and seven routes were followed. Since compound (**A**) differs from **B** and **C** in many respects, it will be dealt with apart [Section (1)]; for **B** and **C**, however, a joint treatment appears appropriate as it facilitates a synopsis and the comparison between the two isomers [Section (2)].



aldehyde	successful entry
A (NH)	b, c
B (1-R)	a, b, c, d, e, f
C (2-R)	a, b, c, d, e, f, g

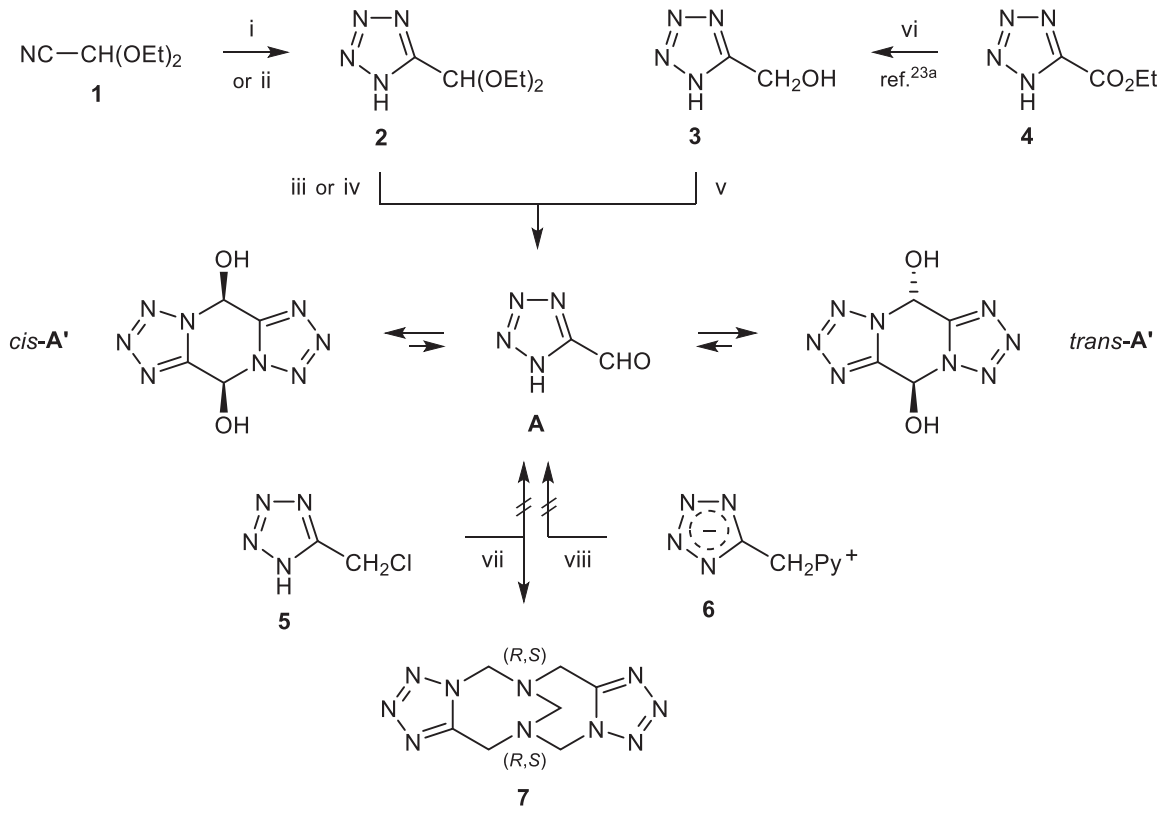
Scheme 1. Routes to aldehydes (**A**–**C**)

1) *N*-UNSUBSTITUTED TETRAZOLECARBALDEHYDE (A)

a) Synthesis

Not unlike the preceding entry to the 1,2,4-triazole congener (**D**; X = H),[6b] the first synthesis of the target aldehyde (**A**) was achieved *via* route (b) of Scheme 1, *viz.* through hydrolysis of the acetal (**2**) (Scheme 2).[3] This compound was provided by treatment of the nitrile (**1**) with hydrogen azide in the presence of pyridine (1 equiv.) at ambient temperature – a then new and expedient protocol for an *N*-unsubstituted tetrazole (*cf.* the entry to ethyl tetrazole-5-carboxylate[5a]). The sequence (**1** → **2** → **A**) has recently been duplicated,[19,20a,b] with the modification of using stannyl azide for making **2**.[20a,b] The second principal route to **A**, *i.e. via* (c) of Scheme 1, implies oxidation of the carbinol (**3**) and has been followed repeatedly.[21–23a]

In contrast to compounds (**2**) and (**3**), 5-(chloromethyl)tetrazole (**5**) proved to be an unsuitable precursor, *i.e.* neither the (i) Sommelet nor the (ii) Kröhnke reaction [*cf.* Section (2a)] met with success: (i) Hexamine effected only aminolysis and, owing to the 'bifunctional' character of the resultant (aminomethyl)tetrazole, gave the methano-bridged ditetrazolotetrazecine (**7**) as final product.[24] (ii) The failure of Kröhnke's route resulted from an insufficient activation of the methylene group of the precursor (**6**) (readily made from **5**): the negative charge of the tetrazolide moiety offsets the promoting power of the pyridinio ligand.[25]



i: HN_3, pyridine, rt ii: Bu_3SnN_3, Et_2O, Δ iii: 4 N HCl, rt iv: 1.25 N HCl, MeOH, Δ v: MnO_2, Me_2CO or DMF, rt
vi: $LiAlH_4$, THF, rt vii: hexamine, aq. EtOH, Δ viii: 4-$NOC_6H_4NMe_2$, EtOH, 1 N NaOH, rt (for nitrone, *cf.* Scheme 12)

	method	yield (%)	ref.	method	yield (%)	ref.	method	yield (%)	ref.
2	i	56 / 70	3 / 19	ii	– [a]	20a,b			
A	iii	77 / 60	3 / 19	iv	– [b]	20a,b	v	93 [b] / – [b] / 71 [c]	21 / 22 / 23a

[a] Not isolated, directly hydrolyzed to **A.** [b] Material directly used for further reaction (see Scheme 6 and 7). [c] Based on **4.**

Scheme 2

b) Properties

In the solid state the aldehyde (**A**) exists as the tricyclic bis-hemiaminal (**A'**) [no IR carbonyl band; mp 180–181 °C (decomp)].[3] This matches the behaviour of certain *C*-substituted 1,2,4-triazolecarbaldehydes (**D**; X = R)[6a–d] including some aldehydes with a pyrazole,[26a–d] imidazole,[6c,d,26e] and 1,2,3-triazole nucleus,[26f] but contrasts with the parent member (**D**; X = H) which does not 'dimerize'.[6b] When **A'** was dissolved in DMSO, the above equilibrium was shifted to the free aldehyde (**A**), depending on the temperature [°C / %: 30 / 50, 80 / 90]. Of the residual component (**A'**), two species were observed [°C / ratio: 30 / 2:3, 80 / 1:3] which are thought to represent the *cis*- and *trans*-isomers of Figure 1 (for stereo forms of hemiaminals, *cf.* refs.[6b,c]). Regarding the proclivity for dimerization, a comparison of the energies of **A'** and (*s-trans*)-1*H*-**A** (Chart 3) revealed that the value of the former was lower than twice the value of the latter;[25] this parallels an

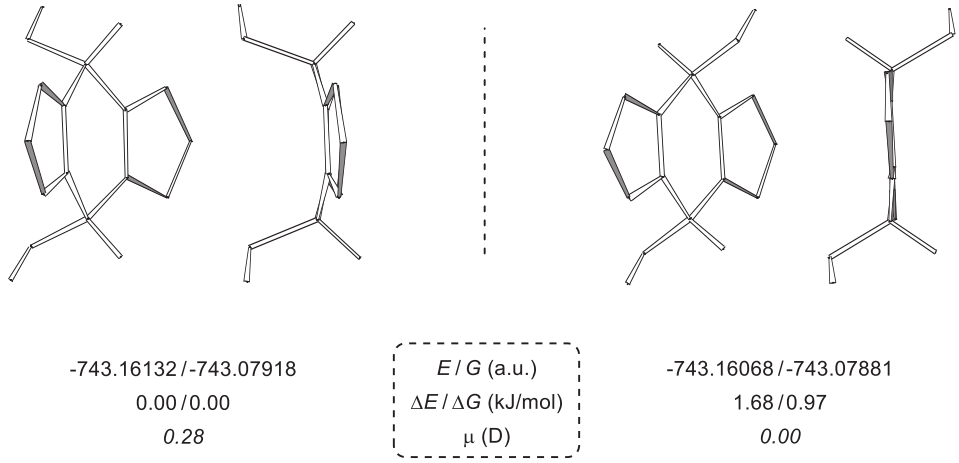


Figure 1. Calculated structures of *cis* and *trans* dimer (**A'**) (absolute minima) according to B3LYP/6-31G** (gas phase)[25]

earlier calculation on benzimidazole-2-carbaldehyde.[27] Also in the case of the triazolecarbaldehyde (**D**; X = Ph) energy values point to dimerization, but with X = H they do not reflect the experimental evidence.[25] Further theoretical interest concerns the annular tautomerism. It is known for *N*-unsubstituted azoles having *C*-linked carbonyl groups that intramolecular hydrogen bonds (N–H···O=C) influence the equilibrium.[28,29] A DFT study including conformational isomerism has shown that the chelated (*s-trans*)-1*H*-**A** form is much

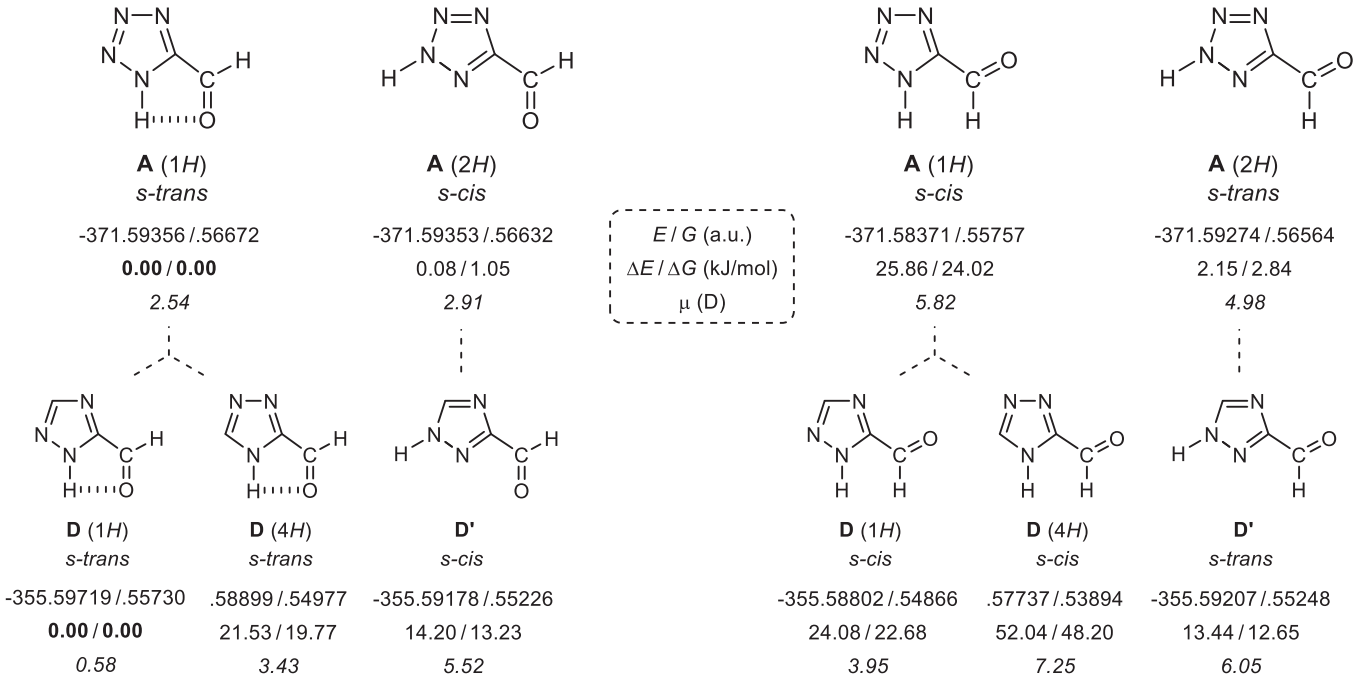
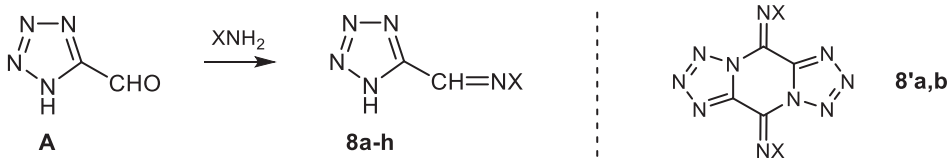


Chart 3. Energies (total, relative) and dipole moment of different tautomers and conformers of aldehyde (**A**) and 1,2,4-triazole analogues (**D, D'**) according to B3LYP/6-31+G** (gas phase)[25]

preferred over the (*s-cis*)-1*H* rotamer.[25] Moreover, the normal energetical preference for 2*H*-tetrazoles[15] appears upset, since the related (*s-cis*)-2*H*-**A** species is not lower in energy (*cf.* also ref.[29]). Only in the absence of chelation, *i.e.* when comparing the (*s-cis*)-1*H*-**A** form with the two conformers of the 2*H*-**A** tautomer, the usual preference is retained. In the case of the 1,2,4-triazolecarbaldehyde (**D**), the stabilizing effect of the above hydrogen bond seems to be even greater, if one considers the (*s-trans*)-1*H*-**D** and the (*s-cis*)-**D'** tautomers. The relatively high energy of the two 4*H*-**D** rotamers is consistent with the unfavoured 4*H* tautomer of this heterocycle,[30] but also here the influence of chelation is obvious [see (*s-trans*)-4*H*-**D**].

c) Reactions

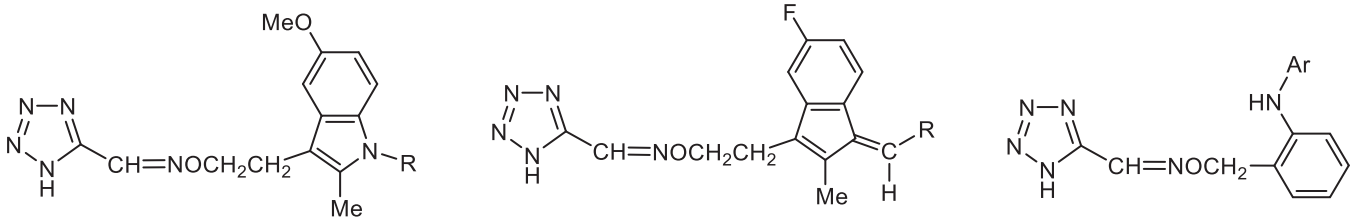
The aldehyde (**A**) gave normal derivatives, as exemplified by the compounds (**8a-d**); structures like **8'** were not observed (Scheme 3). *O*-Substituted oximes representing inhibitors of prostaglandin biosynthesis like **8e-g**[32] and **8h**[33] have been made from the respective *O*-alkylhydroxylamines. – For aldehyde derivatives that were employed in further reactions, see Section (1d).



A **8a-h**

8, **8'** [a]	X	ref.	**8**	X	ref.
a	OH	3	**c**	NHPh	25
b	NH*DNP* [b]	3	**d**	NHTs	31

[a] **8'a,b** erroneously quoted by SciFinder (instead of **8a,b**).
[b] *DNP* = 2,4-$(NO_2)_2C_6H_3$.

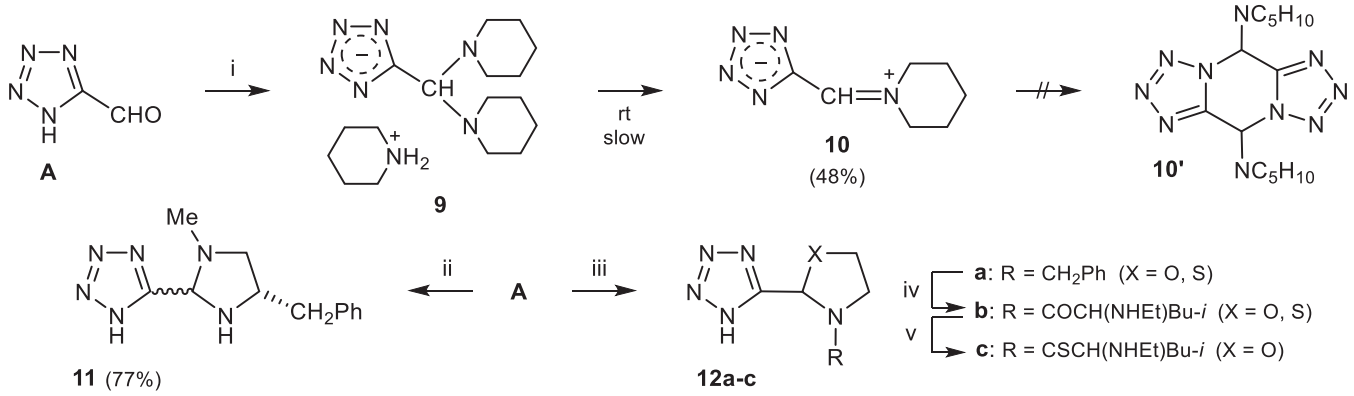


8e: R = $CH_2C_6H_4Cl(4)$ **8f**: R = $C_6H_4[S(O)_nMe](4)$; n = 0 or 1 **8h**: Ar = 2,6-Cl_2-3-MeC_6H_2

g: R = 4- pyridyl

Scheme 3

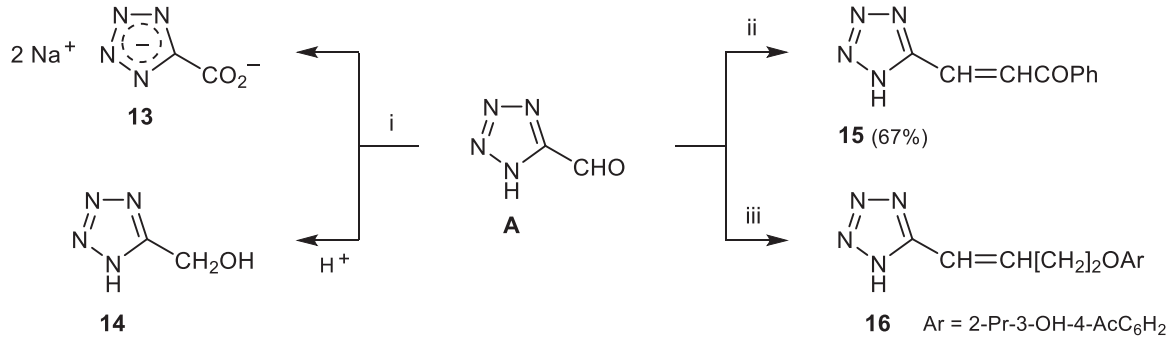
Attempting the conversion of **A** into heterogeminals, an unusual course was encountered with piperidine (Scheme 4): First, the labile salt (**9**) was formed; this material, on exposure to air, lost two molecules of the base to give the betaine (**10**) as final product; remarkably, dimerization to the tricycle (**10'**) did not occur.[3] This contrasts with the behaviour of several *N*-unsubstituted azole aldehydes including the triazole (**D**; X = Ph) which all afford piperidino-substituted tricycles of that type.[6b,c,34,35]



i: piperidine (neat), Δ ii: (*S*)-MeNHCH$_2$CH(NH$_2$)CH$_2$Ph, CH$_2$Cl$_2$, rt iii: HX[CH$_2$]$_2$NHCH$_2$Ph (X = O, S)
iv: H$_2$ (Pd/C), then *i*-BuCH(NHEt)CO$_2$H/MeCH(Cl)CH$_2$NMe$_2$·HCl v: Lawesson's reagent

Scheme 4

Using 1,2-difunctionalized agents, five-membered rings as in **11** and **12** resulted. The chiral imidazolidine (**11**) gained importance as a catalyst for asymmetric Michael additions of nitroalkanes to enones (products with up to 92% ee),[19] whereas the compounds (**12b,c**) (successively made by side-chain exchange) attract interest as dipeptidyl peptidase IV inhibitors.[36]

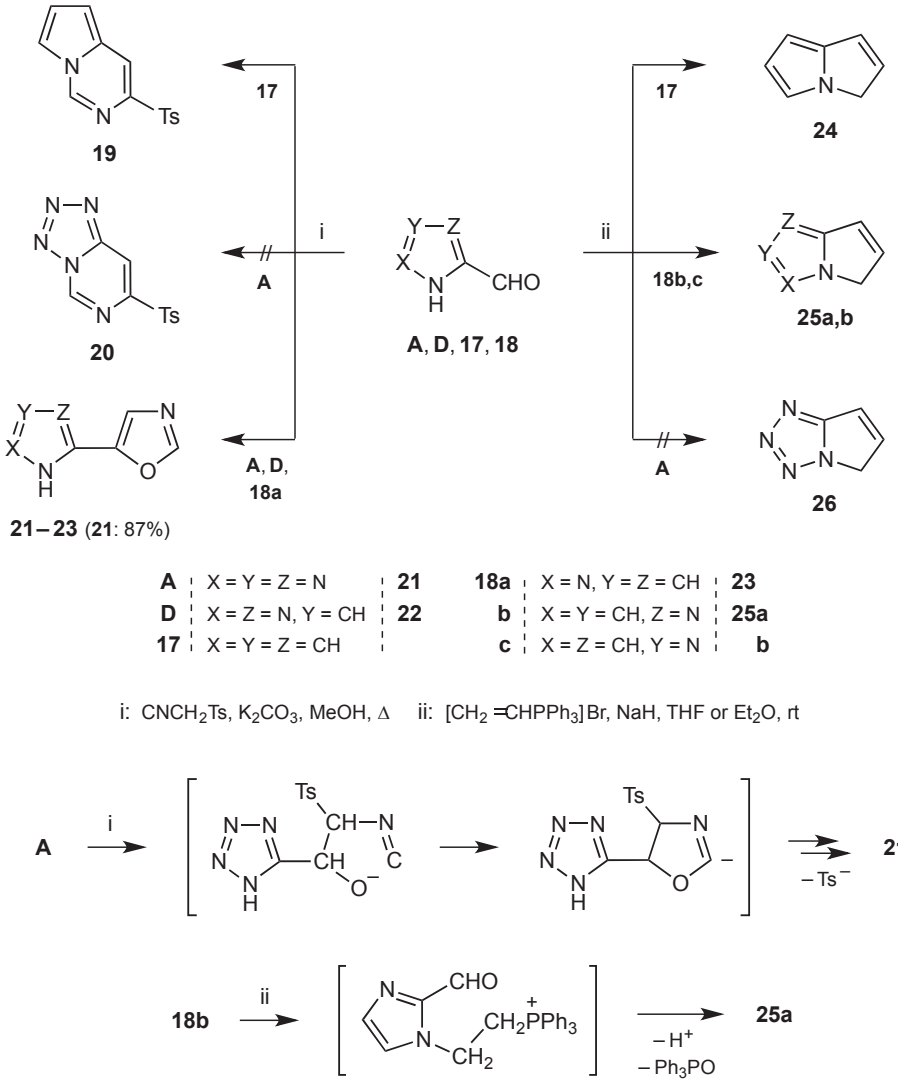


i: 6 M NaOH, rt ii: MeCOPh, KOH, EtOH, rt iii: Ph$_3$P=CH[CH$_2$]$_2$OAr, Et$_2$O, rt

Scheme 5

While aldehydes (**B**) are immediately deformylated when they come in contact with alkali [Section (2c)], the parent aldehyde (**A**) is insusceptible to that reaction. Thus, using dilute alkali hydroxide, the sodium salt of **A** could be prepared ($\nu_{C=O}$ 1708 cm^{-1}), whereas at high concentration the Cannizzaro reaction took place (→ **13** and **14**) (Scheme 5).[3,37] The relative resistence towards alkali allowed aldol condensations to be catalyzed by that reagent, as shown by the synthesis of the chalcon (**15**).[3] Also the Wittig olefination of **A** proceeded well, as shown by the formation of compound (**16**); catalytic hydrogenation gave the appropriate butyltetrazole, *i.e.* the leukotriene antagonist LY 171883; the overall process was a new entry to this drug.[38]

N-Unsubstituted azole aldehydes having the formyl group adjacent to the NH region may lead to fused ring systems when treated with difunctional agents (Scheme 6). Using tosylmethyl isocyanide (TosMIC), it was observed that, out of aldehydes like **A**, **D**, **17**, and **18a**, only the pyrrole representative (**17**) reacted in that way (→ **19**), whereas the title aldehyde (**A**) did not give **20**, but – following a known mechanism – yielded the oxazole derivative (**21**). The same applies to the triazole aldehyde (**D**) and its pyrazole congener (**18a**).[21]



Scheme 6

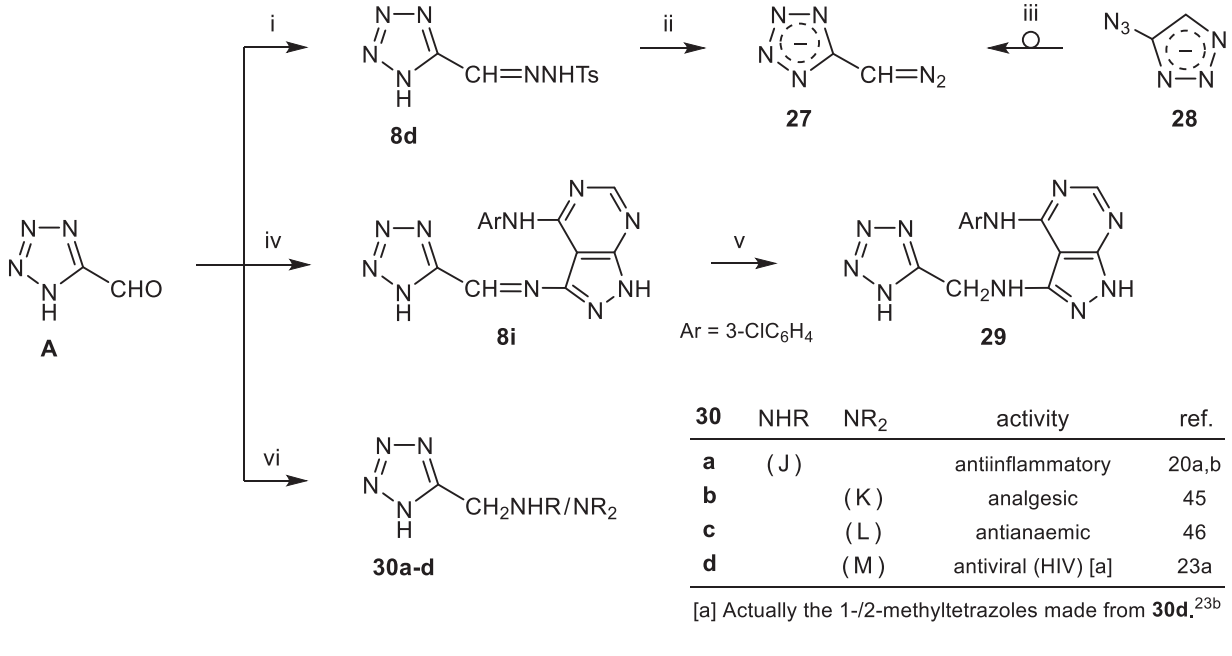
On the reaction with a vinylphosphonium salt azapentalenes should result. This has indeed been found: not only with the aldehyde (**17**) which afforded 3*H*-pyrrolizine (**24**),[39] but also with the congeners (**18b,c**) which gave the 5*H*-pyrroloimidazoles (**25a,b**).[40] However, attempts to obtain the tetrazole analogue (**26**) remained unrewarded.[41] This compound, which has recently attracted theoretical interest,[42,43] still waits for

being synthesized, the more so since an earlier approach, *i.e.* by cyclization of 4-azidobut-2-enenitrile, has failed too.[44]

d) Reactions of derivatives of A

On treatment with base in DMSO the tosylhydrazone (**8d**) readily underwent the Bamford-Stevens reaction to produce the 5-(diazomethyl)tetrazolide ion (**27**); the experiment served to prove the formation of this species through rearrangement of deprotonated azido-1,2,3-triazole (**28**) (Scheme 7).[31]

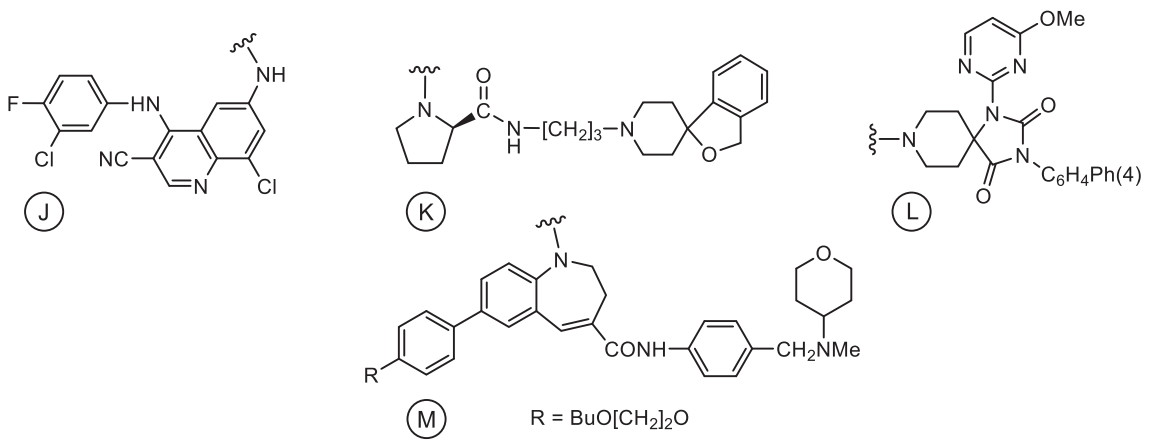
Reduction of the imine (**8i**) using diisobutylalane afforded to the antitumor agent (**29**).[22] Normally, a two-step process like (**A** → **8i** → **29**), *i.e.* reductive alkylation of amines by aldehydes, was carried out as a one-pot procedure; this, indeed, holds for the preparation of the bioactive compounds (**30a-d**).[20a,b, 23a, 45, 46]



30	NHR	NR_2	activity	ref.
a	(J)		antiinflammatory	20a,b
b		(K)	analgesic	45
c		(L)	antianaemic	46
d		(M)	antiviral (HIV) [a]	23a

[a] Actually the 1-/2-methyltetrazoles made from **30d**.[23b]

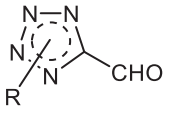
i: $TsNHNH_2$ ii: DBN, DMSO, Δ iii: DMSO, rt iv: $HetNH_2$ v: $AlH(i\text{-}Bu)_2$, 1,3-dimethylimidazol-2-one, rt
vi: RNH_2 / R_2NH; then $Na[BH_3CN]$ (for **30a**) or $Na[BH(OAc)_3]$ (for **30b-d**)



Scheme 7

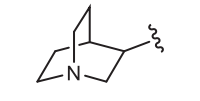
2) 1- AND 2-SUBSTITUTED TETRAZOLECARBALDEHYDES (B) AND (C)

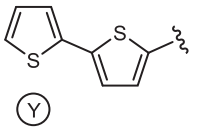
An overview of representatives (**B**) and (**C**) dealt with in this Section is given in Chart 4, with indications where to locate the listed aldehydes in the text.

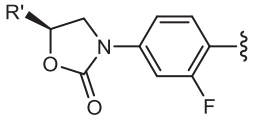


B (1-R)
C (2-R)

B, **C**	R	**B** ---- subsection (paragraph) ---- **C**	
a	Me	a (iii, v); b; c (i, ii, v, vi, vii); d (i, ii)	a (i, ii, iii, v); b; c (i, ii, v, vi, vii); d (i, ii)
b	Et	a (v); b; c (i); d (i)	a (v); b; c (i)
c	Bu	a (v); b; c (i)	
d	*c*-C_6H_{11}	a (iii, v, vi); b; c (i, ii, iii, iv, vi, vii); d (i, iv)	a (v); b; c (i)
e	CH_2Ph	a (v, vii); b; c (i); d (i)	a (v, vii); b; c (i); d (i)
f	$CH_2C_6H_4OMe(4)$	a (ii, iv); c (vi); d (i)	a (iv); c (vi)
g	CH_2CO_2Me	a (iv); c (vi)	a (iv); c (vi)
h	$[CH_2]_3CO_2Et$		a (iv); c (vi)
i	Ph	a (i, v); b; c (i, ii, v); d (i)	a (i, iv, v); b; c (i, ii, iv, vi); d (i)
j	2-HSC_6H_4	c (ii)	
k	2-F-5-MeC_6H_3		a (vii); c (iii, iv)
l	2-F-5-ClC_6H_3		a (vii); c (iii, iv); d (i)
m	3-MeC_6H_4		a (iv, vii); c (iii, iv); d (i)
n	3-ClC_6H_4		a (vii); c (iii, iv); d (i)
o	3-IC_6H_4		a (vii); c (iii, iv)
p	3-NCC_6H_4		a (vii); c (iii, iv)
q	4-MeC_6H_4	a (v); b; c (i)	a (v); b; c (i)
r	4-$NO_2C_6H_4$	a (v); b; c (i)	a (v); b; c (i)
s	(X)		a (ii)
t	(Y)		a (iv); c (v)
u	(Z)		a (vii)







R' = $CH_2NHCOMe$

Z

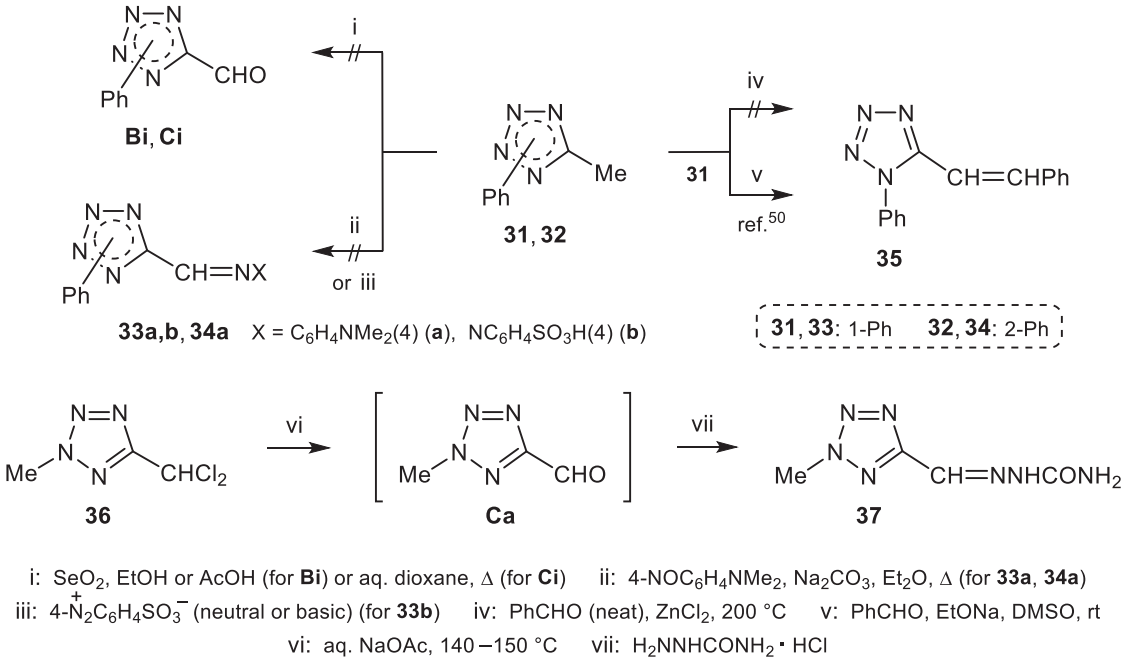
Chart 4. List of aldehydes (**B**) and (**C**) dealt with in Section (2)

a) Synthesis

(i) Early history: First approaches to the above classes date back to the 1950s (Scheme 8). Efforts to obtain a member of series (**B**) were undertaken in conjunction with studies on the reactivity of the 5-methyl group of 1*H*-tetrazoles, *viz.* of compound (**31**). Since this material was found capable of undergoing a Claisen condensation with diethyl oxalate to give the respective pyruvate, other reactions that are typical of active methyl compounds were attempted, *i.e.* treatment with selenium dioxide, *N*,*N*-dimethyl-4-nitrosoaniline or 4-diazoniobenzenesulfonate (both in the presence of base), and benzaldehyde in the presence of zinc chloride.[47] Yet, the expected products (**Bi**), (**33a,b**), and (**35**) were not obtained.[48–50] Moreover, since also oxidation of 5-(hydroxymethyl)-1-phenyltetrazole with lead tetraacetate as well as treatment of the 5-(anilinomethyl) congener with potassium permanganate did not proceed as expected, the authors believed the desired aldehyde (**Bi**) was extremely reactive.[51] In view of the less pronounced electron-withrawing

influence of the 2*H*-tetrazol-5-yl system (*cf.* Chart 2), it appears conceivable that attempts to transform compound (**32**) into the aldehyde (**Ci**) or the (dimethylamino)anil (**34a**) were unrewarding too.[5a]

More successful was an approach to series (**C**): When the (dichloromethyl)tetrazole (**36**) was strongly heated in aqueous sodium acetate [*cf.* Scheme 1, route (b)] and the hydrolysate treated with semicarbazide, the derivative (**37**) was found; however, isolation of the respective aldehyde (**Ca**) did not take place.[52]

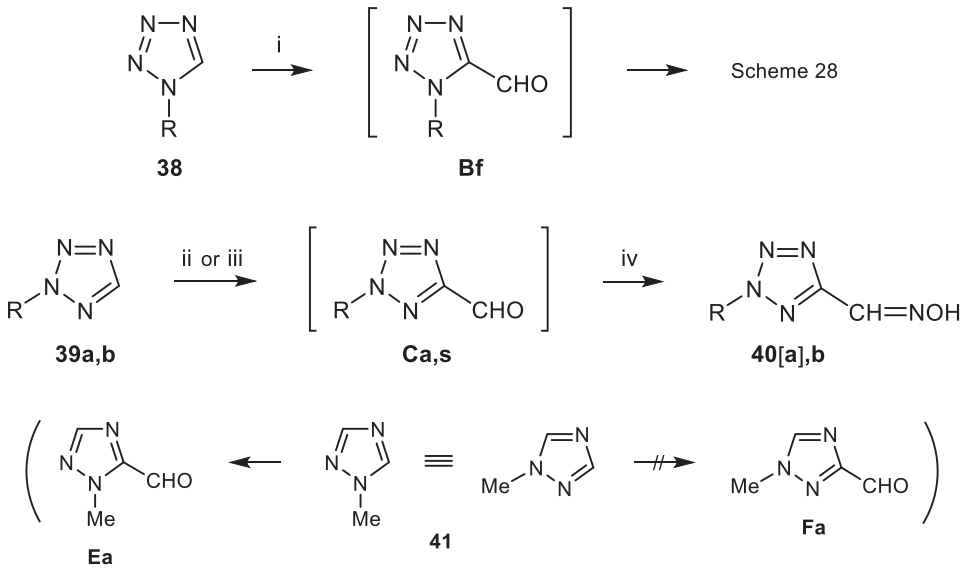


Scheme 8

(ii) Direct formylation [Scheme 1, route (a)]: Functionalization of C(5) *via* ring metallation, first reported in 1971 for the 1*H* series,[53] has since been an expanding area,[54] but the introduction of a formyl group is still rare (Scheme 9). There are only three cases and the first example for a 1*H*-tetrazole did not become known until recently, *viz.* the process (**38** → **Bf**). As the aldehyde was accompanied by much starting material and said to be fairly unstable, it was not isolated but directly used for further transformation (Scheme 28).[55]

Metallation of 2*H*-tetrazoles requires more powerful reagents (due to the lower kinetic acidity of 5-H of this series[56]). Applying *tert*-butyllithium (instead of *n*-butyllithium) and *N*-methylformanilide, compound (**39a**) could be converted to the aldehyde (**Cs**); without being isolated, it was sequentially transformed to the oxime (**40a**) and the corresponding nitrile (see Scheme 31); the latter was needed in a search for cholinergic agonists.[57a,b] Using lithium diisopropylamide and DMF, also the tetrazole (**39b**) underwent formylation to yield the aldehyde (**Ca**) which was derivatized *in situ* to give the oxime (**40b**).[58a,b]

A graduated reactivity as observed with the tetrazoles (**38**) and (**39**) is also typical of 1*H*-1,2,4-triazoles: 1-Substituted representatives having two free ring positions are primarily attacked at C(5), since the kinetic



i: *n*-BuLi, $Me_2N[CH_2]_2NMe_2$, THF, −98 °C; then HCO_2Et, rt ii: *t*-BuLi, HCON(Me)Ph, hexane / THF, <− 50 °C
iii: $LiN(i\text{-}Pr)_2$, $HCONMe_2$, heptane / THF / EtC_6H_5, −75 °C iv: $NH_2OH \cdot HCl$, MeOH, rt

39, 40	C	R	method	ref.	
38, Bf		$CH_2C_6H_4OMe(4)$	i	55	
a [a]	**s**	(X)	ii	57a,b	⊗
b	**a**	Me	iii	58a,b	

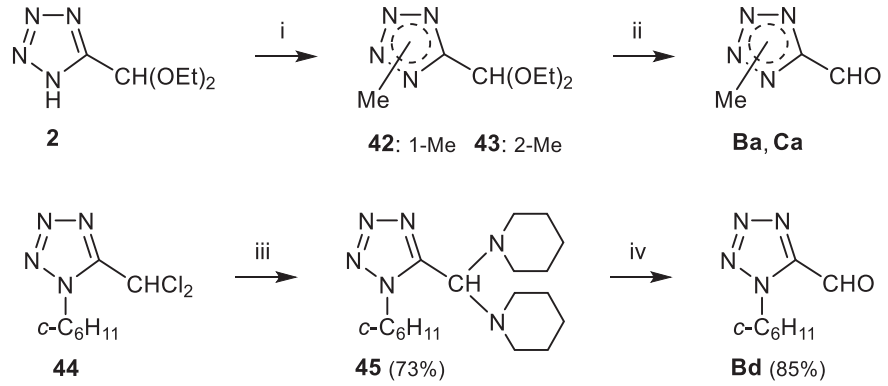
[a] Oxime (**40a**) was directly converted to the respective nitrile (see Scheme 31).

Scheme 9

acidity of 5-H is much higher than that of 3-H (ratio ca. 10^5 : 1).[56] Thus, formylation of **41** led exclusively to the aldehyde (**Ea**);[8a,b,18] a literature report on the formation of **Fa** is erroneous,[59a,b] as detailed elsewhere.[60]

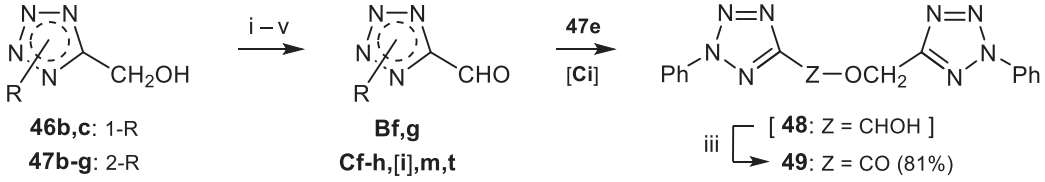
(iii) Hydrolysis of heterogeminals [Scheme 1, route (b)]: In analogy to the process (**2** → **A**) of Scheme 2, the acetals (**42**) and (**43**) – obtained as a mixture from **2** – were treated with dilute acid to give the aldehydes (**Ba**) and (**Ca**) (Scheme 10); without being separated, they were used in a further reaction (Scheme 26).[20a] Another mild hydrolysis performed with the aminal (**45**) led to the aldehyde (**Bd**) which was isolated as *gem*-diol [*cf.* Section (2b)].[4a] However, a direct conversion of the precursor (**44**) into **Bd** under the rigorous conditions that have been applied in the process (**36** → **Ca**) (Scheme 8) was not possible, as this aldehyde is highly prone to deformylation [*cf.* Section (2c)]. Using morpholine, the above two-step route has recently been followed to obtain 1,3-diaryl-1,2,4-triazole-5-carbaldehydes (**E**; X = R = Ar) (Chart 1).[61]

(iv) Oxidation of carbinols [Scheme 1, route (c)]: Diverse oxidants have successfully been used to convert substrates like **46** and **47** to the respective aldehydes (**B**) and (**C**) (Scheme 11). Employing chromium(VI) reagents, the representatives (**Bf,g**) and (**Cf,g,t**) were prepared,[62a–c,63] and treatment of **47d** with manganese



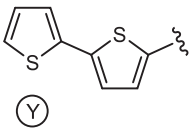
Scheme 10

dioxide gave the aldehyde (**Ch**),[62b] whereas Swern oxidation of **47f** afforded the product (**Cm**).[64] Attempts with lead tetraacetate, however, met with failure. This concerns not only the fruitless approach towards **Bi** mentioned in Section [(2a (i)], but also the reaction of **47e**: In this case the ditetrazolyl derivative (**49**) arose, presumably *via* oxidation of the transient hemiacetal (**48**) which resulted from addition of unconsumed **47e** to **Ci**.[5b] Compounds of the type (**49**) were formed also in the 1,2,4-triazole series,[7a] but only in negligible amounts, while the formation of aldehydes (**E**), (**E'**), and (**F**) proceeded with high yields.[7a, 10a,b, 18, 65]



i: $[PyH]_2Cr_2O_7$, CH_2Cl_2, molecular sieves (4 Å), rt ii: MnO_2, Me_2CO, rt iii: $Pb(OAc)_4$, pyridine, rt
iv: DMSO, $(COCl)_2$, CH_2Cl_2, rt v: $[PyH]CrClO_3$, CH_2Cl_2, rt

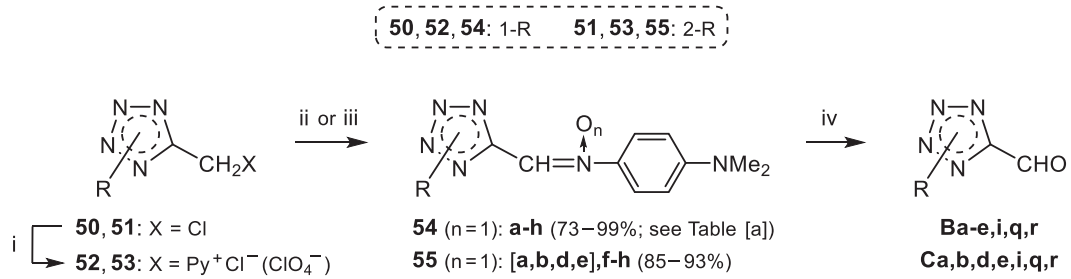
46, **47**	R	**B**, **C**	method	yield (%)	ref.
b	$CH_2C_6H_4OMe(4)$	**f**	i	47 [a]	62a-c
c	CH_2CO_2Me	**g**	i	54 [a]	62a-c
d	$[CH_2]_3CO_2Et$	**h**	ii	23	62b
e	Ph	**i**	iii	[b]	5b
f	$3\text{-}MeC_6H_4$	**m**	iv	64	64
g	(Y)	**t**	v	90	63



[a] Mixture of **B** and **C** (from **46** + **47**). [b] Ester (**49**) instead of **Ci**.

Scheme 11

(v) Kröhnke reaction[66a,b] [Scheme 1, route (d)]: After the Sommelet reaction had failed,[4a] the present route was found most appealing (Scheme 12). The essential precursors (**52**) and (**53**) were obtained from **50** and **51** (an entry from methyltetrazoles, *i.e.* by applying the Ortoleva-King variant,[66c] was not possible for lack of reactivity[67]). Beyond the usefulness of this aldehyde synthesis (which can be performed as a one-vessel reaction) another point of interest exists: The two processes (**50** → **52** → **54**) and (**51** → **53** → **55**) clearly reflect the different electron withdrawal of the isomeric tetrazolyl systems (*cf.* Chart 2: σ values of **I** and **II**): (a) The reaction of the 1*H* isomer (**50a**) with pyridine proceeds about 2.2 times faster than that of **51a** (2.5 times for **50f** *vs.* **51f**);[13b] (b) deprotonation of the pyridiniomethyl group of the alkyl-substituted 2*H* isomers (**53a-e**) needs a stronger base;[5a] alkali carbonate is suitable only with R = aryl (**53f-h**).[5b, 68a] Such graduations have also been observed in the 1,2,4-triazole series: (a) While the nitrones which precede the aldehydes (**E**) could be prepared after the procedure that was successful for **54**, the nitrones of the aldehydes (**E'**) and (**F**) were formed only in the presence of alkali (*cf.* Chart 2: σ constants of **III**, **III'**, and **IV**).[7a, 18]



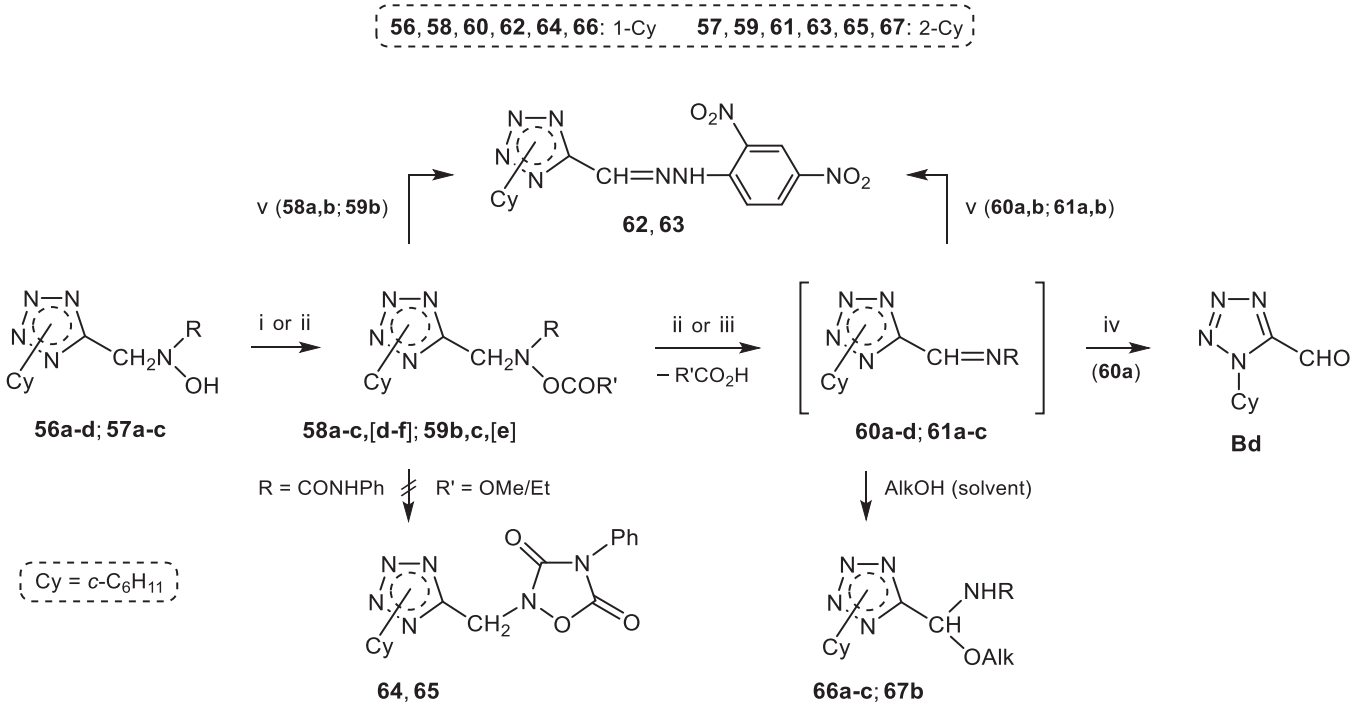
i: pyridine, EtOH (or $MeNO_2$[5b]), Δ, then $NaClO_4$ (for **52a-c**) ii: 4-$NOC_6H_4NMe_2$, aq. pyridine, K_2CO_3, 5 °C → rt (for **54a-h** and **55f-h**)
iii: 4-$NOC_6H_4NMe_2$, EtOH, 1 N NaOH, 10 °C → rt (for **55a-e**) iv: 5 N H_2SO_4, rt

50–55	R	B	yield (%) [b]	mp [bp / Torr] (°C)	ref.	C	yield (%)	mp [bp / Torr] (°C)	ref.
a [a]	Me	**a**	80	76–79	4a	**a**	74 [c]	[73 / 1]	5a
b [a]	Et	**b**	81	[61 / 0.5]	4a	**b**	75 [d]	[58 / 0.5]	5a
c	Bu	**c**	92	[75 / 0.3]	4a				
d	*c*-C_6H_{11}	**d**	93	47–49	4a	**d**	86 [c]	[95–96 / 0.4]	5a
e [a]	CH_2Ph	**e**	95	[87–89 / 0.01]	4a	**e**	79 [c]	[102–103 / 0.05]	5a
f	Ph	**i**	85	97	4a	**i**	74 [e] / 91 [f]	73–74 / 72–72.5	5a / 5b
g	4-MeC_6H_4	**q**	97	90–97	4a	**q**	88 [e]	64–65	13d
h	4-$NO_2C_6H_4$	**r**	96	134–137	4a	**r**	88 [e]	137–138 [g]	13d

[a] Besides **54a,b,e** some **54'a,b,e** (n = 0). [b] Yields of **Bd,e,i,q,r** and **Ba,c** relate to the respective hydrates (**71**) and hemihydrates (**73**) (Chart 5). [c] Based on **53**. [d] Based on **51**. [e] Crystallized from water, then sublimed *in vacuo*. [f] Crude material, directly sublimed *in vacuo*. [g] Decomp.

Scheme 12

(vi) β-Elimination with hydroxylamine derivatives [Scheme 1, route (e)]: According to the long known principle [RCH_2–N(OCOR')R → RCH=NR + R'CO_2H],[69] *O*-acylhydroxylamines like **58**[4b, 70, 71] and **59**[13b] (easily obtained from **56** and **57**) are potential aldimines due to their active methylene group (Scheme 13). Adopting the procedure that is capable of transforming *O*-carbamoylated 2-(hydroxyamino)alkanamides into 2-oxoalkanamides by gentle heating with dilute mineral acid,[72] the representative (**58a**) was converted



i: R'NCO, CH_2Cl_2, rt (for **58a**, **59c**), 40 °C (**58b**, **59b**) or dioxane, rt (**58c**) ii: $ClCO_2Me$/Et, 1 N NaOH, MeOH or EtOH, Δ (for **58d-f** and **59e**)
iii: benzene, Δ (for **60a,c**) iv: 2 N HCl, MeOH, Δ v: 2,4-$(NO_2)_2C_6H_3NHNH_2$, 12 N HCl, MeOH, rt

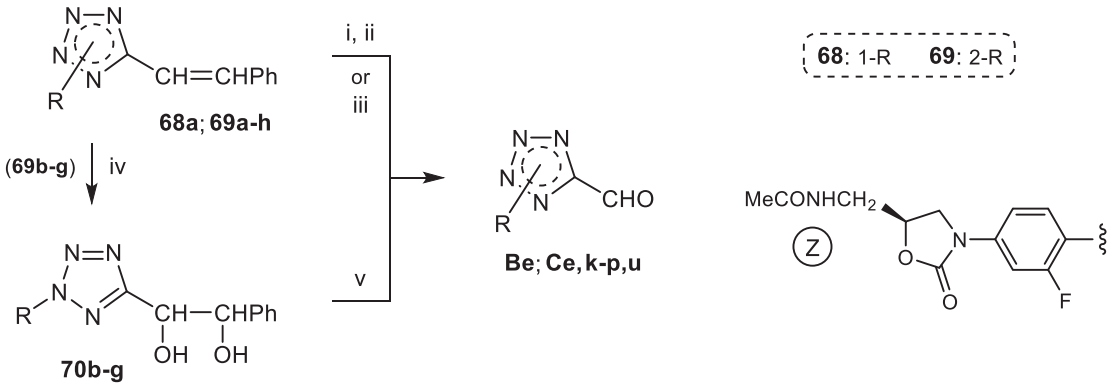
56, **57**, **60**, **61**	R	R'	**58**, **59**	**66**, **67**	Alk	method	product	yield (%)	ref.
a	Me	NHPh	**a**			iii, iv	**Bd**	81 [b,c]	4b, 70
	Me	$NHC_6H_4Cl(4)$	**b**			v	**62** / **63**	94 [b], 75 [d] / 40 [d]	70, 13b / 13b
b	$CH_2Tet^{1/2}$ [a]	NHPh	**c**			iii, v	**62**	33 [e]	70
c	CONHPh	OMe	[**d**]	**a**	OMe	ii	**66a,b**	86, 85 [f]	71, 71
	CONHPh	OEt	[**e**]	**b**	OEt	ii	**66c**	67 [g,h]	71
d	COPh	OEt	[**f**]	**c**	OEt	ii	**67b**	65 [i]	13b

[a] $Tet^{1/2}$ = 1-/2-cyclohexyltetrazol-5-yl. [b] Based on **56a** (route through **58a**). [c] Isolated as hydrate (**71d**) (Chart 5). [d] Based on **58b** / **59b**. [e] Based on **58c**. [f] Based on **56c**. [g] Based on **56d**. [h] Besides 16% **58f**. [i] Based on **57c**.

Scheme 13

to the aldehyde (**Bd**).[4b,70] The proclivity for undergoing β-elimination is so pronounced that – even at room temperature – quantitative formation of the hydrazone (**62**) took place when **58a** was treated with the acidified reagent.[4b] As a consequence of the reduced electron withdrawal of the 2-substituted tetrazol-5-yl moiety, the yield of **63** was appreciably lower (found on reacting both **58b** and **59b**).[13b] Also the thermally induced β-elimination shows that difference: On heating the derivatives (**58c**) and (**59c**) at 80 °C, the former released carbon dioxide and aniline in less than 3 h (→ **60b**), whereas decomposition of the latter (→ **61b**) required more than 30 h.[13b] The ease of the process (**58** / **59** → **60** / **61**) is especially high with the carbonates (**58d-f**) and (**59e**). Of these compounds, **58d,e** and **59e** were expected to give the oxadiazolidinediones (**64**) and (**65**) on treatment with alcoholic sodium hydroxide,[73] but all (including **58f**) disintegrated to the imines (**60c,d**) and (**61c**) which in turn added the solvent to ultimately yield N,O-acetals of the type (**66**) and (**67**).[71]

(vii) Ozonolysis and glycol fission [Scheme 1, routes (f) and (g)]: As apparent from Scheme 14, only part of the aldehydes resulted *via* (f), *i.e.* by splitting of the styryl group in **68** / **69** (→ **Be** / **Ce**,[74] **Cn**,[64] **Cp**,[76] **Cu**[77a]), while the majority were obtained by a two-step procedure that implies dihydroxylation of **69** and fission of the glycol (**70**).[75,76] The aldehyde (**Cu**), representing a linezolid analogue, was synthesized as a potential antibacterial agent;[77a] later, a QSAR study of **Cu** including numerous azole congeners was performed.[77b]



i: O_3, conditions not specified (**68a** and **69a**) ii: O_3, CH_2Cl_2, −78 °C (**69e**) or rt (**69g**)
iii: O_3, CH_2Cl_2, −78 °C; then Me_2S, rt iv: $K_2OsO_2(OH)_4$, 4-methylmorpholine *N*-oxide, citric acid, aq. *t*-BuOH, rt
v: $Pb(OAc)_4$, K_2CO_3, toluene, rt

68–70	**B**, **C**	R	method	yield (%)	ref.
a	**e**	CH_2Ph	i	[a]	74a,b
b	**k**	2-F-5-MeC_6H_3	iv, v	[b]	75
c	**l**	2-F-5-ClC_6H_3	iv, v	60 [c]	75
d	**m**	3-MeC_6H_4	iv, v	84 [c]	75,76
e	**n**	3-ClC_6H_4	ii / iv, v	[d] / 68 [e]	64 / 64,75,76
f	**o**	3-IC_6H_5	iv, v	[b]	75
g	**p**	3-NCC_6H_4	ii / iv, v	92 / [b]	76 / 75
h	**u**	(Z)	iii	> 90	77a

[a] Unreported (both **Be** and **Ce**). [b] Unreported. [c] Based on **69c** and **69d**, respectively.
[d] *In situ* reduced with $NaBH_4$. [e] Based on **70e.**

Scheme 14

b) Properties

Aldehydes (**B**) and (**C**) represent well defined solids or liquids (*cf.* Scheme 12); yet, in some cases those properties have not been reported (*cf.* Schemes 9, 11, 14). The aldehyde group shows usual spectroscopic behaviour with an IR band between 1713 and 1730 cm^{-1} [4a,5a,b,13d] and a ^1H NMR signal between δ 10.20 and 10.55 ppm (depending on the solvent)[4a,5a,b,13d,55,62b,63,76,77,81]; significant differences between **B** and **C** were not observed. Particular attention deserves the capability of **B** and **C** to form isolable hydrates (*gem*-diols), hemiacetals, and -aminals – a feature typical of aldehydes with stronger electron-withdrawing substituents. This property is most pronounced with series (**B**) to give derivatives (**71d-h**)[4a,b] and, with smaller alkyl groups, hemihydrates (**73a-c**)[4a] which, however, fragment to **B** and **71** when dissolved in DMSO (Chart 5).

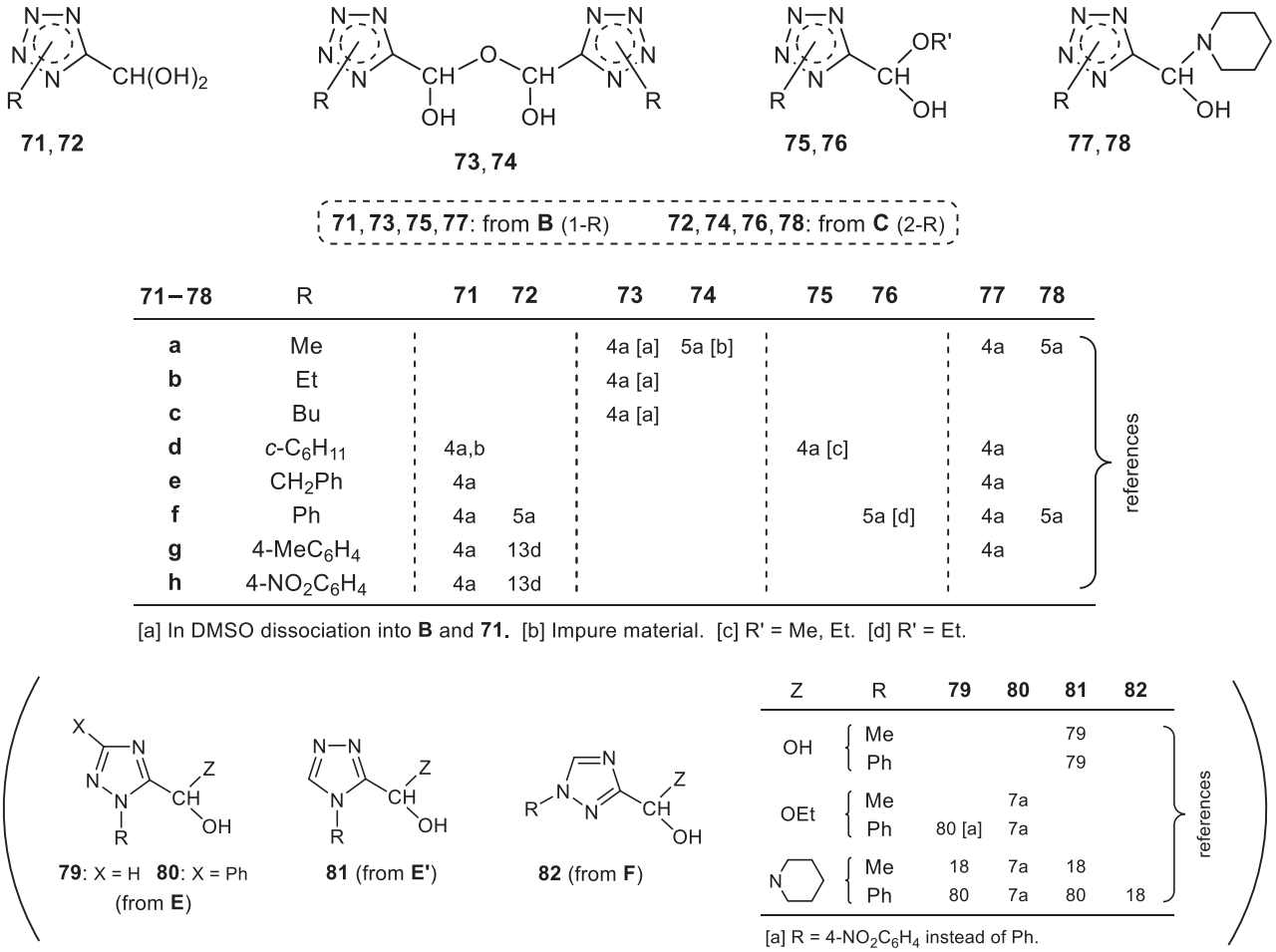
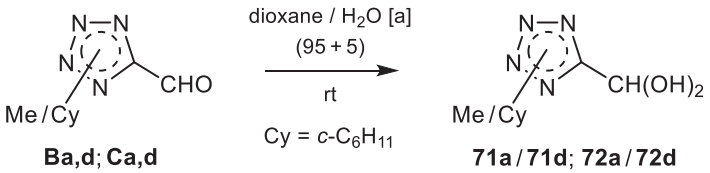


Chart 5. Isolated hydrates, hemihydrates, -acetals, and -aminals from aldehydes (**B**, **C**) and (**E**, **E'**, **F**)

Since addition of water takes place even in the solid state, the free aldehydes must be rigorously protected from moisture.[78] Owing to the weaker electron-withdrawing influence of the 2*H*-tetrazol-5-yl moiety, the aldehydes (**C**) are more resistant. Nevertheless, members with aryl substituents (**Ci,q,r**) gave hydrates too (→ **72f-h**), but only on treatment with water, not on exposure to air.[5a, 13d] A solid hemihydrate like **74a** arose slowly (*cf.* kinetics below) when the liquid aldehyde (**Ca**) was left in an open vessel, while the homologue (**Cb**) was fully restored on evaporation of an aqueous solution.[5a] Accordingly, hemiacetals were preferably formed in the 1*H* series [→ **75d** (R' = Me, Et)], whereas in the 2*H* series again an aryl substituent was necessary [→ **76f** (R' = Et)].[5a] Since hemiaminals are generally more stable, derivatives were obtained from both aldehyde series, irrespective of the R group, *viz.* **77a,d-g**[4a] and **78a,f**.[5a] Concerning the less activated triazolecarbaldehydes (*cf.* Chart 2: σ constants), only the 4*H* series (**E'**) gave hydrates (→ **81**; Z = OH),[79] not series (**E**) (as one would expect), but from the latter – in particular from members having a phenyl group at C(3) – hemiacetals could be isolated (→ **80**; Z = OEt).[7a] Hemiaminals were obtained throughout,[7a, 18, 80] although the least active aldehyde (**F**) needs an electron-withdrawing phenyl group (→ **82**; Z = NC_5H_{10}).[18]

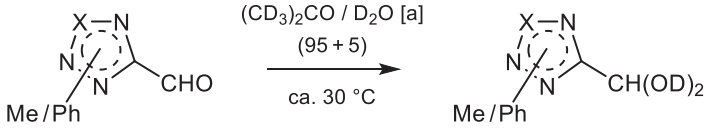
A kinetic study of the hydration of the aldehydes (**B**) and (**C**) showed as expected that the process is much faster with the isomers (**B**); hydration attains also a higher degree [Scheme 15; compare: (i) rate constants and half-lives: **Ba** *vs.* **Ca** and **Bd** *vs.* **Cd**, and (ii) $CH(OD)_2$ fractions: **Ba** *vs.* **Ca** and **Bi** *vs.* **Ci**].[81] In the triazole series hydration is most favoured with the aldehydes (**E**) and – as earlier observed with **B** and **C**[81] – is enhanced by a phenyl group.[7a,18] Of the aldehydes (**F**), only **Fb** shows some reactivity (*cf.* also Chart 5).[18]



Ba,d; **Ca,d** **71a / 71d**; **72a / 72d**

		$10^5 k_{obs}$ (s^{-1})	$t_{1/2}$ (min)	ref.
Ba / Bd	1-Me / 1-Cy	59.5 / 41.4	19 / 28	81
Ca / Cd	2-Me / 2-Cy	7.87 / 5.37	146 / 214	81

[a] UV study; total aldehyde concentration: 0.03 (**Ba**, **Ca**) or 0.02 mol / l (**Bd**, **Cd**), H_2O concentration: 2.78 mol / l.



Ba–**Fb**

		X	$CH(OD)_2$ fraction (%)	ref.
Ba / Bi	1-Me / 1-Ph	N	85 / 92	81
Ca / Ci	2-Me / 2-Ph	N	42 / 65	81
Ea / Eb	1-Me / 1-Ph	CH	29 / 47	18
Ea / Eb	1-Me / 1-Ph	CPh	24 / 44	7a
E'a / E'b	4-Me / 4-Ph	CH	18 / 17	18
Fa / Fb	2-Me / 2-Ph [b]	CH	< 1 / 8	18

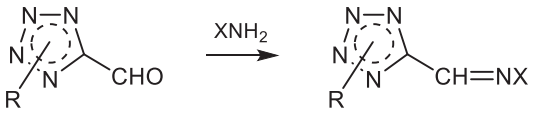
[a] ^{1}H NMR study; total aldehyde concentration: 0.44–0.47 (**B**, **C**) or 0.1 mol / l (**E**, **E'**, **F**), D_2O concentration: 2.78 mol / l. [b] Unsystematic numbering.

Scheme 15. Hydration of aldehydes (**B**, **C**) and (**E**, **E'**, **F**)

c) Reactions

(i) Derivatives: Both classes (**B**) and (**C**) gave the usual derivatives; examples that have been sufficiently characterized are gathered in Scheme 16. – For derivatives employed in further reactions, see Section (2d).

(ii) Strong bases: In their behaviour towards bases, **B** and **C** exhibit major differences (Scheme 17). On exposure to alkali, the isomers (**B**) – like aldehydes with strong electron-withdrawing groups – were rapidly deformylated to **91** [mode (1)]. Even prolonged heating with boiling water can induce the process such as to vitiate the synthesis of **Bd** by hydrolysis of compound (**44**) (Scheme 10).[4a] A similar sensitivity to alkali had



B, **C** **83**–**90**

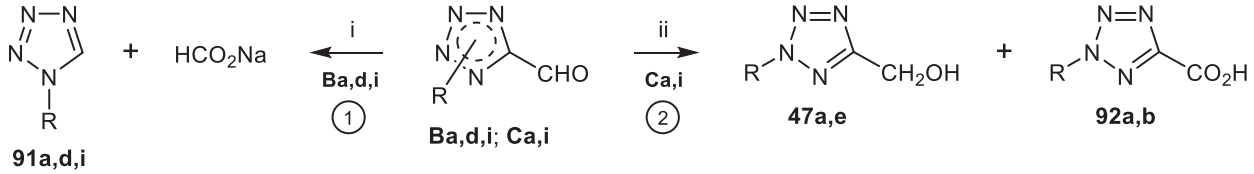
1-R	2-R	X
83	**84**	OH
85	**86**	NH*DNP* [a]
	87	NHPh
	88	$NHCONH_2$
89	**90**	NHTs

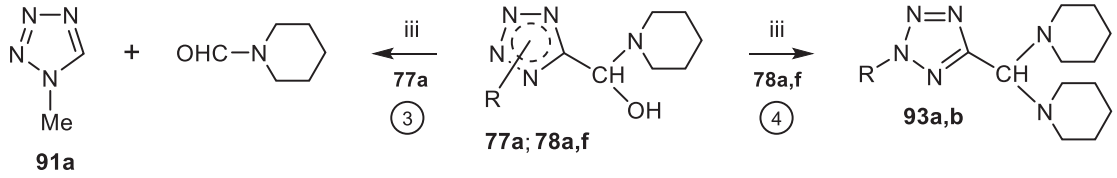
B,**C**	R		**83**	**84**	**85**	**86**	**87**	**88**	**89**	**90**
a	Me	**a**	4a	5a [b]	4a	5a		5a, 52 [d]	13d	13d
b	Et	**b**			4a	5a				
c	Bu	**c**			4a					
d	*c*-C_6H_{11}	**d**	4a	13b	4a,b [c]	5a [c]			13d	13d
e	CH_2Ph	**e**			4a	5a			13d	13d
i	Ph	**f**	13c	13c	4a	5a	5b		13d	13d
q	4-MeC_6H_4	**g**			4a	13d			13d	13d
r	4-$NO_2C_6H_4$	**h**			4a	13d			13d	13d

references

[a] *DNP* = 2,4-$(NO_2)_2C_6H_3$. [b] Corresponds to **40b** of Scheme 9. [c] Corresponds to **62** and **63** of Scheme 13, respectively. [d] Corresponds to **37** of Scheme 8.

Scheme 16



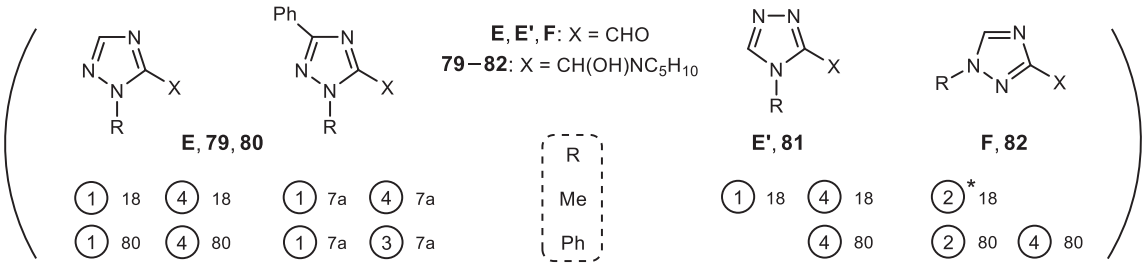


i: 1 N NaOH, rt ii: 4 N NaOH, rt; then 12 N HCl iii: piperidine, K_2CO_3, abs. benzene, Δ

					yield (%) / reference			
B, **C**, **91**	**47**	**77**, **78**	**92**, **93**	R	**47**	**91**	**92**	**93**
a	**a**	**a**	**a**	Me	70 / 5a	100 [a] / 4a	91 / 5a	68 / 5a
d				*c*-C_6H_{11}		100 / 4a		
i	**e**	**f**	**b**	Ph	94 / 5a	100 / 4a	95 / 5a	92 / 5a

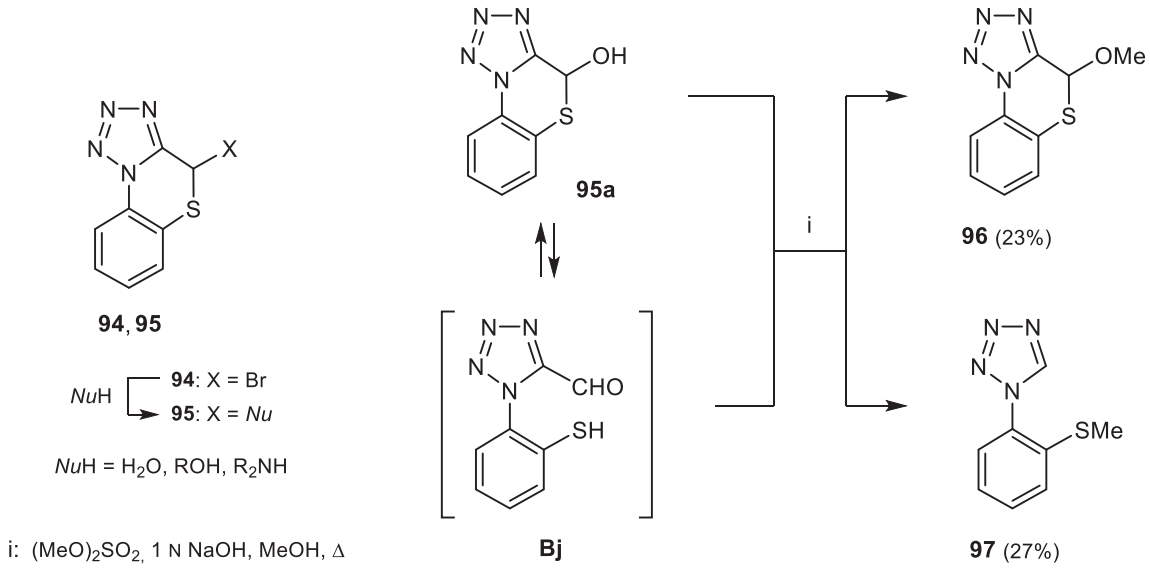
[a] From **Ba**.

Occurrence of the above reaction modes (1)–(4) with **E**, **E'**, **F** and **79**–**82**:



Scheme 17

earlier been reported of 5-acetyl-1-phenyltetrazole (loss of the acyl group).[82] In contrast to **B** the isomers (**C**) underwent the Cannizzaro reaction to give the respective carbinol (**47**) and the acid (**92**) [(2)].[5a] This disproportionation is not primarily owing to the weaker electron withdrawal of the 2*H*-tetrazol-5-yl moiety [the value *per se* (Chart 2) would allow for deformylation, as shown below by the behaviour of **E** and **E'** which are activated to the same extent as **C**]; the likely background is a stereoelectronic one: Deformylation proceeds through an anionized ring species, the formation of which is impeded by the lone pairs of the *two* adjacent pyridine-type nitrogen atoms (*cf.* ref.[56]). Hence, deformylation of **C** was observed only at very high concentrations of alkali, but the products (**47**) and (**92**) still prevailed.[5a] The marked propensity of **B** to transferring the formyl group onto nucleophiles extends also to certain amines: The reaction of the hemiaminal (**77a**) with piperidine at elevated temperature did not yield the desired aminal but gave **91a** and formopiperidide [(3)],[4a] while in the 2*H* series aminal formation proceeded smoothly (**78** → **93**) [(4)].[5a]
In this context the behaviour of the triazolecarbaldehydes (**E**, **E'**, **F**) and the hemiaminals (**79–82**) deserves interest (Scheme 17). Both compounds (**E**) and (**E'**) were deformylated by alkali [mode (1)],[7a, 18, 80] whereas the aldehyde (**F**) underwent the Cannizzaro reaction [(2)].[18, 80] Unlike the hemiaminal (**77a**), the triazole congeners (**79–81**) did not extrude formopiperidide on action of piperidine but were transformed into the respective aminals (as happened to **82**) [(4)];[7a, 18, 80] the occurrence of mode (3) was observed only once: with a hemiaminal derived from the (more activated) 1,3-diphenyl substituted aldehyde (**E**).[7a] – For an abridged, more general comparison between the aldehydes (**B**, **C**) and (**E**, **E'**, **F**), *cf.* also reference.[83]

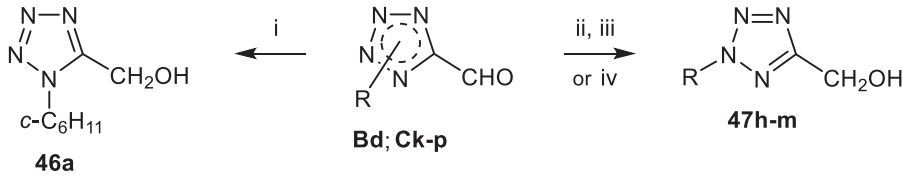


Scheme 18

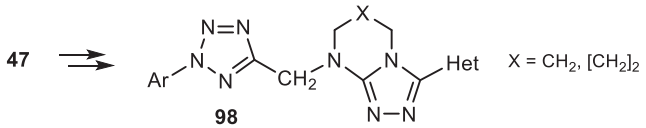
Finally, deformylation of an aldehyde (**B**) was encountered during studies on nucleophilic displacement reactions performed with the tricycle (**94**) (Scheme 18).[84] On methylation of the hydroxy derivative (**95a**),

conducted in an alkaline medium, not only the desired compound (**96**) resulted but also substantial amounts of the aryltetrazole (**97**). This led the authors to think of an equilibrium between the substrate (**95a**) and the aldehyde (**Bj**); the latter was methylated at the thiol function, but it lost the formyl group under the reaction conditions. As a precedent for this deacylation the behaviour of the above acetyltetrazole[82] was cited,[84] not the direct parallel offered by the earlier examples of class (**B**).[4a]

(iii) Reducing agents: Hydroborate salts easily converted aldehydes (**B**) and (**C**) to the respective carbinols (**46**) and (**47**) (Scheme 19).[4a,64,75,76] Most of these materials were used as building blocks for constructing glutamate receptor antagonists, *inter alia* compounds of the type (**98**).[75,76]



i: $NaBH_4$, MeOH, rt ii: $LiBH_4$, THF, Δ iii: $NaBH_4$, DMF / Et_2O, 0 °C

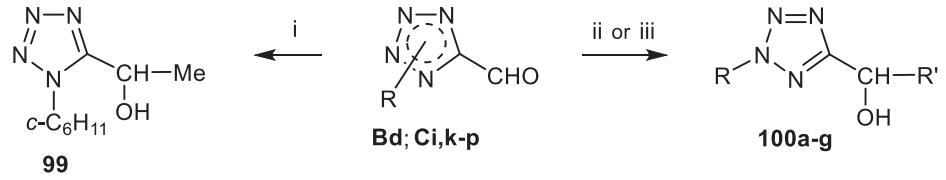


B, C	46	47	R	method	yield (%)	ref.
d	**a**		*c*-C_6H_{11}	i	80 [a]	4a
k		**h**	2-F-5-MeC_6H_3	ii	[b]	75
l		**i**	2-F-5-ClC_6H_3	ii	75	75
m		**j**	3-MeC_6H_4	ii	96	75, 76
n		**k**	3-ClC_6H_4	i / ii	31 [c] / '106'	64 / 75
o		**l**	3-IC_6H_5	ii	[b]	75
p		**m**	3-NCC_6H_4	ii / iii	[b] / 85	75 / 76

[a] From hydrate (**71d**). [b] Unreported. [c] Based on **69e** of Scheme 14.

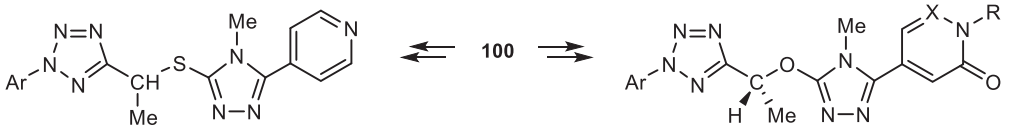
Scheme 19

(iv) Grignard reagents: Methyl- as well as benzylmagnesium halides added readily to the carbonyl group of **B** and **C** to afford compounds like **99** and **100**, respectively (Scheme 20). The product (**99**) had previously been obtained in poor yield from the respective (1-chloroethyl)tetrazole by sequential conversion to the acetoxy derivative and alkaline hydrolysis of the latter[85] (this unsatisfying approach was later replaced by an expedient one-pot synthesis using acetaldehyde, cyclohexyl isocyanide, and hydrogen azide[71]). Out of the 5-(hydroxyalkyl)tetrazoles (**100**), the derivatives (**100b-g**) – like the above carbinols (**47**) – served as precursors to glutamate receptor antagonists, *e.g.* **101**[75] and **102**.[64]



99 **Bd**; **Ci,k-p** **100a-g**

i: MeMgI, Et_2O, Δ ii: $PhCH_2MgCl$, Et_2O, Δ iii: MeMgBr, THF, 0 °C

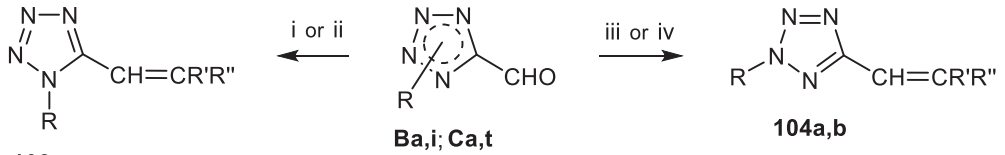


101 **102:** X = CH, N; R = H, Me, $CH_2O[CH_2]_2SiMe_3$

B, **C**		R	R'	method	yield (%)	ref.
d	**99**	*c*-C_6H_{11}	Me	i	61	4a
i	**100a**	Ph	CH_2Ph	ii	74 [a]	5b
k	**b**	2-F-5-MeC_6H_3	Me	iii	[b]	75
l	**c**	2-F-5-ClC_6H_3	Me	iii	77 [a]	75
m	**d**	3-MeC_6H_4	Me	iii	74 / 96 [a]	64 / 75
n	**e**	3-ClC_6H_4	Me	iii	77	64, 75
o	**f**	3-IC_6H_4	Me	iii	[b]	75
p	**g**	3-NCC_6H_4	Me	iii	[b]	75

[a] Crude. [b] Unreported.

Scheme 20

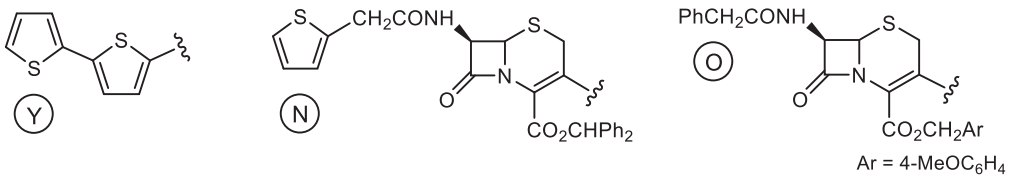


103a-c **Ba,i**; **Ca,t** **104a,b**

i: Ph_3P=CR'R", CH_2Cl_2, rt ii: see (i), benzene, rt iii: see (i), CH_2Cl_2, 0 °C iv: Ph_3P=CHCH=CHPh, THF, rt

B, **C**	R	product	R'	R"	from	method	yield (%)	ref.
a	Me	**103a**	H	(N)	**Ba**	i	40	86
i	Ph	**b**	H	CO_2Me	**Bi**	ii	65	88
t	(Y)	**c**	Br	CO_2Me	**Bi**	ii	81	88
		104a	H	(O)	**Ca**	iii		89
		b [a]	H	CH=CHPh	**Ct**	iv [b]	50	63

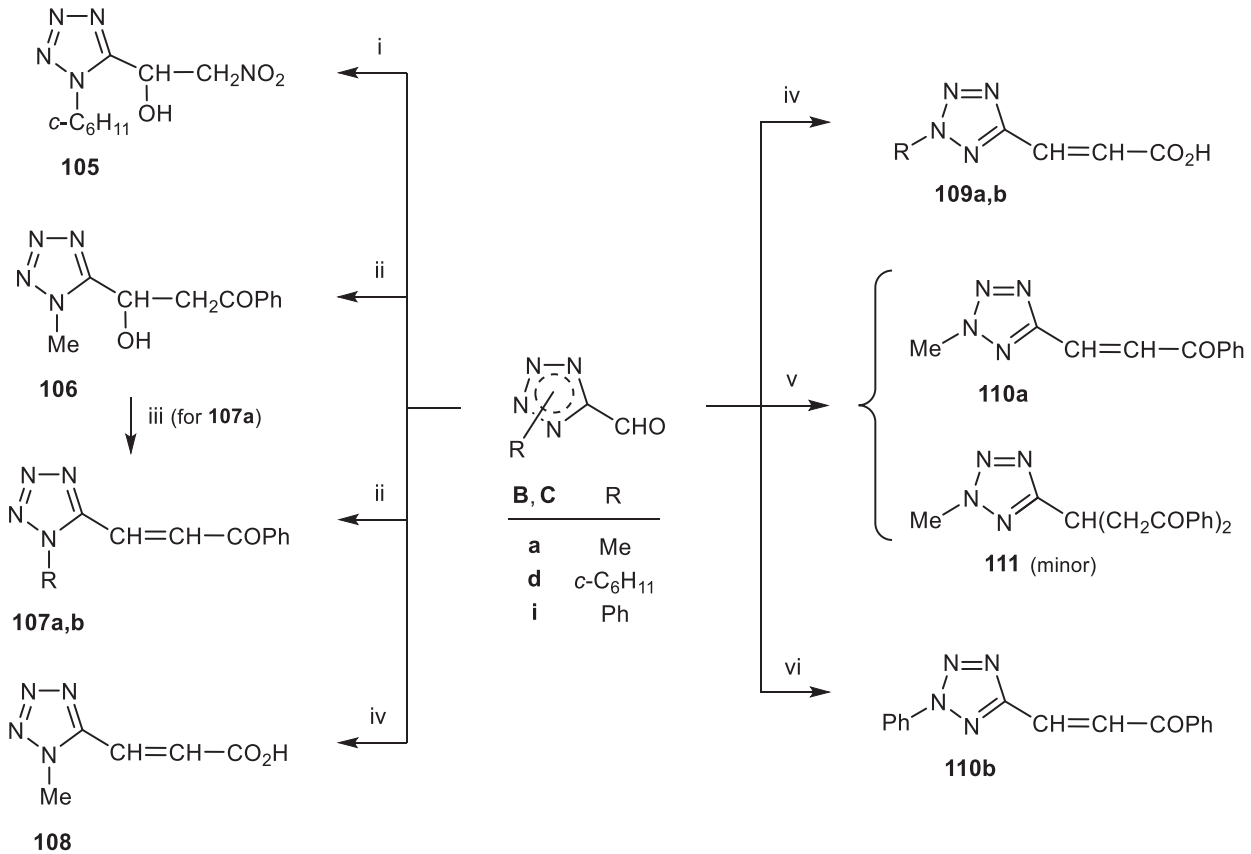
[a] Side chain: 1*E*, 3*E*. [b] Wittig reagent generated *in situ* (−70 °C).



Ar = 4-$MeOC_6H_4$

Scheme 21

(v) Wittig reagents: These materials have been used occasionally as a tool for vinyltetrazoles (Scheme 21). During a synthetic study on novel cephalosporin compounds the aldehyde (**Ba**) has been reacted with a cephem-substituted methylenephosphorane to afford the derivative (**103a**).[86] Prior to this entry the inverse route which started from a cephem-3-carbaldehyde and [(1-methyltetrazol-5yl)methylene]phosphorane had been followed.[87] Products like **103b,c** resulted from the reaction of the aldehyde (**Bi**) and the appropriate methylenephosphorane.[88] Among vinyl compounds made from aldehydes (**C**) another cephem derivative (**104a**) exists;[89] however, especially worth mentioning is the recently described diene (**104b**), it belongs to a new class of laser activatable tetrazoles with extended π-systems which upon 405 nm laser light irradiation were found to undergo extremely rapid 1,3-dipolar cycloaddition reactions with dimethyl fumarate.[63]



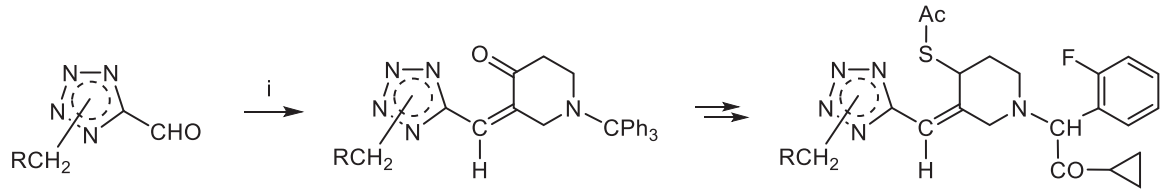
i: $MeNO_2$, MeOH, pyridine / Et_3N, rt ii: MeCOPh, AcOH, Δ iii: conc. H_2SO_4, rt
iv: $CH_2(CO_2H)_2$, pyridine / piperidine, Δ v: MeCOPh, 3 N KOH, EtOH, rt vi: MeCOPh, NaOMe, MeOH, rt

product	from	method	yield (%)	ref.	product	from	method	yield (%)	ref.
105	**Bd**	i	52	4a	**109a**	**Ca**	iv	89	5a
106	**Ba**	ii		4a	**109b**	**Ci**	iv	43	5b
107a	**106**	iii	57 [b]	4a	**110a**	**Ca**	v	51	5a
107b	**Bd**	ii	43	4a	**110b**	**Ci**	vi	67	5b
108	**Ba** [a]	iv	31	4a	**111**	**Ca**	v	10	5a

[a] Used: hemihydrate (**73a**) of **Ba** (Chart 5). [b] Based on **Ba.**

Scheme 22

(vi) Reagents showing CH-activity: Both aldehydes (**B**) and (**C**) react easily to allow standard conversions in great number (Scheme 22). As these reactions usually require a base, the extreme sensitivity of class (**B**) towards alkali must be regarded (*cf.* Scheme 17). Thus, while the Henry and Knoevenagel reactions, which were performed in the presence of a weak base, proceeded smoothly to afford **105** and **108**, respectively, alkali-assisted aldol condensations, for example with acetophenone, failed because of deformylation of **B**. However, the desired product (**107**) could be obtained when working in acetic acid; in the case of **Ba**, the adduct (**106**) was isolated first and then dehydrated to **107a** with conc. sulfuric acid; the analogue (**107b**), however, arose directly. An alternative entry to the latter is provided by pyrolysis of the Mannich base (**181**) which itself is easily accessible (see Scheme 35).[4a] Out of the compounds resulted from aldehydes (**C**), the products (**109**) and (**110a,b**) were anticipated,[5a,b] whereas compound (**111**) arose unexpectedly.[5a] Further condensation products obtained from reactive methylene partners constitute the derivatives (**112**) and (**113**) (Scheme 23). These materials served as precursors to compounds such as **114** and **115** which, like a plethora of congeners with azole groups other than tetrazole, attracted interest for their platelet activation inhibitory property.[62a-c]



i: 1-tritylpiperidin-4-one, pyrrolidine, benzene, Δ

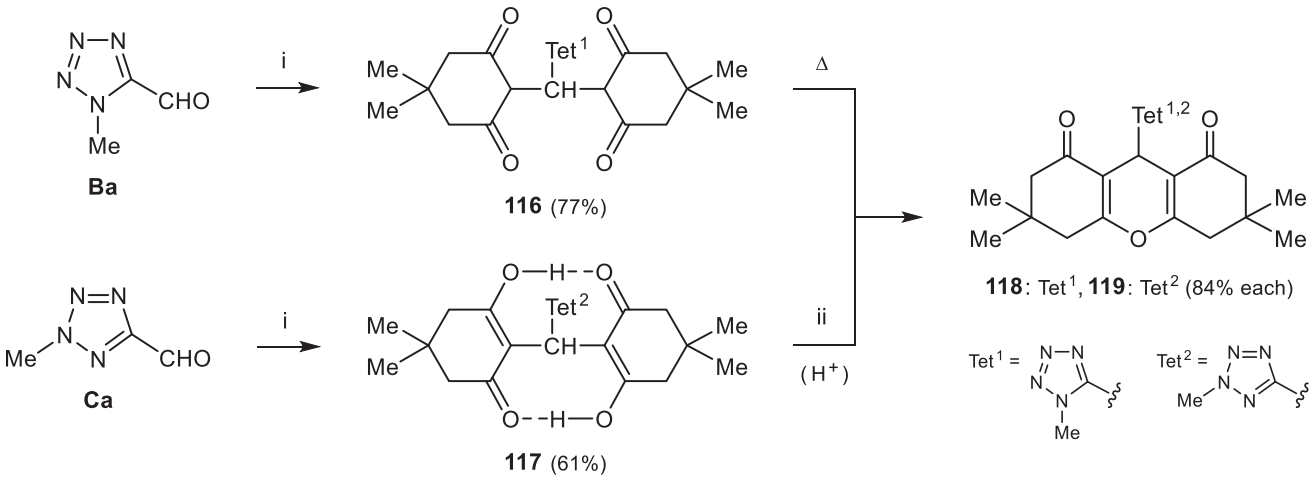
112, **114**: 1-CH_2R | **113**, **115**: 2-CH_2R

B, C	R	product	from	yield (%)	ref.
f	4-$MeOC_6H_4$	**112a** + **113a**	**Bf** + **Cf**	57 [a]	62a-c
g	CO_2Me	**112b** / **113b**	**Bg** + **Cg**	13 / 32	62a-c
h	$[CH_2]_2CO_2Et$	**113c**	**Ch**	32	62a-c

[a] Mixture, products not separated.

Scheme 23

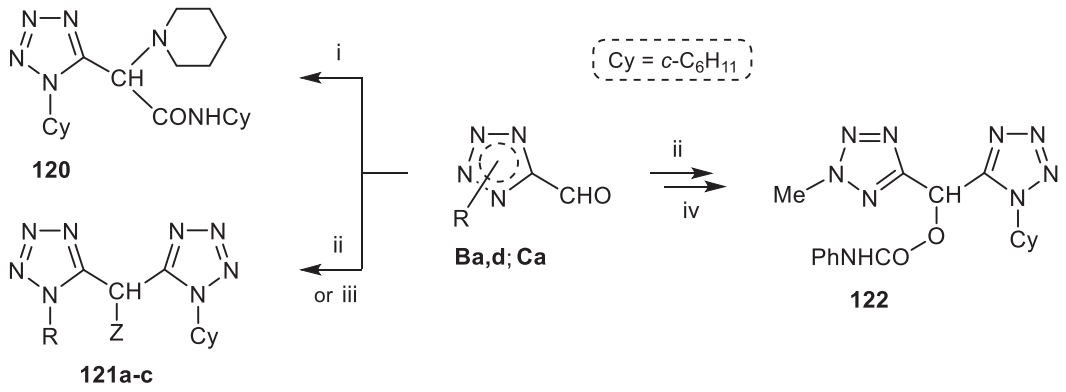
Depending on the aldehyde class, products of different character resulted from dimedone (Scheme 24).[13b] While **Ba** led to the bis(diketone) (**116**) along with enolized species as minor components, the isomer (**Ca**) gave the highly symmetric bis(hydroxyenone) (**117**) showing two eight-membered hydrogen chelates. The reason for this difference is sterical demand, as illustrated by space-filling models: If the tetrazole ring is substituted at N(1), it cannot rotate into the position that is necessary for constructing a double chelate as in **117**. Expectedly, both derivatives could be transformed into the corresponding octahydroxanthenes (**118**) and (**119**); but as the structure type of **116** is closer to the fused system (**118**), its formation proceeded more readily than the process (**117** → **119**), *viz.* just on brief heating of **116** above the melting point.



i: dimedone, aq. EtOH, piperidine (trace), Δ ii: EtOH, 12 N HCl (trace), Δ

Scheme 24

(vii) Isocyanides: Both Ugi and Passerini reactions have successfully been conducted with aldehydes (**B**), as exemplified by products like **120** and **121a-c**; the ditetrazolyl structures resulted from application of the hydrogen azide variant (Scheme 25).[4a] Also the aldehyde (**Ca**) was susceptible to this modification; yet, for getting pure material, the crude ditetrazolyl methanol had to be derivatized with an isocyanate (→ **122**).[5a]



i: piperidine, *c*-C_6H_{11}NC, 12 N HCl, aq. MeOH, 0 °C → rt ii: HN_3 / $CHCl_3$ (8%), *c*-C_6H_{11}NC, 0 °C → rt
iii: piperidine, HN_3 / $CHCl_3$ (8%), *c*-C_6H_{11}NC, 0 °C → rt iv: PhNCO, CH_2Cl_2, Δ

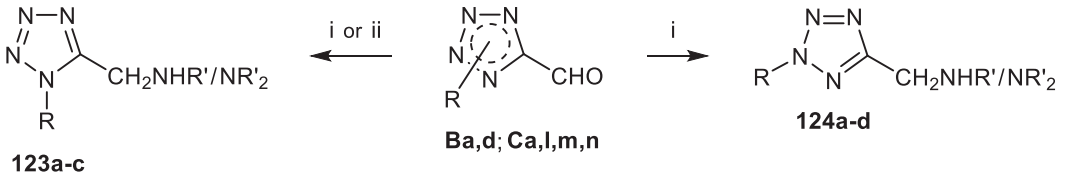
B, **C**	R	product	Z	from	method	yield (%)	ref.
a	Me	**120**		**Bd** [a]	i	6	4a
d	*c*-C_6H_{11}	**121a**	OH	**Ba**	ii	72	4a
		b	OH	**Bd**	ii	90	4a
		c	piperidino	**Bd**	iii	63	4a
		122		**Ca**	ii, iv	23 [b]	5a

[a] Used: Hydrate (**71d**) of **Bd** (Chart 5). [b] Based on **Ca.**

Scheme 25

Reactions of derivatives of B and C [90]

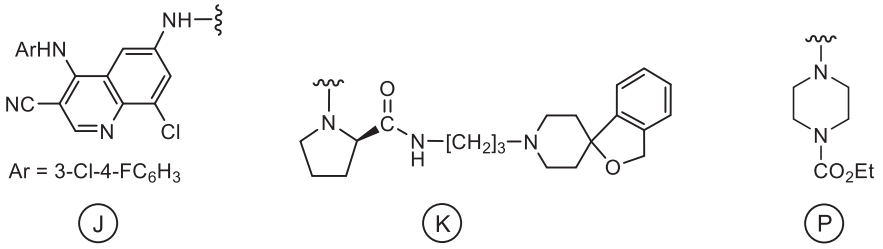
(i) Imines (including transient 1:1 adducts of **B** and **C** with amines): In analogy to the reductive alkylation of amines through the parent aldehyde (**A**) that gave the compounds (**30**) (*cf*. Scheme 7), bioactive materials such as **123a,b** and **124a-d** have been synthesized from **B** and **C** in one-pot procedures using hydroborate reagents (Scheme 26).[20a, 45, 75] In addition to these experiments, a Leuckart reaction has been conducted to yield the (piperidinomethyl)tetrazole (**123c**).[4a]



i: $R'NH_2$ / R'_2NH, then $Na[BH_3CN]$ (for **123a**, **124a**) or $Na[BH(OAc)_3]$ (for **123b-d**)
ii: piperidine, HCO_2H, Δ (for **123c**)

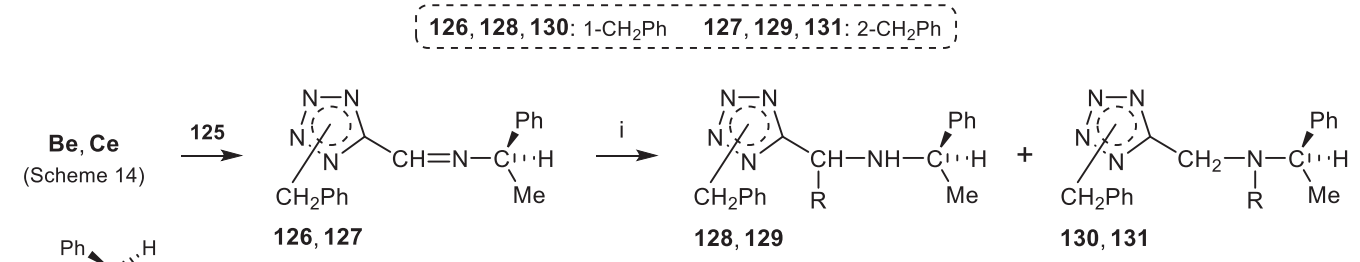
B, C	R	product	NHR'	NR'_2	from	yield (%)	activity	ref.
a	Me	**123a**	(J)		**Ba** [a]	2.3	antiinflammatory	20a
d	*c*-C_6H_{11}	**b**		(K)	**Ba**		analgesic	45
l	2-F-5-ClC_6H_3	**c**		piperidino	**Bd**	52		4a
m	3-MeC_6H_4	**124a**	(J)		**Ca** [a]	7	antiinflammatory	20a
n	3-ClC_6H_4	**b**		(P)	**Cl**	79	[b]	75
		c		(P)	**Cm**	57	[b]	75
		d		(P)	**Cn**	46	[b]	75

[a] Mixture of **Ba** and **Ca** reacted, then products separated. [b] Glutamate receptor antagonist.



Scheme 26

An unexpected reaction course was observed on treating the imines (**126**) and (**127**) with Grignard reagents: here the usual carbophilic addition did not take place throughout (Scheme 27):[74a,b] Using ethyl-, isopropyl-, and benzylmagnesium halides, the 1*H* isomer (**126**) underwent exclusive azophilic addition to afford the products (**130b-d**), whereas the same reagents converted the substrate (**127**) to the 'normal' derivatives (**129b-d**) (predominantly or to an appreciable extent). Also allylmagnesium bromide showed proclivity to azophilic addition, although less pronouncedly (→ **130e**). The sole exception constitutes methylmagnesium bromide which, indiscriminately, effected carbophilic addition (→ **128a**, **129a**)[74a,b] – a finding that appears



R		128 : 130	yield (%)	ref.	129 : 131	yield (%)	ref.
Me	**a**	100 : 0	51 [a]	74a,b	100 : 0	58	74b
Et	**b**	0 : 100	85 [b]	74a,b	76 : 24	54	74b
i-Pr	**c**	0 : 100	81	74a,b	36 : 64	41	74b
CH_2Ph	**d**	0 : 100	76	74a,b	95 : 5	75	74b
$CH_2CH{=}CH_2$	**e**	55 : 45	72	74a,b	99 : 1	61	74b

[a] Two diastereomers (ratio 2 : 1). [b] *N*-Ethylation proved by an independent synthesis.[74a]

Scheme 27

incomprehensible. To rationalize the azophilic addition with the substrate (**126**), the authors pointed to the more extended resonance between the imine function and the ring, *i.e.* the stronger electron-withdrawing influence of the 1*H*-tetrazolyl system (*cf.* Chart 6); this renders the imine nitrogen more positively polarized than with **127** (evidenced by a downfield shift of the methine proton of the PhCHMe substituent).[74b] – As concerns the enhanced resonance effect with aldimines of the 1*H* series, attention may be drawn to another example: the red shift of the UV/Vis absorption of the derivative (**54'f**) compared to the isomer (**55'f**).[13b]

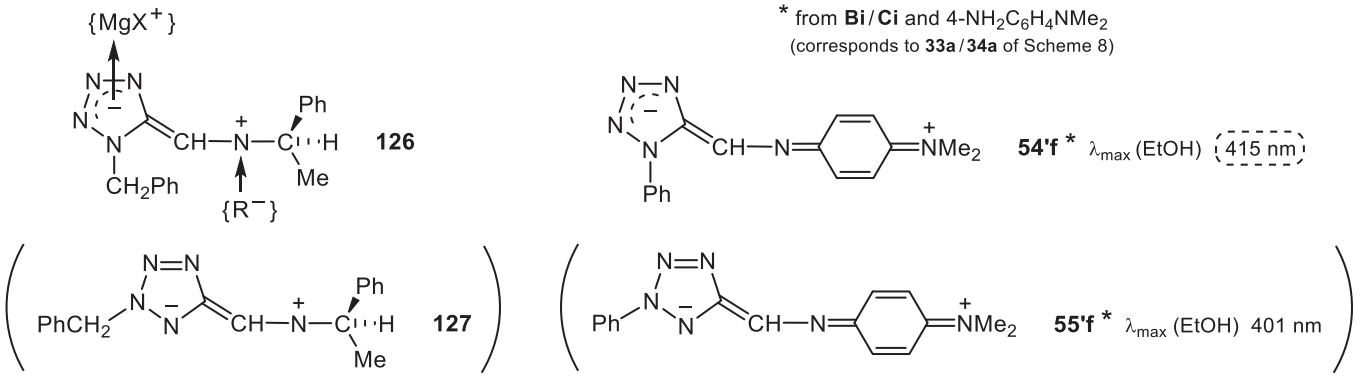
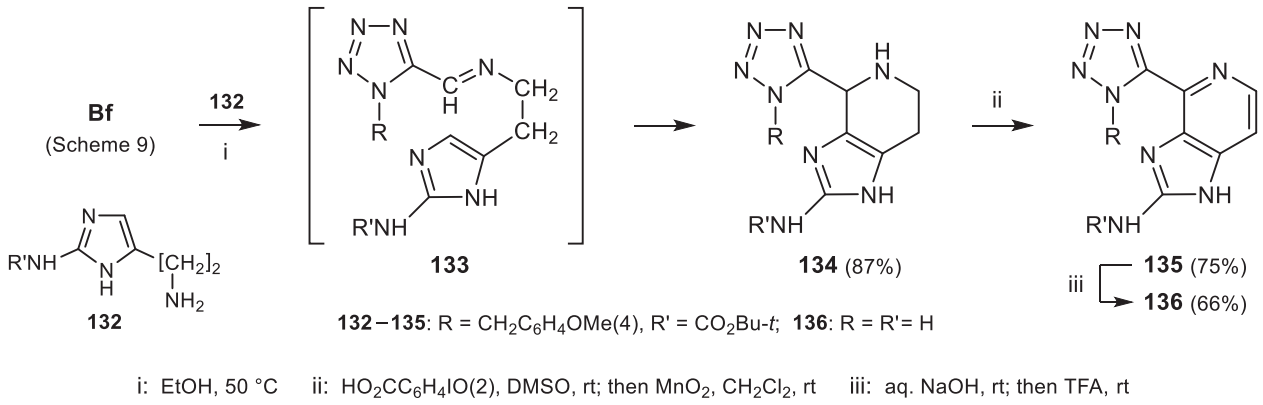


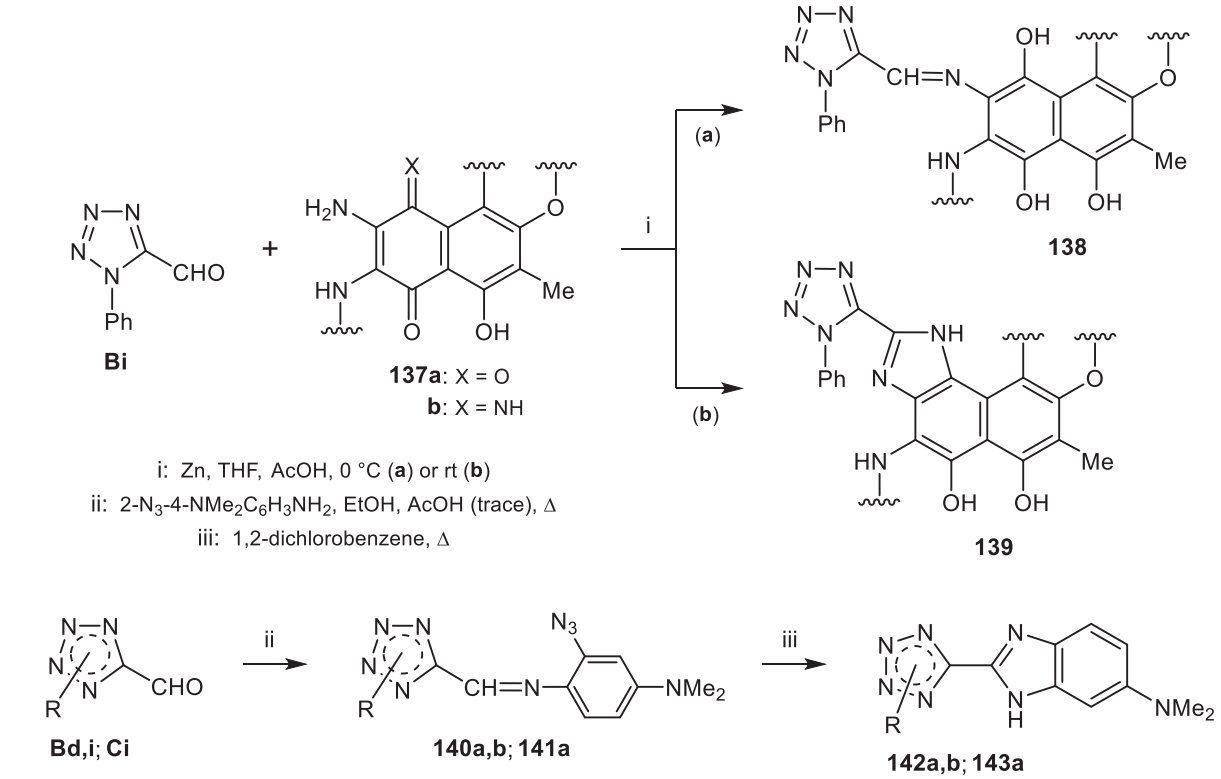
Chart 6. Resonance structures of imines (**126**, **127**) and (**54'f**, **55'f**)

In conjunction with the synthesis of a greater number of azole analogues of ageladine A – a marine alkaloid representing 4-(4,5-dibromopyrrol-2-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-amine with matrix metalloproteinase inhibitory activity – also the tetrazole congener (**136**) has been made (Scheme 28).[55] Key intermediate was the imine (**133**) which underwent intramolecular addition of the imidazole ligand to give the bicycle (**134**). The latter was sequentially dehydrogenated (→ **135**) and deprotected to afford the target compound (**136**).



Scheme 28

Among rifamycin SV antibiotics having an imine function, the tetrazole derivative (**138**) was obtained by a one-pot procedure that includes condensation of **Bi** with 3-aminorifamycin S (**137a**) and quinone reduction of the latter (Scheme 29).[91a,92] Starting from the imino analogue (**137b**), the reaction proceeded further with ring closure to afford the naphthimidazole (**139**).[91b]



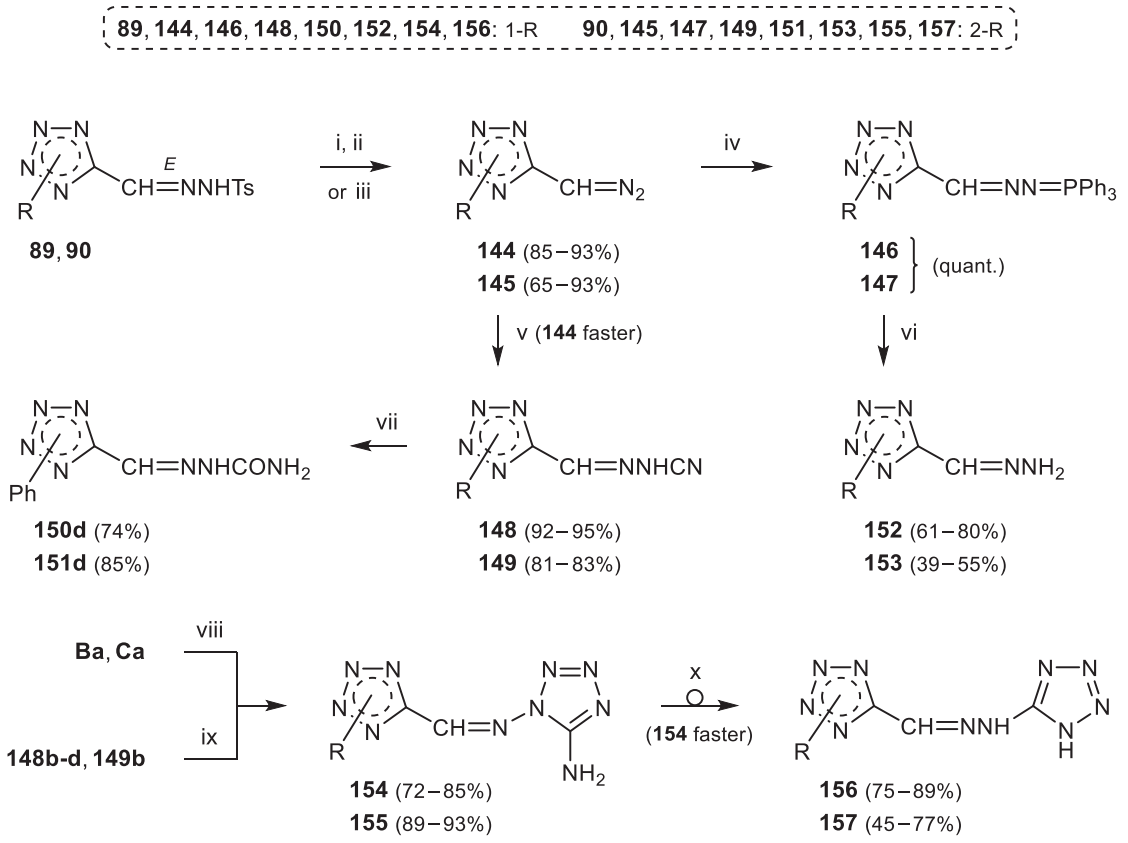
	R	ref.
Bd / **140a** [a] / **142a**	1-*c*-C_6H_{11}	68a
Bi / **140b** [a] / **142b**	1-Ph	68a
Ci / **141a** [a] / **143a**	2-Ph	68a

[a] For preparation from nitrones, *cf.* Scheme 33.

Scheme 29

The principle of cyclizing an ortho-functionalized anil to a fused *N*-unsubstituted imidazole ring occurred also with the 2-azidoanils (**140**) and (**141**): On pyrolysis, the benzimidazoles (**142**) and (**143**) were formed in high yield; diffuse daylight induced the reaction too, albeit slowly.[68a]

(ii) Hydrazones: Perhaps the most important of all hydrazone conversions is the Bamford-Stevens reaction of the derivatives (**89**) and (**90**) which, used as *E* isomers, gave high yields of the (diazomethyl)tetrazoles (**144**) and (**145**)[13d,93] (Scheme 30). Due to the stronger electron withdrawal of the 1*H*-tetrazol-5-yl system



i: aq. Na_2CO_3, Δ ii: aq. Na_2CO_3 / NaOH, Δ iii: NaOMe, $MeO[CH_2]_2OMe$, rt or Δ iv: PPh_3, THF, rt
v: aq. KCN, EtOH, rt, then 3 N H_2SO_4 vi: aq. EtOH, AcOH (trace), Δ vii: EtOH, 12 N HCl, rt
viii: tetrazole-1,5-diamine, TsOH (trace), DMF, rt ix: HN_3 / $CHCl_3$, rt x: xylene, Δ

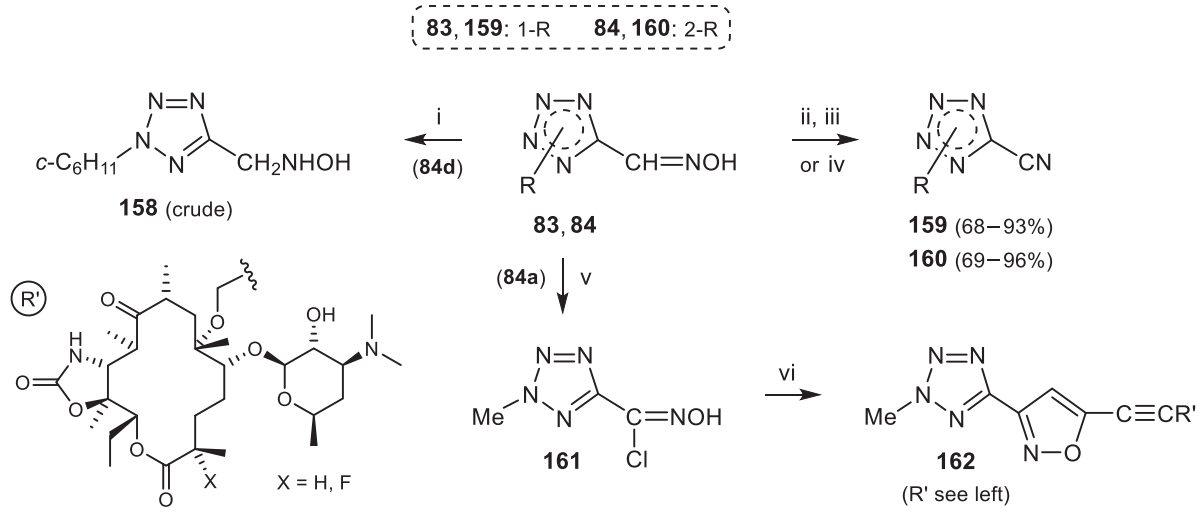
		method / reference													
	R	**144**	**145**	**146**	**147**	**148**	**149**	**150**	**151**	**152**	**153**	**154** [a]	**155**	**156**	**157** [b]
a	Me	ii / 13d	ii / 13d	13d	13d					94	94	viii / 13e	viii / 13e	13e	13e
b	*c*-C_6H_{11}	i / 13d	iii / 13d			13e	13e					ix / 13e	ix / 13e	13e	13e
c	CH_2Ph	i / 13d	iii / 13d			13e						ix / 13e		13e	
d	Ph	i / 13d	i / 13d	94	94	13d	13d	13d	13d	94	94	ix / 13e		13e	
e	4-MeC_6H_4	i / 13d	iii / 13d												
f	4-$NO_2C_6H_4$	i / 13d	i / 13d												

[a] Compound (**154a**) contains ca. 60% hemiaminal. [b] Product (**157b**) represents a mixture of *E* and *Z* isomers.

Scheme 30

deprotonation of **89** occurred more easily. The products (**144**) and (**145**) served as sources for several other aldehyde derivatives: (a) The reaction with triphenylphosphine gave the phosphazines (**146**) and (**147**);[13d] on mild hydrolysis these compounds afforded the unsubstituted hydrazones (**152**) and (**153**)[94] which were difficult to obtain directly. (b) Treatment with potassium cyanide led to the cyanohydrazones (**148**) and (**149**) [then to the semicarbazones (**150d**) and (**151d**)];[13d,e] quite useful appears the sequence (**148** / **149** → **154** / **155** → **156** / **157**) as this route circumvents the delicate synthesis of 5-hydrazinotetrazole otherwise needed for **156** and **157**. – The enhanced rates of the processes (**144** → **148**) and (**154** → **156**) result from the more pronounced electron withdrawal of the 1*H*-tetrazolyl group.

(iii) Oximes: Three reaction modes have been reported (Scheme 31): (a) Reduction to a hydroxylamine, as exemplified by the process (**84d** → **158**);[13b] (b) dehydration to a nitrile – the most frequent mode –, giving

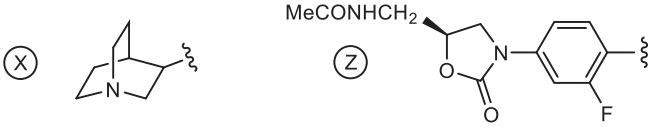


i: $Na[BH_3CN]$, MeOH, pH 3, rt ii: Ac_2O, pyridine, Δ iii: Ac_2O (neat), Δ
iv: PPh_3, CCl_4, MeCN, Δ v: NCS, $\{HCl\}_g$, DMF, < 30 °C vi: NEt_3, HC≡CC≡CR', benzene, rt

R	83, 84	159	160	R	83, 84	159	160
Me	**a**	ii / 13c	ii / 95	Ph	**f**	ii / 13c	ii / 13c
Et	**b**	ii / 13c [a]		4-MeC_6H_4	**g**	ii / 13c	
Bu	**c**	ii / 13c		4-$NO_2C_6H_4$	**h**	ii / 13c [c]	
c-C_6H_{11}	**d**	ii / 68a		(X)	**i** [b]		iii / 57a,b [d]
CH_2Ph	**e**	ii / 13c		(Z)	**j**		iv / 77a

method / reference

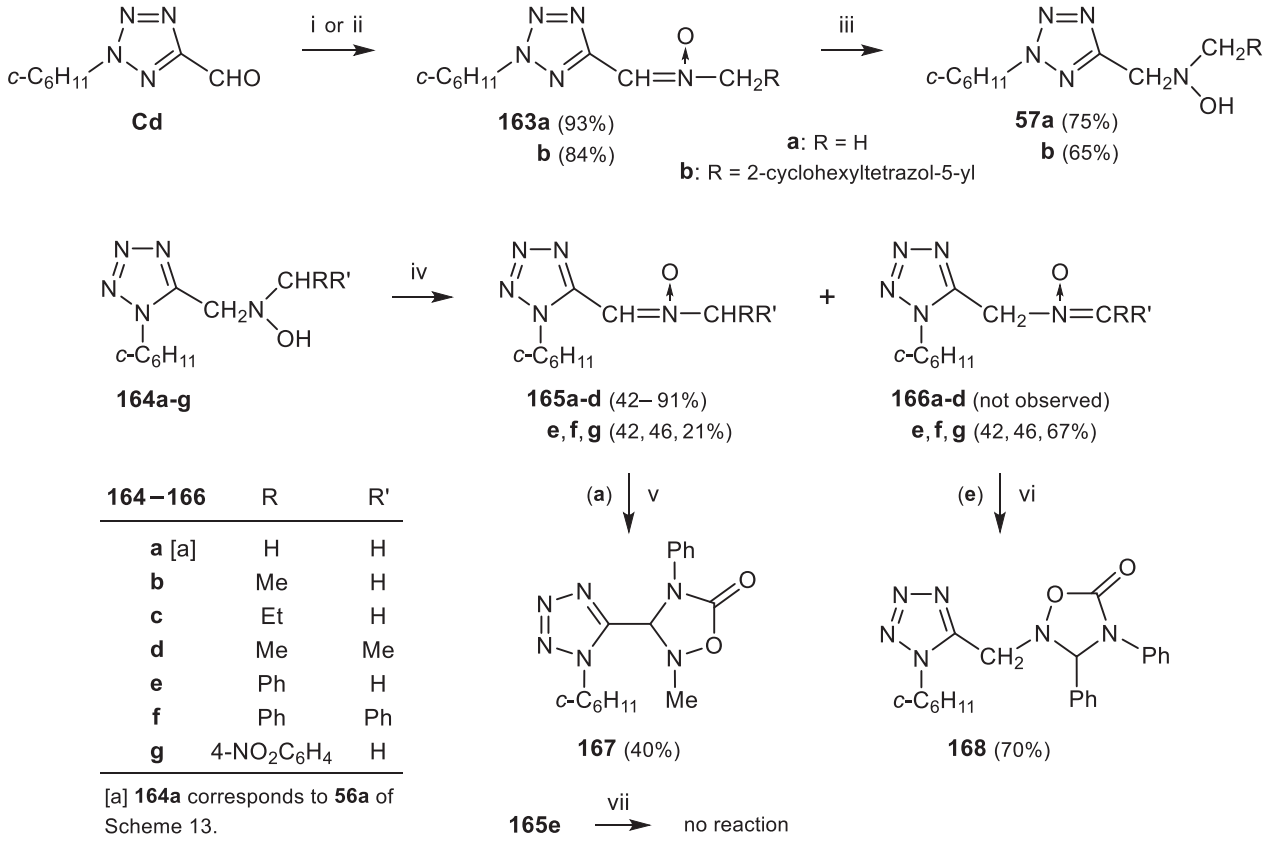
[a] First preparation of this nitrile; material obtained earlier through ethylation of silver 5-cyanotetrazolide and claimed as **159b** represents isomer (**160b**).[96] [b] Oxime (**84i**) corresponds to **40a** of Scheme 9. [c] Side product: 5-acetylcarbamoyl-1-(4-nitrophenyl)tetrazole. [d] One-pot synthesis starting from **39a** of Scheme 9; product crystallized as oxalate salt (overall yield 5.4%).



Scheme 31

fair to excellent yields of **159** and **160**;[13c, 57a,b, 68a, 77a, 95] (c) conversion to a hydroximoyl chloride (**84a** → **161**), which was conducted during the synthesis of erythromycin derivatives with improved gastrointestinal tolerance; in the presence of base, **161** reacted with the appropriate diyne to provide the target (**162**).[58a,b]

(iv) Nitrones: Condensation of aldehydes (**C**) with *N*-alkylhydroxylamines proceeded readily to afford nitrones like **163a,b** (Scheme 32). Hydrogenation of these materials gave the hydroxylamines (**57a,b**),[13b] which received interest as potential imines, just like the isomeric hydroxylamines (**56a,b**) (*cf.* Scheme 13). However, for providing the latter the above sequence (aldehyde → nitrone → hydroxylamine) need not be followed, as these compounds could be obtained directly by the Ugi reaction using cyclohexyl isocyanide,



164–166	R	R'
a [a]	H	H
b	Me	H
c	Et	H
d	Me	Me
e	Ph	H
f	Ph	Ph
g	4-$NO_2C_6H_4$	H

[a] **164a** corresponds to **56a** of Scheme 13.

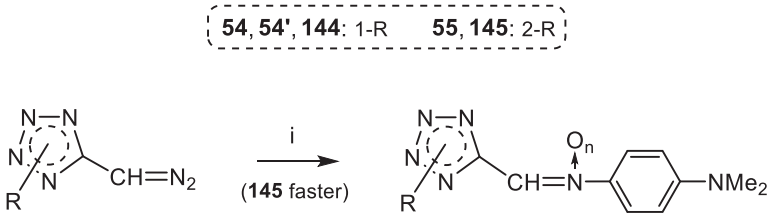
i: $MeNHOH \cdot HCl$, aq. MeOH, K_2CO_3, rt (for **163a**) ii: crude **158** of Scheme 31, MeOH, rt (for **163b**) iii: $LiAlH_4$, ether, Δ
iv: HgO (yellow), Me_2CO, rt v: PhNCO (excess), EtOH, Δ (30 h) vi: PhNCO (1 equiv.), dioxane, Δ
vii: PhNCO (5 equiv.), benzene, Δ (30 h)

Scheme 32

formaldehyde, the appropriate hydroxylamine salt, and sodium azide.[70] In like manner the new derivatives (**164b-g**) were prepared;[70] on treatment with mercury oxide they afforded the nitrones (**165**) and/or (**166**), depending on the CHRR' group of **164**.[97] Thus, in the absence of aromatic substituents, dehydrogenation

led exclusively to tetrazolyl nitrones, *i.e.* to **165a-d**, whereas from **164e-g** nitrones of the type (**166**) were formed in addition, obviously favoured by conjugation. In complementary experiments nitrones of both series were treated with a dipolarophile. But while the type (**166**) reacted smoothly (*e.g.* **166e** → **168**), the isomer **165e** proved to be fully inert, even under forcing conditions. Only its congener (**165a**) could be caused to react (→ **167**), but it had to be treated most drastically.[97]

Nitrones of the type (**54**) and (**55**) arose in the course of the Kröhnke aldehyde synthesis (Scheme 12), but representatives (**55**) having an aliphatic substituent at the tetrazole ring like **55a,b,d,e** could not be isolated. So it is of preparative value that these derivatives were accessible in pure form by another standard route: through conversion of the diazo compounds (**145**) with *N*,*N*-dimethyl-4-nitrosoaniline (Scheme 33).[13d, 94] Since the side chain of **145** is more nucleophilic – a consequence of the less pronounced electronegativity of the 2*H*-tetrazolyl moiety –, the formation of **55** proceeded distinctly faster compared to **54** (with only one exception). There is another advantage of this entry: the nitrones (**55**) did not contain anils – impurities that regularly occur in the 1*H* series (**54'**).



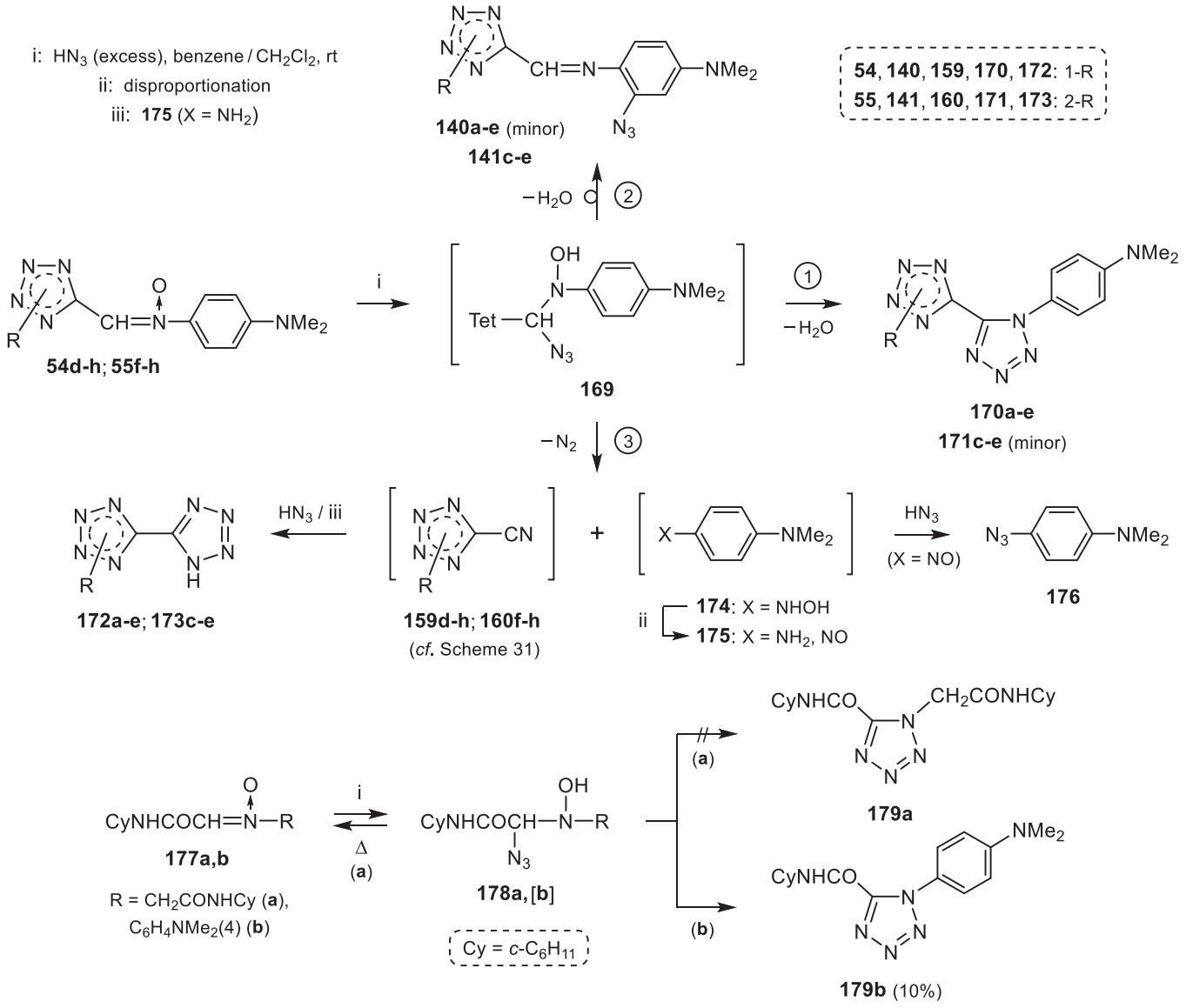
i: 4-$NOC_6H_4NMe_2$, EtOH, rt

			yield (%) / time (d)		
144, 145	R	**54, 54', 55**	**54**	**55**	ref.
a	Me	**a**	72 / 3 [a]	76 / 3	94
b	*c*-C_6H_{11}	**d**	68 / ~20 [a]	71 / 3	94
c	CH_2Ph	**e**	20 / ~20 [a]	73 / 3	13d, 94
d	Ph	**f**	20 / ~20 [a]	72 / 3	94
e	4-MeC_6H_4	**g**	[b] / ~20	57 / 3	94
f	4-$NO_2C_6H_4$	**h**	[c] / ~20	47 / 3	94

[a] Crude product, containing up to 10% **54'**. [b] Mixture, containing 53% **54g**, traces of **54'g**, and 47% **144e**. [c] Mixture, containing ca. 40% **54h** and 60% **144f** (no traces of **54'h**).

Scheme 33

A unique behaviour of the above nitrones was encountered on action of free hydrogen azide in an apolar solvent (sodium azide had no effect) (Scheme 34).[68a] Three competing reaction modes were operative, the extent of which was determined by the tetrazole type:



54, 55	R		yield (%):	140	170	172	141	171	173	ref.
d	*c*-C_6H_{11}	**a**		[a]	61	16				68a
e	CH_2Ph	**b**		[a]	36	32				68a
f	Ph	**c**		[a]	33	23	30	8	37	68a
g	4-MeC_6H_4	**d**		[a]	61	19	[b]	8	30	68a
h	4-$NO_2C_6H_4$	**e**		[a]	62	4	[b]	15	31	68a

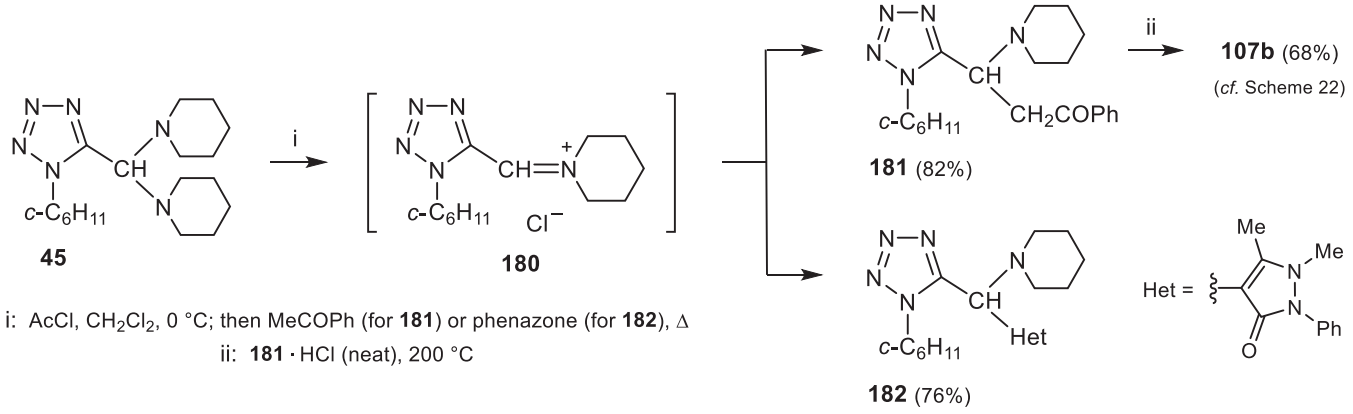
[a] Yield low (exact figure indeterminable). [b] Yield above that of **171** (figure indeterminable).

Scheme 34

(1) Dehydration of the putative intermediate (**169**) led to an imidoyl azide which cyclized to the bitetrazoles (**170**) and (**171**); as proton abstraction from the α carbon atom is facilitated by the stronger electronegativity of the 1*H*-tetrazolyl ligand, the yields of **170** exceeded those of **171**. (2) Transfer of the azido group of **169** to the phenyl ring with extrusion of water afforded azidoanils like **140** and **141**, but here the 2*H* isomers

predominated; this is in line with the behaviour of benzaldehyde nitrones which gave azidoanils rather than tetrazoles.[68b] (3) Cleavage of **169** at the central C–N bond led to the nitriles (**159**) and (**160**) (*cf.* Schmidt fragmentation of aldehydes) along with the hydroxylamine (**174**); however, these species reacted further: **174** disproportionated to **175** (X = NH_2 and NO) with azidation of the nitroso component (→ **176**), whereas **159** and **160** each took up hydrogen azide to afford the bitetrazoles (**172**) and (**173**) – a process that was induced by the amine present (**175**; X = NH_2).[98] Complementary model studies have shown that *N*-phenylnitrones lacking a strong electron-releasing group at C(4) are inert toward hydrogen azide (the methoxy group is still insufficient).[68b] Further, *N*-alkylnitrones having an electron-withdrawing *C*-substituent, such as **177a**, may form a covalent (even isolable) adduct like **178a**;[25,99] however, this material did not afford the corresponding tetrazole (**179a**) but reverted to the starting nitrone – in contrast to the analogue (**178b**) which gave the envisaged product (**179b**) indeed,[68a] although in low yield (because of the moderate electronegativity of the *c*-$C_6H_{11}NHCO$ group[100]).

(v) Aminals: Apart from the role as precursor to the aldehyde (**Bd**) (*cf.* Scheme 10), the aminal (**45**) was employed as a potential iminium species (**180**) (Scheme 35). For example, sequential treatment of **45** with acetyl chloride and acetophenone or phenazone afforded the Mannich bases (**181**) and (**182**) in high yield. Pyrolysis of the hydrochloride salt of **181** opened an alternative route to the aldol condensation product (**107b**) of Scheme 22.[4a]



Scheme 35

CONCLUSION

The preceding sections have illustrated the rich chemistry of tetrazolecarbaldehydes and their derivatives. Besides standard reactions there were quite a number of transformations that took a surprising course. Especially interesting were processes that show to what extent the ring type determines the reactivity of the functional group: As a consequence of the stronger electron-withdrawing influence of the 1*H*-tetrazol-5-yl moiety, substrates (precursors, aldehydes, derivatives) bearing this group underwent certain reactions more

rapidly than their isomers having the 2*H* ring (*cf.* Table 1). In a few cases even a qualitatively divergent behaviour was encountered, *e.g.* towards strong bases. The preparative use of the title aldehydes became widely apparent, none the less in conjunction with the synthesis of bioactive materials.

Table 1. Reactions of 1*H* isomers promoted by electron withdrawal of tetrazole ring [a]

Reaction	Scheme	Reaction	Scheme	Reaction	Scheme
B → 71	15	**54 → 170**	34	**89 → 144**	30
B → 91	17	**58 → 60**	13	**126 → 130**	27
50 → 52	12	**58 → 62**	13	**144 → 148**	30
52 → 54	12	**77 → 91**	17	**154 → 156**	30

[a] Reactions of the respective 2*H* isomers proceed more slowly, require stronger conditions, or take a different course: *cf.* **C → 47** + **92** and **78 → 93** (Scheme 17), **127 → 129** (Scheme 27), and **55 → 141** (Scheme 34).

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