

HETEROCYCLES, Vol. 87, No. 3, 2013, pp. 493 - 526. © 2013 The Japan Institute of Heterocyclic Chemistry
 Received, 5th October, 2012, Accepted, 30th November, 2012, Published online, 7th December, 2012
 DOI: 10.3987/REV-12-755

DIRECT ROUTES TO 2H-TETRAZOLES BY CYCLIZATION AND RING TRANSFORMATION

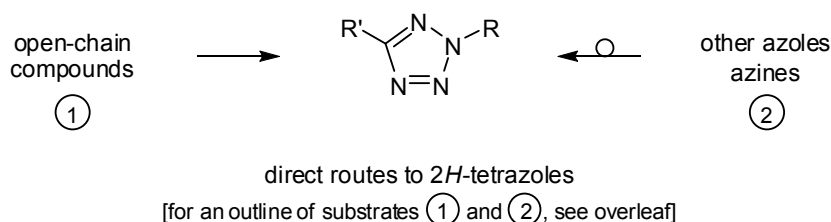
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Abstract – This review summarizes the known routes to the title compounds that were formed from cyclization of open-chain precursors and ring transformation of non-tetrazolic heterocycles, *i.e.* procedures that are *not* based on ring substitution of the corresponding *N*-unsubstituted tetrazoles.

INTRODUCTION

It is well known and has been confirmed by a recent review¹ that the major way of making 2*H*-tetrazoles consists in substitution of the *N*-unsubstituted parents² – a reaction that, in most cases, does not proceed regioselectively and therefore requires separation of isomers. However, a considerable number of title compounds can (or even have to) be prepared directly, *i.e.* (1) by cyclization of open-chain substrates and (2) ring transformation of non-tetrazolic heterocycles (Scheme 1).



Scheme 1

A specific review of these strategies has not been produced till now. Only in a wider context – in general reports on synthesis and properties of 2-aryltetrazoles³ and ring transformations in tetrazole chemistry⁴ – the field has received attention and been treated briefly. The present overview is intended to be more detailed, with the material being organized as outlined in Scheme 2. To provide an integral picture, the historical routes compiled in refs.^{3,4} will be dealt with too.

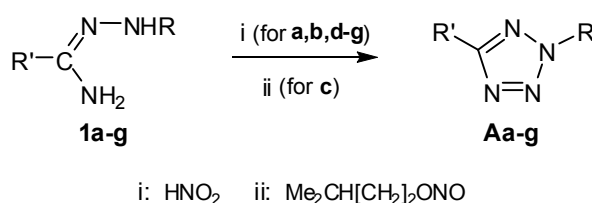
GENERAL

For practical purposes, Scheme 2 shows starting materials rather than intermediates prone to ring closure. Apart from the routes (G), (J), (K), (N), and (O), all approaches are one-pot reactions. Since emphasis is placed on methods, resultant tetrazoles will be signed after the actual procedure; identical products arising from different routes will not be marked as such.

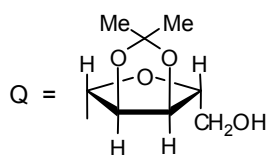
1) CYCLIZATION REACTIONS

A) Amidrazone + Nitrous Acid

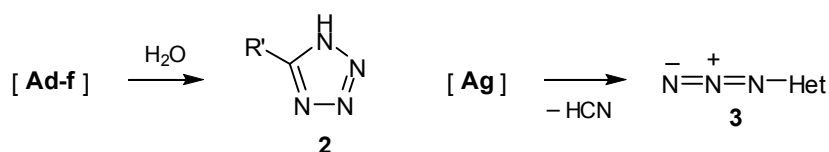
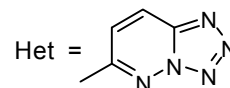
Nitrosation of amidrazones of the type (**1**) has led to the very first tetrazole to be reported, *viz.* the cyano functionalized representative (**Aa**) (Scheme 3).^{5a} Since the precursor (**1a**), which had been obtained from cyanogen and phenylhydrazine, was originally assumed to be phenylated at the adjacent nitrogen, the cyclization product was assigned the isomeric *1H* structure,^{5a} but this error could be corrected soon.^{5b} Later, the preparative procedure (**1a** → **Aa**) was modified: the solid that precipitated on addition of nitrite ion to the acidic solution of **1a** was immediately taken up with an organic solvent like dichloromethane; this also enhanced the yield.^{5c}



1, A	R'	R	yield (%)
a	CN	Ph	50-60, ^{5a} 68 ^{5c}
b	XC ₆ H ₄ [a]	2,4-Br ₂ C ₆ H ₃	[b]
c	CN	Q [c]	57
d [d]	Ph	CHO	95 [e]
e [d]	2-XC ₆ H ₄ [f]	CHO	65, 60, 86, 71 [e]
f [d]	XC ₆ H ₄ [g]	CHO	50, 75 [e]
g	H	Het	



[a] X = H, 3-NO₂. [b] Yield not given. [c] Anomeric form of precursor (**1c**) not specified. [d] Amidrazones (**1d-f**) obtained *in situ* from the respective imidate salt and formohydrazide. [e] Yield pertains to product of deformylation (**2**). [f] X = Cl, Br, I, Ph. [g] X = 3-F, 4-MeO.

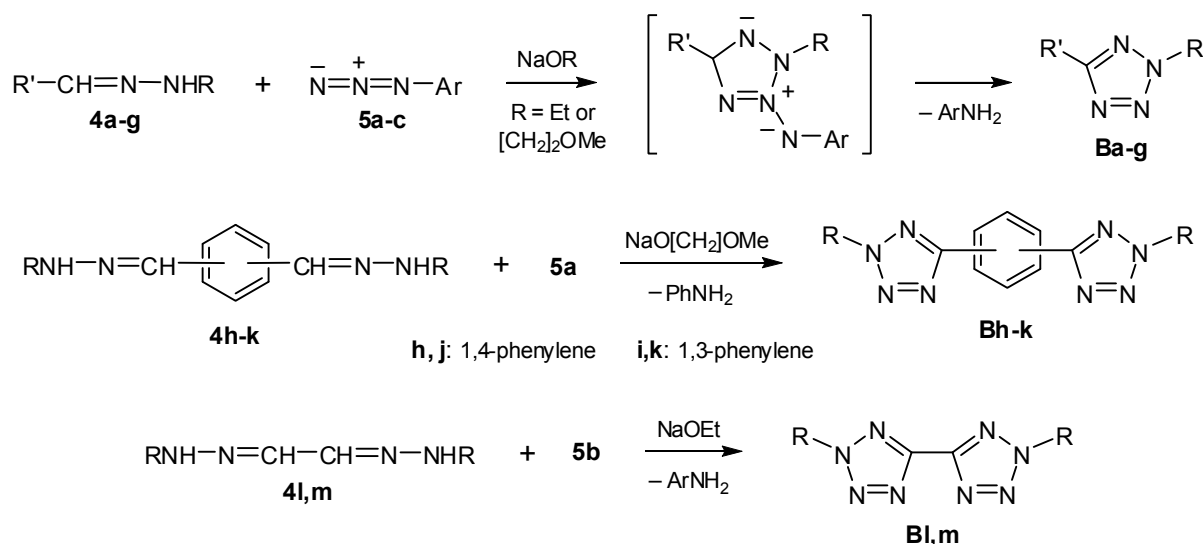


Scheme 3

While the preparation of **Ab** constitutes another early case⁶ of application of this synthesis, more recent examples pertain to tetrazoles like **Ac**⁷ and **Ad-f**.⁸ Regarding the latter, the products are susceptible to hydrolysis; hence, the process was utilized as a convenient route to the *N*-unsubstituted tetrazoles (**2**), and their yields testify to a smooth ring closure.⁸ Finally, also the amidrazonic moiety in compound (**1g**) could be transformed into a tetrazole (**Ag**), but the product was not stable: it expelled hydrogen cyanide to give the azide (**3**).⁹

B) Hydrazone (Anion) + Azide

Not unlike the preceding process, the reaction of the title compounds (**4**) with (**5**) giving tetrazoles (**B**) has already been described in the early literature.^{10a,b} The transformation requires a strong base and has been interpreted as proceeding *via* a linear adduct, but later a [3+2] cycloadduct was postulated as intermediate



4, B	R'	R	5	Ar	yield (%)	(from)
a	Ph	4-MeC ₆ H ₄	a	Ph	45 ¹² / 58 ¹³	(4a + 5a)
b	4-XC ₆ H ₄ [a]	4-XC ₆ H ₄ [b]	b	2,4,6-Br ₃ C ₆ H ₂	35-65	(4b + 5a)
c	4-pyridyl	Ph	c	2,4-(NO ₂) ₂ C ₆ H ₃	81	(4c + 5a)
d	CO ₂ H	4-MeC ₆ H ₄			54	(4d + 5b)
e	CO ₂ H	Ph			80 ¹⁸ /20 ¹⁹	(4e + 5b / 5c)
f	Het [c]	CONH ₂			20 [e]	(4f + 5c)
g	Het [d]	CH ₂ CO ₂ Et			25/23 [e]	(4g + 5c)
h/i		Ph			47 (70)/67 (37) [f]	
j/k		4-XC ₆ H ₄ [g]			85/31 [h]	
l		Ph			82	
m		4-XC ₆ H ₄ [i]			11, 31, 73, 75	

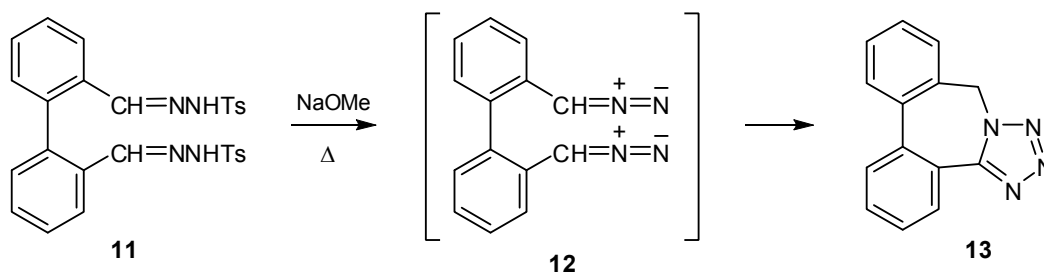
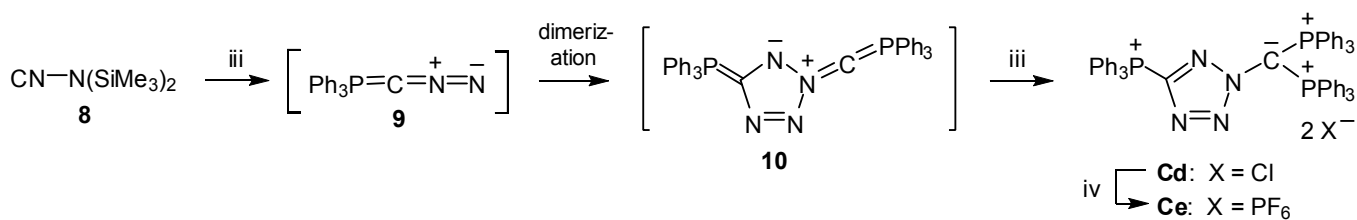
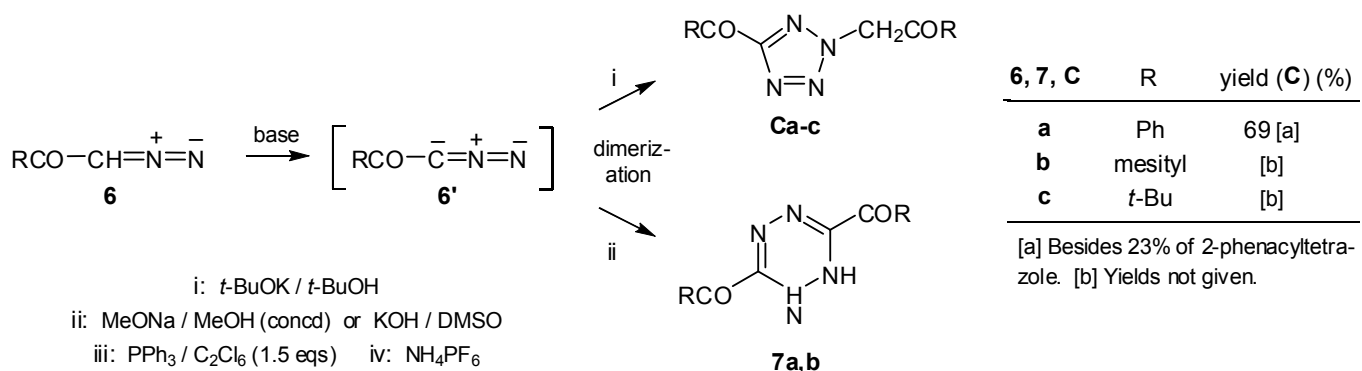
[a] X = Me, MeO, CN. [b] X = Me, MeO, Cl. [c] Het = 5-(4-NO₂C₆H₄)-2-furyl. [d] Het = 5-(4-XC₆H₄)-2-furyl; X = NO₂ / Br. [e] Result questionable (see text). [f] Yields shown in brackets from ref.^{15b} [g] X = Me, MeO, Cl. [h] Yields pertain to X = Cl. [i] X = Me, MeO, Cl, Br.

Scheme 4

(Scheme 4).¹¹ While the older and most of the newer examples for this reaction have been collected in a previous review,³ the list may be complemented by **Ba**^{12,13} and its di-*p*-tolyl analogue,¹³ **Bb**,¹² **Bc**,¹³ **Bd**,¹⁴ **Bh**,^{15a,b} **Bi**,^{15a,b} **Bj** (X = Cl),^{15b} **Bj** (X = Me, MeO),¹⁶ **Bk** (X = Cl),^{15b} **Bk** (X = Me, MeO),¹⁶ and **Bl,m**.¹⁷ Regarding preparation of the carboxylic acid (**Be**),³ two further protocols using the azides (**5b**)¹⁸ and (**5c**)¹⁹ have appeared. Moreover, reactions of **5c** with respective hydrazones were claimed to afford also tetrazoles such as **Be-g** [including derivatives having (i) R' = R = Ph and (ii) R' = 2-furyl or (1-R'')-indol-3-yl, R = Ar; all isolated as salts of hydrochloric acid !].^{19,20} However, for this and other inconsistencies – *e.g.*, authentic **Bg** (Het: X = Br)²¹ melts distinctly lower (*ca.* 130 °C) – the work needs to be revisited.

C) Diazoalkane + Diazoalkane (same or different)

It is known that diazoketones such as (**6a-c**) readily dimerize in the presence of a strong base, and the participation of the anion (**6'**) as an active species is suggested (Scheme 5). The nature of the products depends on the conditions: applying potassium *t*-butoxide–*t*-butyl alcohol, tetrazoles like **Ca-c** were obtained,^{22a} whilst with concentrated methanolic sodium methoxide or potassium hydroxide–DMSO the

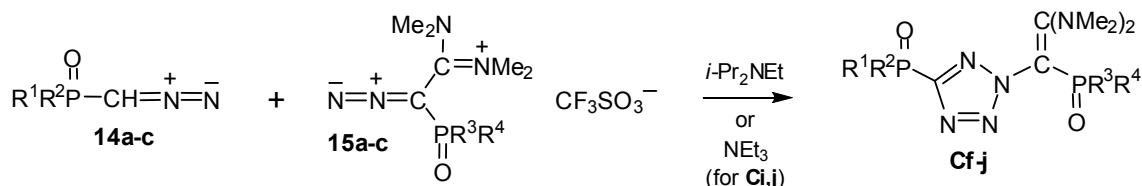


Scheme 5

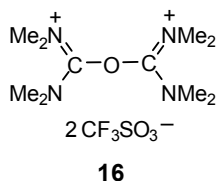
dihydro-*s*-tetrazines (**7a,b**) resulted.^{22b} However, studies with **6a** performed in *dilute* methanolic sodium methoxide gave rise to complex mixtures that were devoid of **Ca** and contained only traces of **7a**.^{22c}

A very interesting process was found to occur when the *N*-isocyanide (**8**) was treated with an excess of triphenylphosphine–hexachloroethane. Attack at the isocyanide carbon and concomitant loss of the silyl groups led to a diazo compound like **9**; dimerization of this putative intermediate gave rise to another transient species (**10**), which took up unconsumed reagent to furnish the final product (**Cd**) in 85% yield. The remarkable structure was established by X-ray diffraction performed with the congener (**Ce**).²³

It should be added that two diazomethyl groups residing at appropriate positions in the same molecule are also capable of 'dimerizing.' This has been encountered with the intermediary biphenyl derivative (**12**) [generated by Bamford-Stevens reaction of the bishydrazone (**11**)], but here such process, evidently, can only lead to a 1*H*-tetrazole (\rightarrow **13**).²⁴



14, 15 C	(from)	R ¹	R ²	R ³	R ⁴	yield (%)
a	f (14a + 15a [a])	OMe	OMe	OMe	OMe	34
b	g (14b + 15b [a])	OMe	Ph	OMe	Ph	37
c	h (14c + 15c [a])	Ph	Ph	Ph	Ph	42
	i (14c + 15a)	Ph	Ph	OMe	OMe	20
	j (14c + 15b)	Ph	Ph	OMe	Ph	21



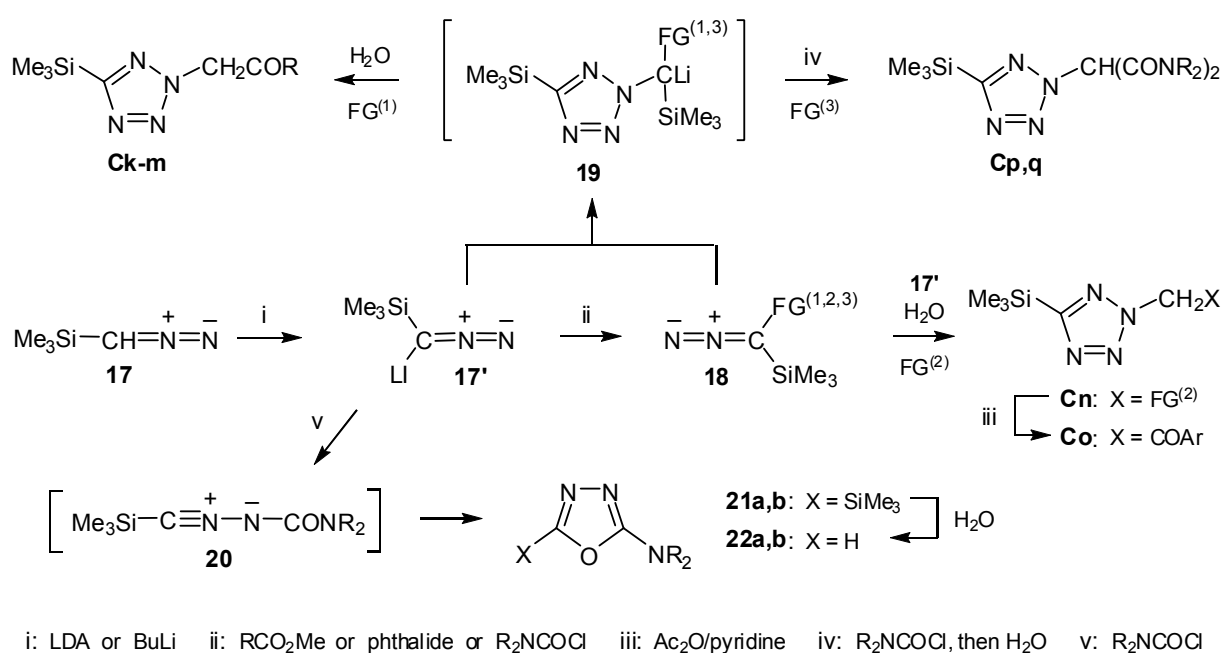
[a] Species (**15**) generated *in situ* from **14** and the ether (**16**).

Scheme 6

Regarding interaction of two *different* diazoalkanes, the first example on record pertains to the synthesis of the conspicuously substituted tetrazoles (**Cf-j**), which were obtained in moderate yield (Scheme 6).²⁵ The formation of these compounds requires the presence of a tertiary amine. For making **Cf-h**, the second reactant (**15**) was simply generated *in situ* by treatment of the respective diazophosphoryl compound (**14**) with 0.5 eq. of the bis(tetramethylamidinio) ether (**16**). Identification of this series of 2*H*-tetrazoles was, *inter alia*, achieved by an X-ray diffraction study of the representative (**Ch**).

A useful preparative method for 2*H*-tetrazoles bearing acylmethyl groups at ring nitrogen (**Ck-m**) has turned out treatment of diazo(trimethylsilyl)methane (**17**) with LDA or butyllithium and a carboxylic ester (*ca.* 0.5 eq.); also phthalide proved reactive, giving the hemiketal (**Cn**) that could be acetylated to the ketone (**Co**) (Scheme 7).^{26,27} The formation of **Ck-m** was understood as follows: after metallation of **17** to **17'** half of the latter species was acylated to **18** (FG⁽¹⁾), which cycloadded across unconsumed **17'** to yield a

transient tetrazole (**19**; FG⁽¹⁾) that led to the final product. Later, this principle served to prepare tetrazoles having dicarbamoylmethyl groups at N(2) like **Cp,q**; of the latter product, X-ray diffraction data exist.²⁸ Yet, the straightforward entry was accompanied by a side reaction: part of **17'** was functionalized at the terminal nitrogen, forming a nitrile imine (**20**) that cyclized to the respective 1,3,4-oxadiazole (**21a,b**) [isolated as the silicon-free derivatives (**22a,b**)]. Comparing the yields of **Cp** and **22a** with those of **Cq** and **22b**, it is apparent that carbamoylating agents having bulkier groups favour this unwanted reaction.



C	R	yield (%)	C 22	R	yield (%)	FG
k	Alk [a]	49-62	o	Ar [c]	[d] (1)	COR
l	Ar [b]	81-90	p / a	Et	27 / 10 (2)	1-hydroxy-1,3-dihydro-2-benzofuran-1-yl
m	3-pyridyl	60	q / b	<i>i</i> -Pr	22 / 32 (3)	CONR ₂

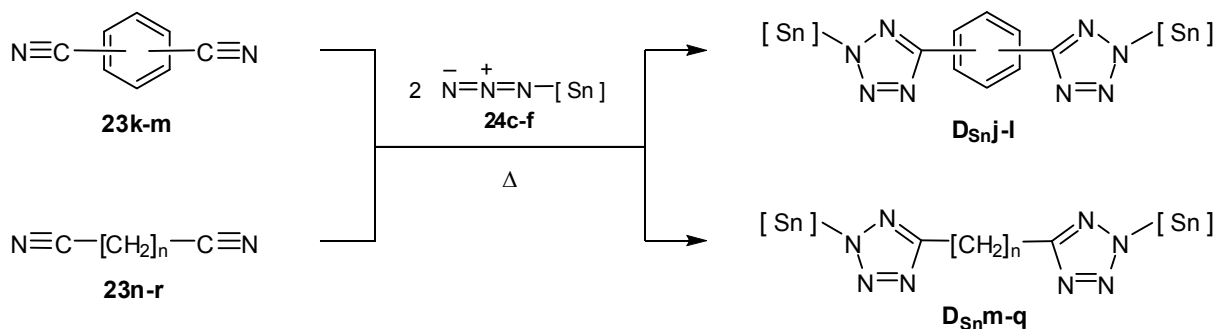
[a] Alk = Et, CH₂Ph. [b] Ar = Ph, 4-Me/Cl/MeOC₆H₄. [c] Ar = 2-AcOCH₂C₆H₄. [d] Yield not reported (yield of **Cn**: 42%).

Scheme 7

D) Nitrile + Azide

As a rule, cycloadditions of organic azides across nitriles do not yield *2H*-tetrazoles, but lead to the *1H*-isomers.²⁹ However, an inverse regioselectivity is observed with silyl and stannyl azides. The first known example constitutes the process (**23a** + **24a** → **D_{Si}a**) (Scheme 8).³⁰ Further, heating trimethylsilyl iodide and sodium azide (1:1) in acetonitrile as a solvent gave the tetrazole (**D_{Si}b**) (small quantity), whilst the same procedure using the silyl iodide (**24b**; I instead of N₃) led to the compound (**D_{Si}c**), the structure of which was determined by X-ray diffraction.³¹ However, the formation of regioisomers, *e.g.* 5-phenyl-³² and 5-(trihalomethyl)-1-(trimethylsilyl)tetrazoles,³³ has been communicated too – findings that, in part, appear

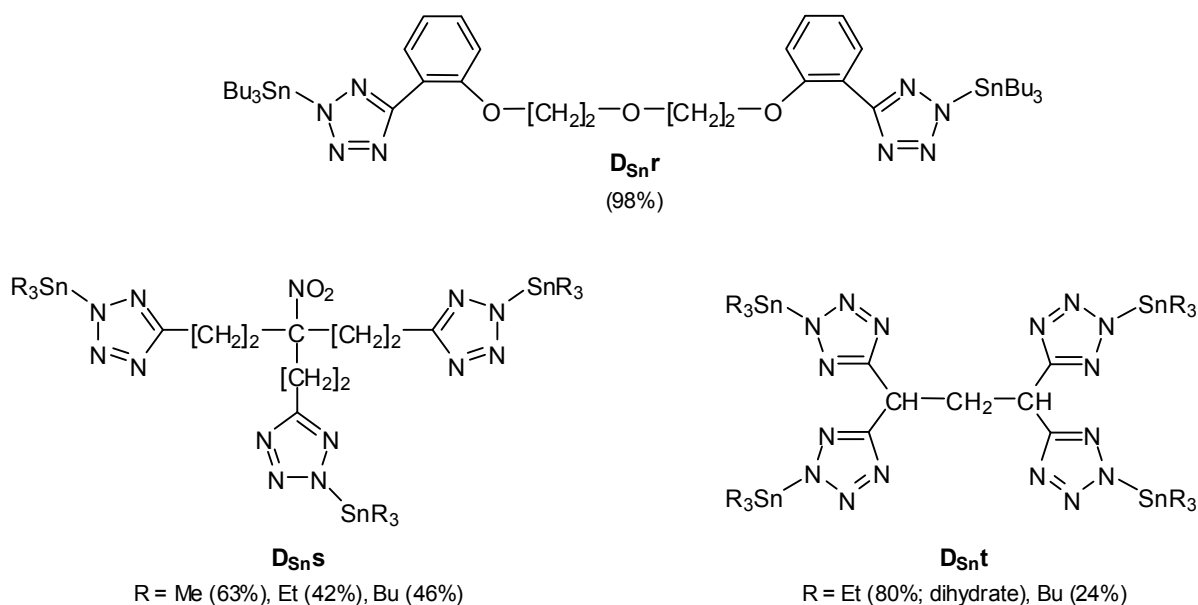
On extending this cycloaddition to substrates having more than one nitrile functions, poly(tetrazoles) were obtained (Scheme 10). Representatives containing two heterocyclic moieties include the phenylene- and alkylene-bridged species (**D_{Snj-l}**)⁴³ and (**D_{Snm-q}**)⁴⁴. An additional, quite remarkable example constitutes the product (**D_{Snr}**).⁴² Tris(tetrazole) derivatives of the type (**D_{Sn s}**) also arose in reasonable yield; the same



23k / D_{Snj} : 1,2-phenylene	23l / D_{Snk} : 1,3-phenylene	23m / D_{Snl} : 1,4-phenylene
23n / D_{Snm} : n = 1	23o / D_{Sn n} : n = 2	23p / D_{Sn o} : n = 4
		23q / D_{Sn p} : n = 5
		23r / D_{Sn q} : n = 6

24	D_{Sn}	[Sn]	yield (%)	(from)	D_{Sn}	[Sn]	yield (%)	(from)
c		SnMe ₃			m_a	SnMe ₃	44	(23n + 24c)
d	j_a	SnBu ₃	60	(23k + 24d)	m_b	SnBu ₃	45	(23n + 24d)
e	j_b	SnEt ₃	63	(23k + 24e)	m_c	Sn(<i>i</i> -Pr) ₃	22	(23n + 24f)
f	j_c	Sn(<i>i</i> -Pr) ₃	48	(23k + 24f)	n	SnBu ₃	65	(23o + 24d)
	k_a	SnBu ₃	77 [a]	(23l + 24d)	o_a	SnBu ₃	58	(23p + 24d)
	k_b	SnEt ₃	68	(23l + 24e)	o_b	SnEt ₃	62	(23p + 24e)
	l_a	SnBu ₃	70	(23m + 24d)	p	SnBu ₃	34	(23q + 24d)
	l_b	Sn(<i>i</i> -Pr) ₃	33	(23m + 24f)	q	SnBu ₃	13	(23r + 24d)

[a] Obtained as a bis(methanol) solvate.



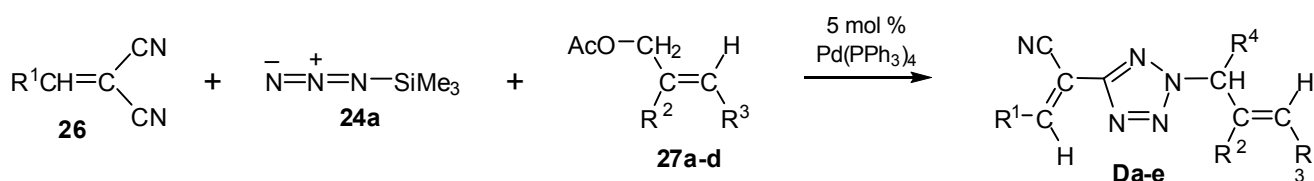
Scheme 10

procedure can be applied to benzene-1,3,5-tricarbonitrile.⁴⁵ Similarly, tetrakis(tetrazole) derivatives such as **D_{Sn}t** were prepared from propane-1,1,3,3-tetracarbonitrile and the corresponding ones were obtained in 30–70% yields from pentane-1,3,3,5-tetracarbonitrile and benzene-1,2,4,5-tetracarbonitrile.⁴⁶

A number of the (triorganostannyl)tetrazoles (**D_{Sn}**) have been studied by X-ray crystallography, such as **D_{Sn}c** (Ar = 2-MeC₆H₄),³⁷ **D_{Sn}i** (Het = 4-pyridyl, [Sn] = SnEt₃),⁴² **D_{Sn}k_a**,⁴³ **D_{Sn}q**,⁴⁴ **D_{Sn}s** (R = Bu),⁴⁵ and, in addition, the tetrakis(tetrazole) obtained from benzene-1,2,4,5-tetracarbonitrile and **24e**.⁴⁶ A prominent feature of these compounds is the propensity to oligomerize – *via* coordination of N(4) of the tetrazole unit(s) – to afford supramolecular structures with a *trans*-trigonal-bipyramidal geometry around tin (*cf.* also refs.^{35b, 40b}).

Finally, it should be mentioned that besides the processes shown in Schemes 8–10 further applications of that mode exist. However, in such cases the *N*-unsubstituted tetrazoles are the proper targets; therefore the respective cycloadducts of the type (**D_{Si}**) or (**D_{Sn}**) were demetallated *in situ* and never isolated.⁴⁷

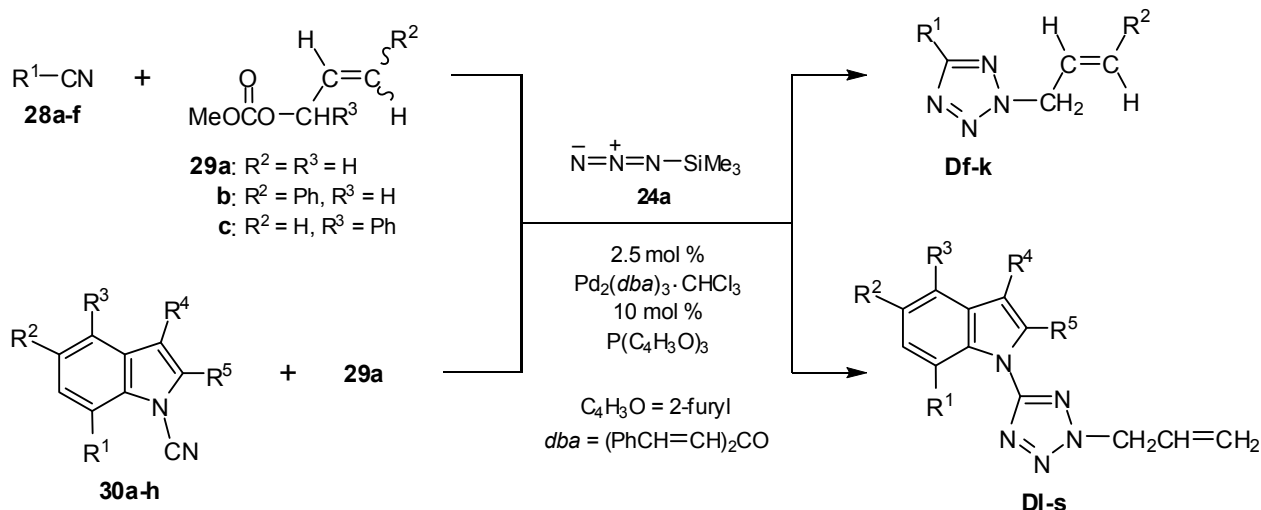
In contrast to the **D_{Si}**-yielding processes shown in Scheme 8, this kind of reaction which was performed in the presence of an allyl acetate and a palladium catalyst gave rise to products that are *carbon*-substituted at N(2) (Scheme 11).⁴⁸ Treatment of the alkylidenemalononitriles (**26**) with the azide (**24a**), the respective alkene (**27**), and a certain amount of tetrakis(triphenylphosphine)palladium(0) afforded the tetrazoles (**Da-e**). Their structure was confirmed by an X-ray study of the derivative (**Da**; R¹ = Ph). Expectedly, isomers were encountered on reacting (*E*)-but-2-enyl acetate (**27b**): besides the tetrazole (**Db**; *E* or *Z*) the 1-methylprop-2-enyl congener (**Dc**) was formed; however, a parallel run with (*E*)-cinnamyl acetate (**27d**)



27	D	R ¹	R ²	R ³	R ⁴	yield (%)	(from)
a	a	[a]	H	H	H	79, 93 [b], 97, 81	(27a)
b	b [c]	Ph	H	Me	H	39	(27b)
	c	Ph	H	H	Me	60	(27b)
c	d	Ph	Me	H	H	99	(27c)
d	e	Ph	H	Ph	H	69 [d]	(27d)

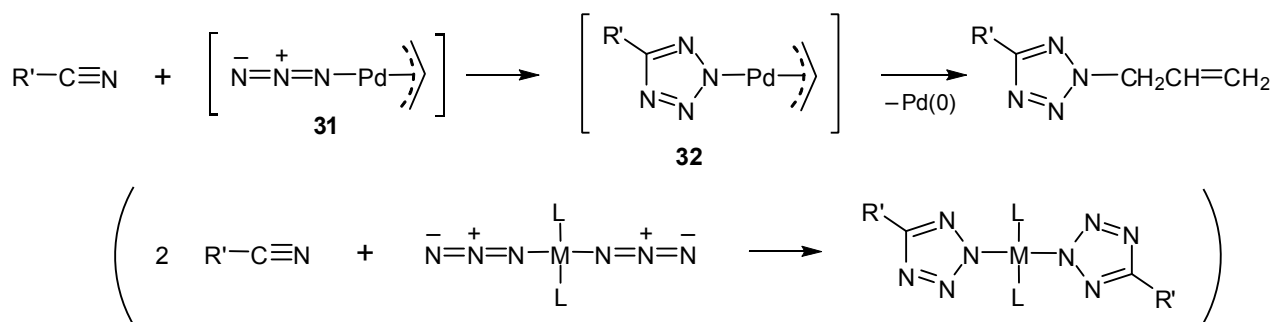
[a] R¹ = *t*-Bu, Ph, 3-MeOC₆H₄, 2-furyl. [b] Applying the conditions of Scheme 12, product (**Da**; R¹ = Ph) was obtained in 68% yield. [c] Using (*E*)-**27b**, product (**Db**) was either *E* or *Z* configured (*cf.* text). [d] Besides 21% of cinnamyl azide.

Scheme 11



28	D	R ¹	R ²	yield (%)	from	30	D	R ¹	R ²	R ³	R ⁴	R ⁵	yield (%)
a	f	R ₂ N [a]	H	52, 77	29a	a	l	H	H	H	H	H	96
b	g	morpholino	Ph	66	b	b	m	Me	H	H	H	H	67
b	g	morpholino	Ph	58	c	c	n	H	[c]	H	H	H	78-99
c	h	Me ₂ C(CN)	H	87	a	d	o	H	H	Me	H	H	81
d	i	Ar [b]	H	40, 72	a	e	p	H	H	H	[d]	H	91, 90
e	j	PhO	H	77	a	f	q	H	H	H	H	[e]	80, 71
f	k	Ts	H	45	a	g	r	H	H	H	[f]	[f]	86, 54
						h	s	H	[g]	H	[g]	[g]	51-75

[a] R₂N = Me₂N, morpholino. [b] Ar = 4-NO₂C₆H₄, 3,5-(NO₂)₂C₆H₃. [c] R² = Me, MeO, CO₂Me, NO₂. [d] R⁴ = Me, CO₂Me.
 [e] R⁵ = Me, Ph. [f] R⁴R⁵ = CH=CHCH=CH; R⁴ = allyl; R⁵ = SiMe₃. [g] R² = MeO, Cl, CF₃, CO₂Me; R⁴ = allyl; R⁵ = SiMe₃.



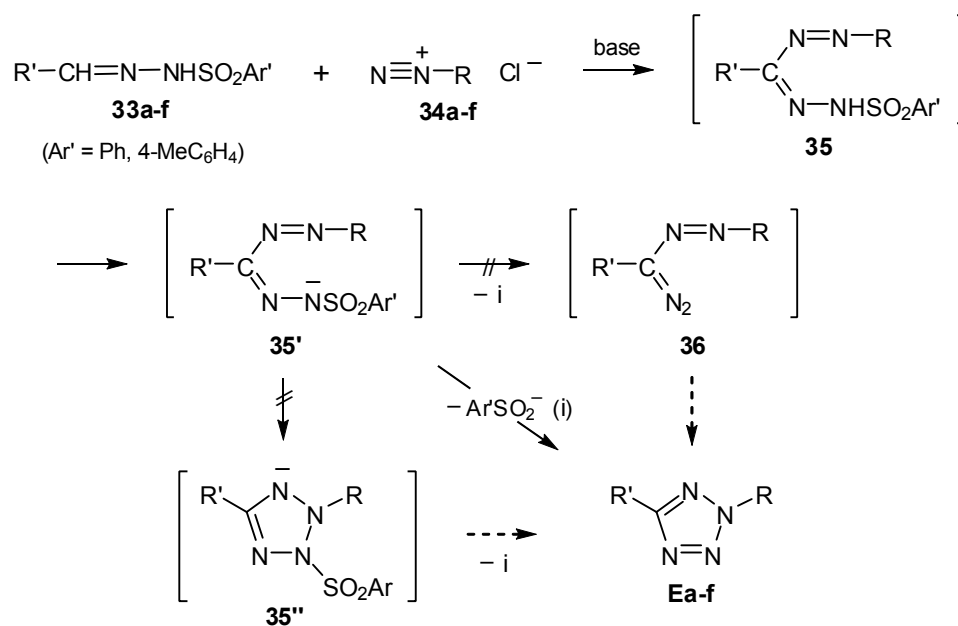
Scheme 12

gave a single tetrazole (**De**), and in place of the phenyl analogue of **Dc** some cinnamyl azide was isolated. This important regiospecific route to 2-allyltetrazoles was in turn applied to make other representatives (Scheme 12).⁴⁹ Using an allyl methyl carbonate (**29**) and a modified palladium catalyst together with a special phosphine, a wider range of cyano substrates (**28**, **30**) could be converted to tetrazoles like **Df-k** and **DI-s**, respectively. Mechanistically, a π -allylpalladium azide complex (**31**) was proposed as the key intermediate; its cycloaddition across the nitrile would generate the species (**32**), which on demetallation would yield the final product. It may be noted that **32** differs by type from the traditional metallotetrazoles

obtained from nitriles and metal-coordinated azides (see process in brackets). Work on this field – a subject considered to fall outside the scope of the present review – has been commenced around 1970⁵⁰ and is in rapid progress:⁵¹ It calls for a specialized account.⁵²

E) Diazonium Ion + Hydrazone

Interaction of the title reagents in the presence of a base constitutes a standard route to formazans. However, treatment of sulfonylhydrazones (**33**) with diazonium salts (**34**) does not afford the expected open-chain compounds (**35**), but leads directly to *2H*-tetrazoles (**E**) (Scheme 13). The process has been discovered in the early 1970s.^{53a} In the ensuing decades it proved successful to such an extent as to gradually displace the classical entry *via* route (B) (Scheme 2). Actually, it is the most frequently used method. Of the plethora of examples reported in the literature, only selected ones such as **Ea-f**, which show the wide scope of the reaction and were obtained in reasonable (often excellent) yields, can be presented here. Since no intermediates could be isolated, it has been speculated whether the product (**E**) arises by a concerted elimination of arenesulfinate ion from the formazanide ion (**35'**) or from the preformed diazo derivative



33, 34, E	R'	R	ref.	33, 34, E	R'	R	ref.
a	Ar [a]	Ar [b]	53-56, 61, 62	d	Het [g]	Het [h]	54, 57
b	Ar [c]	Het [d]	54, 62	e	PhCH=CH	Ar [i]	53b, 59
c	Het [e]	Ar [f]	53b, 54, 57, 58, 60a-c	f	EtO ₂ C	Ar [j]	61

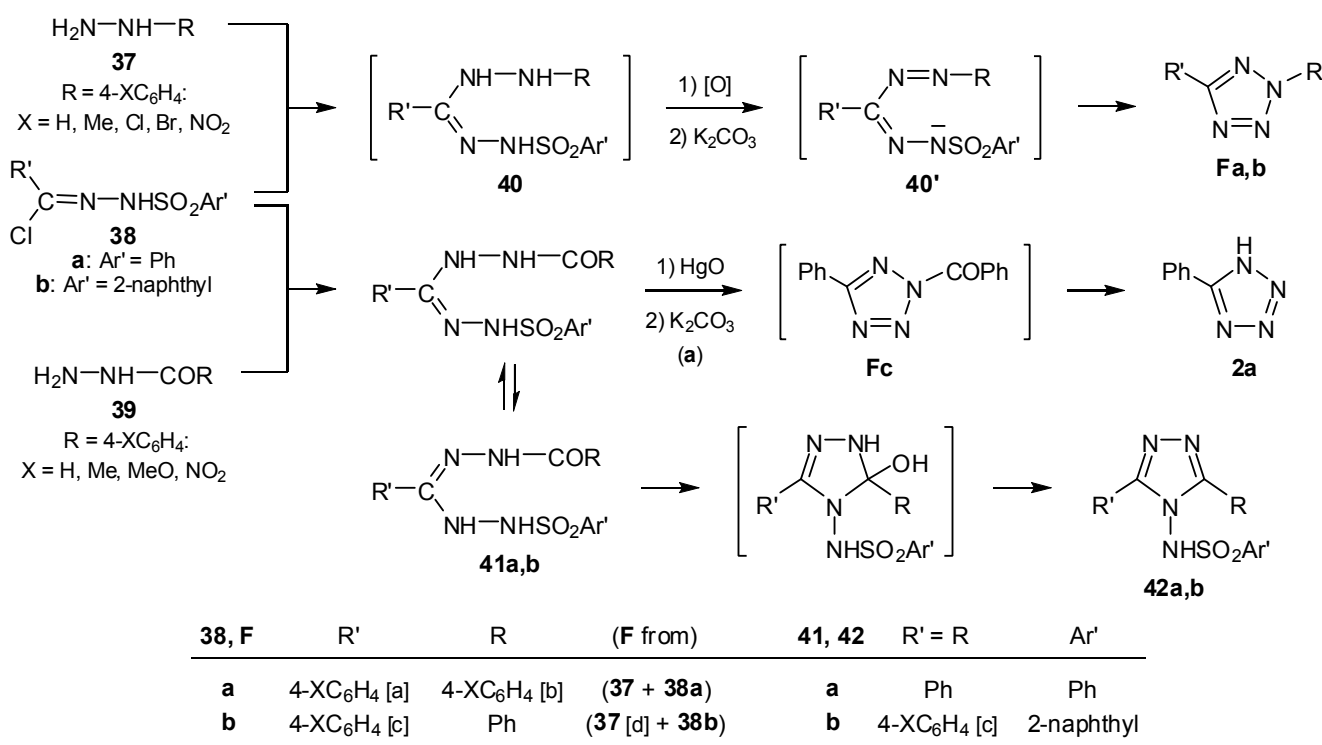
[a] Ar = Ph, 2-/3-/4-XC₆H₄, 3-X-4-YC₆H₃. [b] Ar = Ph, 4-XC₆H₄, 6-X-2-naphthyl. [c] Ar = Ph, 4-XC₆H₄. [d] Het = 3-pyridyl, 4-methyl-2-oxo-2*H*-chromen-7-yl. [e] Het = 2-furyl, 5-X-2-furyl, 2-thienyl, 2-/3-/4-pyridyl, pyrazol-3-yl, imidazol-2-/4-yl, thiazol-2-/4-yl. [f] Ar = Ph, 3-/4-XC₆H₄, 3-X-5-YC₆H₃. [g] Het = 5-X-2-furyl, 3-/4-pyridyl. [h] Het = 3-pyridyl. [i] Ar = Ph, 4-XC₆H₄, 2-X-4-YC₆H₃. [j] Ar = Ph, 4-MeC₆H₄.

Scheme 13

(36). Considering the electronic structure of the species (35') and its potential for cyclization and, in particular, the slower rate of the Bamford-Stevens reaction of α -ylidenesulfonylhydrazones to give pyrazoles,^{53b,54} the first mentioned pathway appeared to be the most probable one. Ring closure of 35' prior to release of the sulfinate ion, *i.e.* the transient formation of a dihydro tetrazolide ion like 35'', was deemed unlikely, too.⁵⁴

F) Hydrazine + Hydrazonoyl Chloride

With respect to the starting materials, this approach can be regarded a counterpart to the preceding route: here *N*-phenylsulfonylarenehydrazonoyl chlorides (38a) were reacted with arylhydrazines (37) to afford tetrazoles like **Fa** in 16–70% yield (Scheme 14).⁶³ Although again no intermediates could be isolated, the overall conversion was understood to proceed as follows: Nucleophilic attack of 37 onto 38a afforded the



[a] $\text{X} = \text{H, Me, Cl, MeO, CN, NO}_2$. [b] $\text{X} = \text{H, Me, Cl, Br, NO}_2$. [c] $\text{X} = \text{H, Me, MeO, NO}_2$. [d] $\text{X} = \text{H}$.

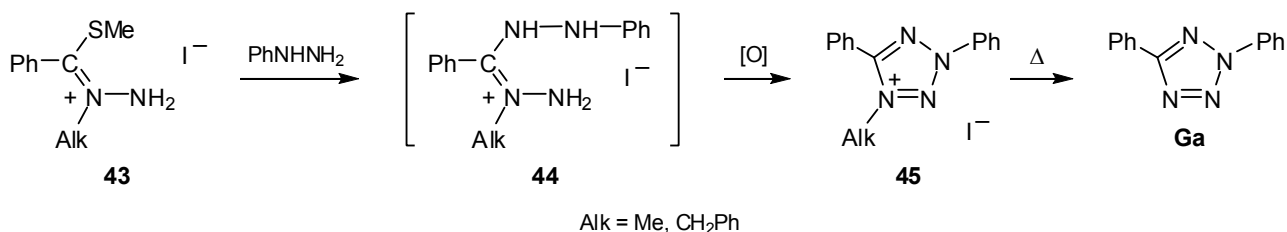
Scheme 14

hydrazidine (40) which, susceptible to air oxidation, was in turn converted into the respective formazan; deprotonation of the latter and ring closure of the resulting 40' (*cf.* above 35' \rightarrow E) led to 2*H*-tetrazole (F). Later, experiments using phenylhydrazine (37: $\text{R} = \text{Ph}$) and the 2-naphthylsulfonyl congeners of 38a gave **Fb** (with $\text{R}' = \text{R} = \text{Ph}$: 50% yield).⁶⁴ An interesting deviation was found on replacing 37 with benzohydrazide (39: $\text{R} = \text{Ph}$):⁶⁵ In contrast to 40, isolation of the hydrazidine (41a) was possible (92% yield); treatment of this compound with mercury(II) oxide and potassium carbonate led to the 2-benzoyltetrazole (Fc) which in

turn was hydrolyzed to **2a** (56%). When the oxidant was absent, **41a** cyclized to a 4-sulfonamido-4,5-dihydro-1*H*-1,2,4-triazole and then was aromatized to **42a** – a process accompanied by the formation of side products, *inter alia* 2,5-diphenyl-1,3,4-oxadiazole and hydrazine derivatives. Without citing that result, the authors of the above tetrazoles (**Fb**) also reported on triazoles (**42**), *viz.* the derivatives (**42b**); the materials were obtained from the respective substrates (**38b**) and (**39**) in 70–90% yield.⁶⁴

G) Hydrazine + Thiohydrazonate (Quaternary Salt)

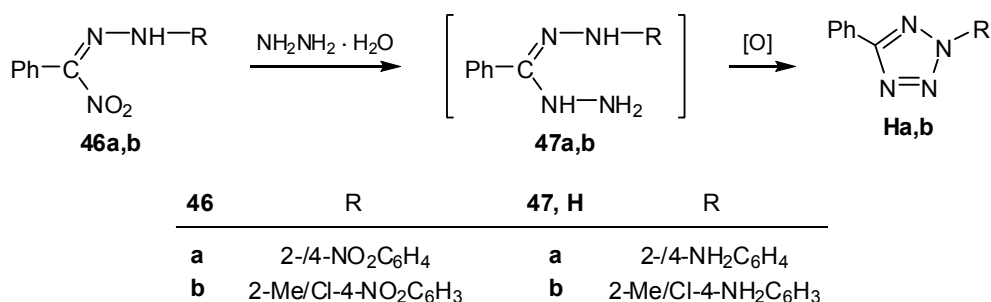
Another route involving a transient hydrazidine starts from thiohydrazonate salts like **43**. Treatment with phenylhydrazine led to the species (**44**) which underwent spontaneous cyclodehydrogenation to afford the 2*H*-tetrazolium salts (**45**) in 64 and 83% yield, respectively (Scheme 15). These products proved rather labile, especially **45** with Alk = CH₂Ph: they were dealkylated on heating to give the target (**Ga**).⁶⁶



Scheme 15

H) α -Nitrohydrazone + Hydrazine

The third approach *via* a labile hydrazidine stage is given by the reaction of α -nitrohydrazones (**46a,b**) with hydrazine hydrate (Scheme 16). The latter component acts in a twofold manner: as a nucleophile it displaces the nitro group at the hydrazonic carbon, and as a reductant it converts the nitro group in the R-substituent into an amino group (\rightarrow **47a,b**).⁶⁷ The final step (\rightarrow **Ha,b**) has been compared with the ring closure of the *linear* adduct originally assumed to have formed from a hydrazone and an aryl azide (*cf.* Section B).¹⁰

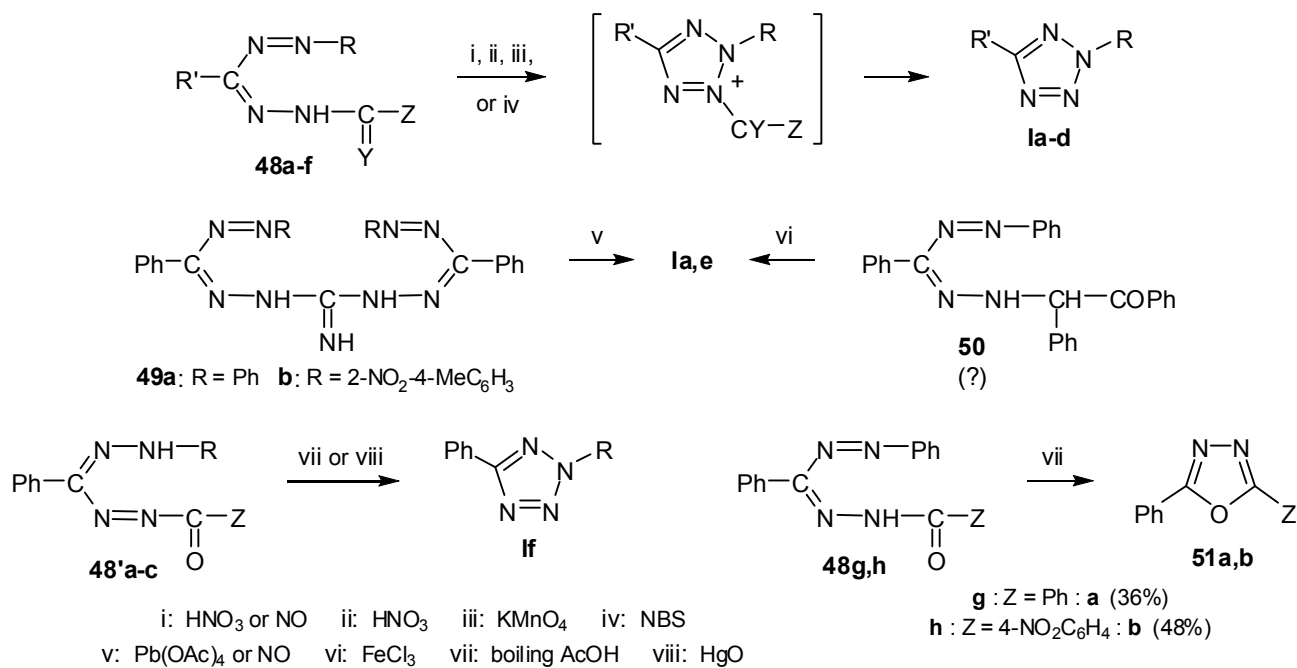


Scheme 16

I) *N*-Acyl-, *N*-Carbamoyl- or *N*-Amidinoformazan + Oxidant

Formazans are well established substances for constructing diverse classes of heterocycles – a topic that has recently been highlighted.⁶⁸ Suitable precursors to 2*H*-tetrazoles are formazans having a functional group at one of the terminal nitrogens which can readily be split off, *viz.* either during the course of ring closure or from the tetrazolium species formed. The starting formazans of both the present and the following section belong to this category.

First experiments in the field date back to the 1890s when treatment of the formazans (**48a,b**) with nitrous and/or nitric acid led directly to the tetrazoles (**Ia,b**) (Scheme 17).⁶⁹ Later, analogous findings resulted from oxidation of **48c** (\rightarrow **Ic**); the reagent is crucial, as the use of bromine produced 3-aryl-6-bromo-*s*-tetrazines.⁷⁰ Also bis(formazans) like **49a,b** underwent this kind of conversion to give **Ia** (100%) and **e**, respectively.⁷¹ Formation of **I** from **48** having $Y = O$ was first encountered during oxidation studies with the carbamoyl



48	48'	R'	R	Y	Z	I	yield (%) / method
a		Ph	Ph	NH	NH ₂	a	[a]/i
b		4-NO ₂ C ₆ H ₄	Ph	NH	NH ₂	b	75/ii
c		4-XC ₆ H ₄ [b]	tetrazol-5-yl	NH	NH ₂	c	70-77/iii
d		Ph	Ph	O	NPh ₂	a	10/iv
e		Ph	Ph	O	NR ¹ R ² [c]	a	[a]/iv
f		2-furyl	Ph	O	NPh ₂	d	[d]/iv
			2-NO ₂ -4-MeC ₆ H ₃			e	[a]/v
	a		4-NO ₂ C ₆ H ₄		Ph	f	42/vii
	b		4-NO ₂ C ₆ H ₄		3-NO ₂ C ₆ H ₄	f	84/vii; 75/viii
	c		4-NO ₂ C ₆ H ₄		4-NO ₂ C ₆ H ₄	f	52/vii; 60/viii

[a] Yield not given. [b] X = H, Cl, NO₂. [c] R¹ = Ph, R² = 2-naphthyl. [d] Small amount, not isolated pure.

Scheme 17

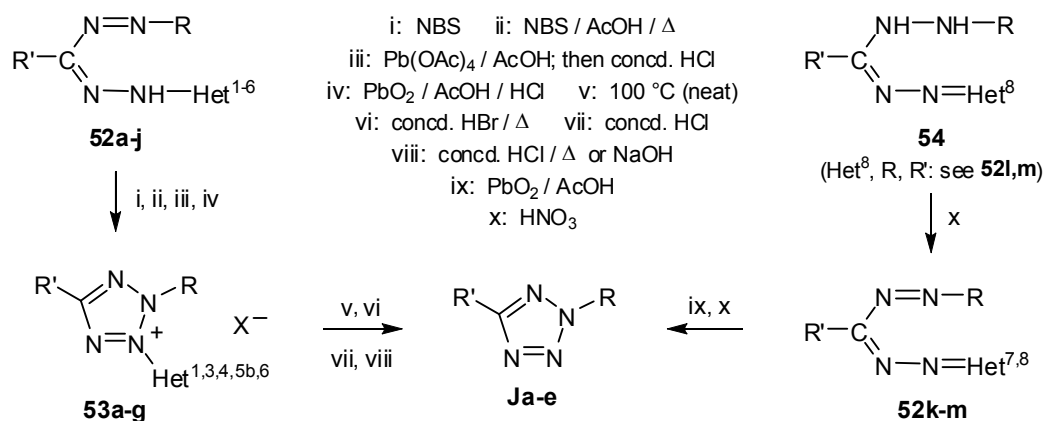
derivatives (**48d-f**); again, the products (**Ia,d**) were obtained directly and the expected tetrazoliums not observed.⁷² Regarding *N*-acyl formazans, transformation into **I** could be achieved in hot acetic acid – obviously an air-assisted process – , but for success the presence of an electron-withdrawing substituent at the other terminal nitrogen in the substrate is necessary.⁷³ Thus, while **48g,h** were cyclized to the oxadiazoles (**51a,b**),⁷⁴ the species having R = 4-NO₂C₆H₄ gave rise to **If**. This divergent behaviour was realized by considering the tautomeric form (**48'**). In a complementary study, **If** was also made by treating **48'b,c** with yellow mercury(II) oxide, but these experiments were not extended to **48g,h**.⁷³

As an excursion to the foregoing, oxidation of a substrate viewed as compound (**50**) should be mentioned here. This material, which resulted from the action of phenylmagnesium bromide on diazodeoxybenzoin, furnished the tetrazole (**Ia**) when treated with aqueous iron(III) chloride.⁷⁵ This scattered result appears worthwhile to be duplicated.

J) *N*-Hetarylformazan + Oxidant

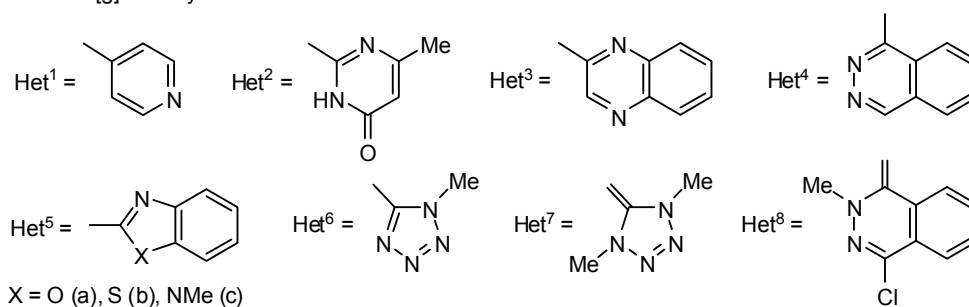
As a source of 2*H*-tetrazoles, the title reaction is lavishly documented in the literature. As apparent from Scheme 18, formazans bearing ten different heterocyclic moieties (including three dihydro systems) have been studied. Isolation of a tetrazole originating from this kind of substrate was first reported in the 1950s and at that time caused surprise: When the product from **52a** and *N*-bromosuccinimide [*i.e.* the tetrazolium salt (**53a**)] was dried *in vacuo* at 100 °C, it decomposed to the tetrazole (**Ja**) and 4-hydroxypyridinium bromide (almost quantitatively within 12 hours).⁷⁶ Later, the high proclivity of **53** to undergo *N*-Het bond fission became notorious. Thus, the pyrimidine congener generated from **52b** eluded isolation and was directly converted into **Jb**; the same behaviour applies to the analogue having Het = 4-methoxy-6-methylpyrimidin-2-yl.⁷⁷ Oxidation of the quinoxalylformazan (**52c**) with lead tetraacetate gave rise to the tetrazolium salt (**53b**) which was not isolated in pure state but directly treated with *ca.* 6 M hydrochloric acid to afford a 1:1 mixture of **Jb** and quinoxalin-2(1*H*)-one.⁷⁸ This conversion has been extended to the phthalazine series, as exemplified by the process (**52d** → **53d** → **Jb**).⁷⁹

Regarding benzazolyl-substituted formazans, derivatives bearing a benzoxazolyl moiety like **52e,f** were directly converted into the tetrazoles (**Jb,c**) when oxidized with *N*-bromosuccinimide.^{80a,b} By contrast, the benzothiazolyl analogues (**52g,h**) gave isolable tetrazolium salts (**53d,e**), but on being treated with boiling hydrobromic acid they were dequaternized to the tetrazoles (**Jb,c**).^{80b} This two-step procedure applies also to the benzimidazolyl and tetrazolyl substrates, as illustrated by the sequences (**52i** → **53f** → **Jd**)⁸¹ and (**52j** → **53g** → **Jb**),⁸² respectively. The latter process, however, could be abridged by treatment of **52j** with an alkaline solution of potassium hexacyanoferrate(III) to furnish **Jb** quantitatively as well; another direct approach to this tetrazole consists in oxidation of the ylideneformazan (**52k**) with lead(IV) oxide in



52	R'	R	Het	53	X	J	method	yield (%) [a]
a	Ph	4-MeC ₆ H ₄	Het ¹	a	Br	a	i; v	nearly 100
b	Ph	Ph	Het ²			b	ii	[b]
c	Ph	Ph	Het ³	b [c]	OAc	b	iii	88
d	Ph	Ph	Het ⁴	c [c]	OAc	b	iii	72
e	Ph	Ph	Het ^{5a}			b	i	[b]
f	Ph	1-/2-naphthyl	Het ^{5a}			c	i	97 [d]
g	Ph	Ph	Het ^{5b}	d	Br	b	i; vi	[b]
h	Ph	1-/2-naphthyl	Het ^{5b}	e	Br	c	i; vi	90 [d]
i	Me	4-XC ₆ H ₄ [e]	Het ^{5c}	f [c]	OAc	d	iii; vii	94 each
j	Ph	Ph	Het ⁶	g	Cl	b	iv; v (or viii)	ca. 100
k	Ph	Ph	Het ⁷			b	ix	99
l	Ph	Ph	Het ⁸			b	x	54 [f]
m	Ph	4-NO ₂ C ₆ H ₄	Het ⁸			e	x	50 [g]

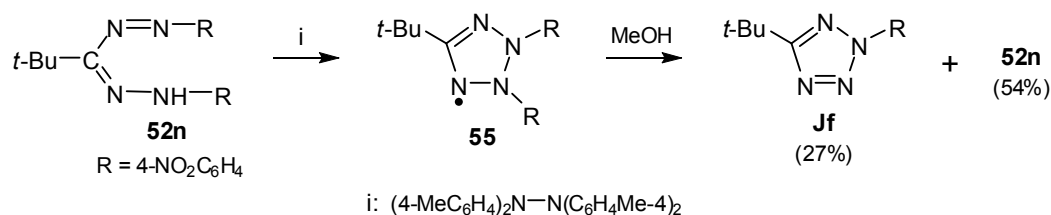
[a] Refers to overall process or, if isolated, to degradation of **53**. [b] Yield not reported. [c] Not isolated. [d] Yield for R = 1-naphthyl; no yield for R = 2-naphthyl. [e] X = H, SO₂NH₂. [f] Directly from **54** besides 20% **52l**. [g] Directly from **54** besides 30% **52m**.



Scheme 18

acetic acid.⁸² Concerning the transformation of ylidenehydrazidines (**54**), these materials gave tetrazoles accompanied by the respective formazans as side products; thus, treatment with nitric acid produced the mixtures (**Jb/52l**) and (**Je/52m**).⁸³

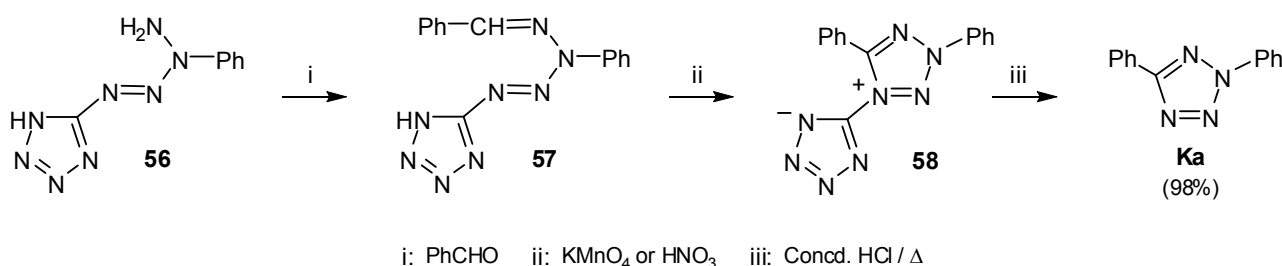
Finally, two loosely related processes are added: (i) the oxidative degradation of 3-(4-hydroxyphenyl)-2,5-diphenyl-2*H*-tetrazolium chloride to **Jb**,⁸⁴ and (ii) the rapid decomposition of the tetrazolinyl radical (**55**) to **Jf** and the formazan (**52n**) on exposure to methanol; species (**55**) – the first tetrazolinyl to be isolated in crystalline state – was obtained from **52n** almost quantitatively (Scheme 19).⁸⁵



Scheme 19

K) Ylidenetetrazene + Oxidant

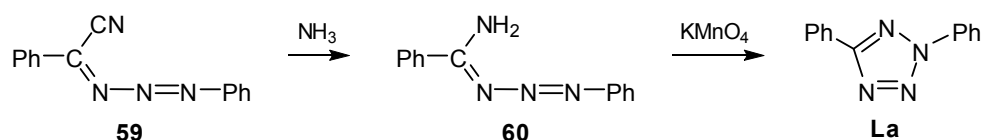
Direct precursors to 2*H*-tetrazoles are not only tetrazolium salts of the series (**53**), but the 4-substituted congeners having an appropriate leaving group at this position should also possess this potential. Indeed, when the substrate (**58**) – obtained from the tetrazene (**57**) – was heated with concentrated hydrochloric acid, the unit at N(4) was split off as 1*H*-tetrazol-5(4*H*)-one to leave 2,5-diphenyltetrazole (**Ka**) in high yield (Scheme 20).⁸⁶ While the sequence (**57** → **58** → **Ka**) seemed reasonable, the formation of **57** from **56** was not self-evident, as the reaction of a 1,3-diaryltetrazene with an aromatic aldehyde was known to give a formazan (*via* rearrangement).⁸⁷ Thus, the condensation with benzaldehyde might have produced a derivative (**52**: R' = R = Ph, Het = tetrazol-5-yl), but this possibility could easily be excluded, because an authentic sample of that formazan had earlier been shown to give an oxidation product of the type (**53**).⁸⁸



Scheme 20

L) (α-Aminoalkylidene)triazene + Oxidant

A new kind of oxidative cyclization leading to a 2*H*-tetrazole was reported in conjunction with studies on the behaviour of the (α-cyanobenzylidene)triazene (**59**) towards nucleophiles (Scheme 21). When this compound was treated with ammonia, the product (**60**) (or a tautomer) resulted. To prove above conversion, this material (**60**) was exposed to potassium permanganate in hot aqueous alkali to form the corresponding tetrazole (**La**) (crude yield: 8%).⁸⁹

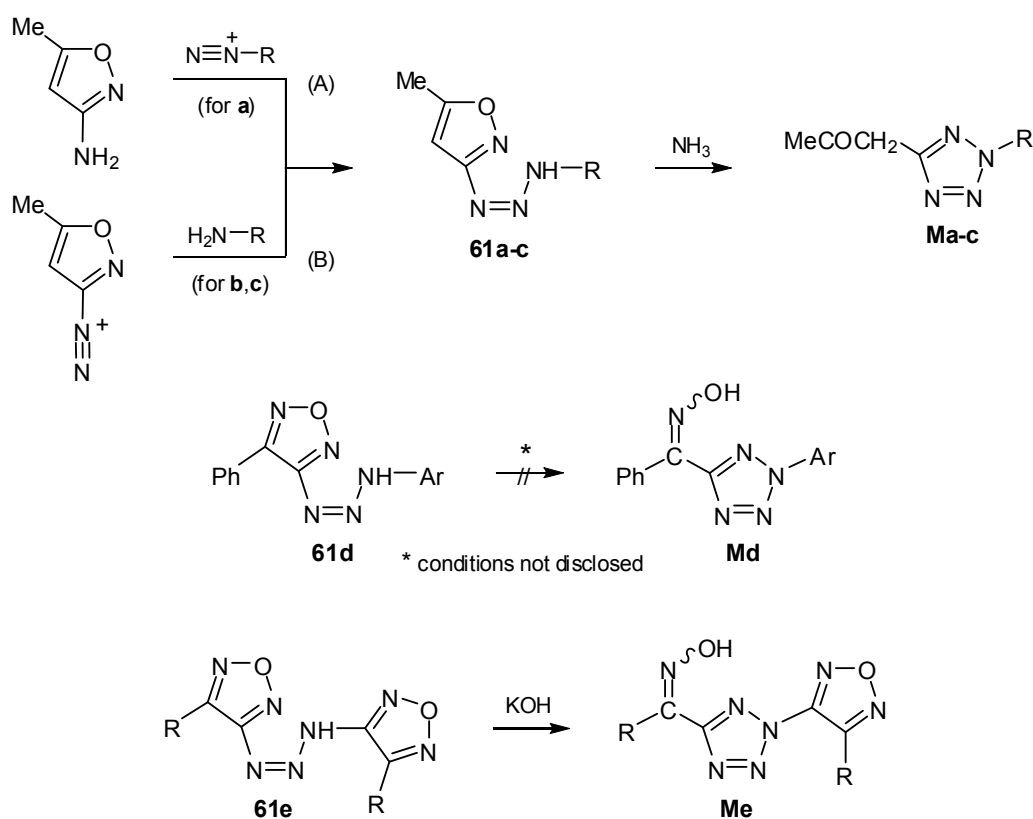


Scheme 21

2) RING TRANSFORMATIONS

M) 3-Triazeno-isoxazole and -1,2,5-oxadiazole

Azoles having an =N–O– unit are widely used as a source for other heterocycles with functional groups originating in the substrates.⁹⁰ According to this principle isoxazole derivatives (**61a-c**) smoothly gave 5-acetyltetrazoles like **Ma-c** on treatment with a base (Scheme 22).^{91,92} While the conditions for causing this rearrangement proved effective to all of the triazenes (**61**), their synthesis required different preparative



61, M	R	yield (%)
a	3-/4-NO ₂ C ₆ H ₄	94.5/56
b	Ph	57
c	5-Me-isoxazol-3-yl	81
e	Me/NH ₂	86/74

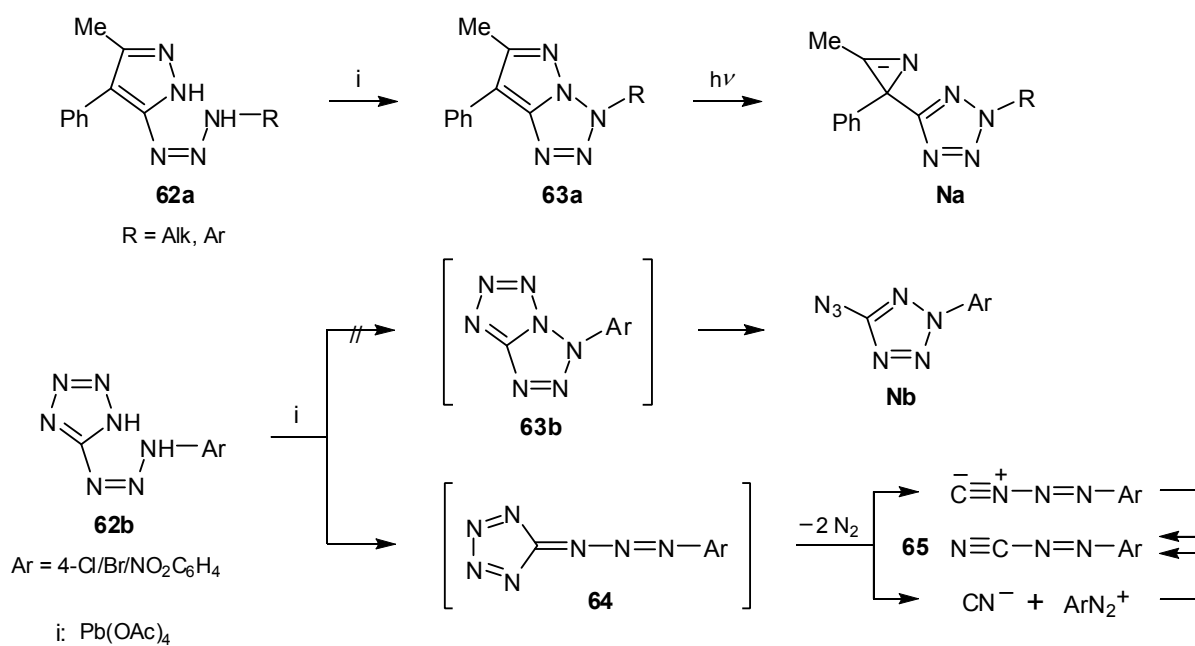
Scheme 22

modes, depending on the R ligand. Thus, the nitrophenyl derivatives (**61a**) were accessible *via* coupling of the isoxazolamine with the respective arenediazonium ion [mode (A)],⁹¹ but application of this mode for making **61b** gave 1,3-diphenyltriazene instead; here, only the inverse protocol (B) was successful.⁹² Regarding **61c**, this derivative resulted directly on diazotization of the starting amine.⁹¹

Efforts to achieve the analogous transformation with the triazeno-1,2,5-oxadiazole (**61d**) were reported to be fruitless.⁹³ Since the substrate (**61d**) bears the same side chain as occurring in **61a-c**, the failure to form **Md** illustrates the lower reactivity of the starting ring with respect to the isoxazole – a gradation that has been generalized some time later.^{90b} Yet, in contrast to the foregoing trial, the derivatives (**61e**) having an oxadiazolyltriazeno side chain could be caused to undergo the ring transformation very readily (\rightarrow **Me**).⁹⁴

N) 5-Triazeno-1*H*-pyrazole and -1*H*-tetrazole

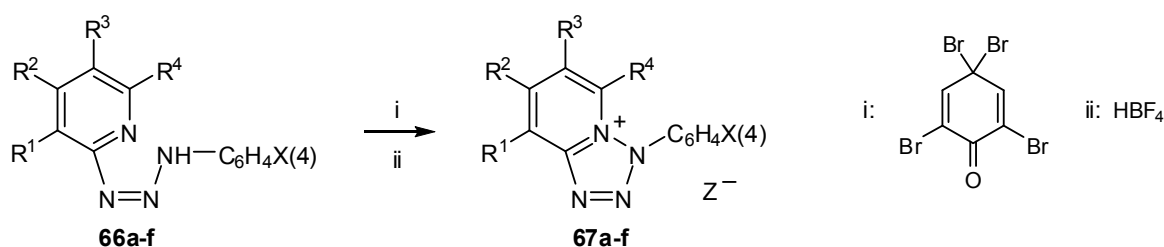
Substrates in which the =N–O– moiety of **61a-c** is replaced with an =N–NH– unit can yield azapentalenes on treatment with an oxidant. Thus, from the pyrazoles (**62a**) the fused tetrazoles (**63a**) resulted (Scheme 23).⁹⁵ When these materials were irradiated in dichloromethane, the original pyrazole underwent N–N bond scission to produce the 5-(2*H*-azirin-2-yl)tetrazoles (**Na**).⁹⁶



In view of the above step (**62a** \rightarrow **63a**) one has speculated that oxidation of the tetrazole analogue (**62b**) should generate the system (**63b**) and, since such an azapentalene is higher in energy than its open-chain isomer, expected that the bicycle once formed should ring-open to the azidotetrazole (**Nb**).^{97,98} However, the related experiments showed that the process (**62b** \rightarrow **63b** \rightarrow **Nb**) did not occur, nor could the conceivable alternative, *i.e.* the linear coupling of two molecules of **62b** giving a hexazene, be observed. Rather, the oxidant produced the tetra-azafulvene (**64**) which after elimination of molecular nitrogen gave the diazocyanide (**65**) as the final product.⁹⁷ This species might have formed *via* a transient *N*-isocyanide⁹⁹ or by combination of an arenediazonium ion and cyanide ion as additional fragments of **64**.⁹⁷

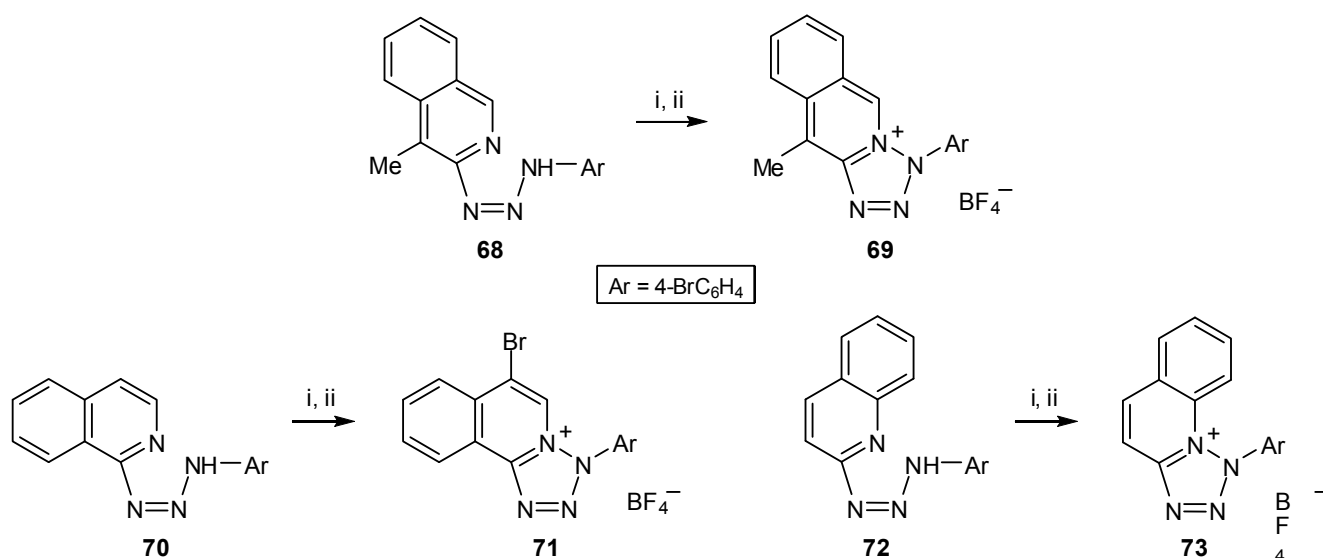
O) 2-/3-Triazeno-pyridine, -quinoline, and -isoquinoline

An important entry to 2*H*-tetrazoles bearing a diene functionality at C(5) has turned out the two-step procedure consisting of (i) oxidative ring closure of 2-triazenopyridines (or appropriate benzologues) to tetrazoloaziniums and (ii) cleavage of the latter with a nucleophile. While step (i) became known already in the mid 1960s,¹⁰⁰ the crucial ring opening was first described in the early 1970s¹⁰¹ and then studied consecutively over three decades.^{102–110} The access to the tetrazoloaziniums is illustrated by Scheme 24. Oxidation of the triazenes (**66a-f**) with 2,4,4,6-tetrabromocyclohexa-2,5-dienone gave the salts (**67a-f**) in good yield.¹¹¹ In a like manner the benzologues (**69**),¹⁰⁵ (**71**),¹⁰² and (**73**)¹⁰² were prepared from **68**, **70**, and **72**, respectively. In the case of **70**, ring closure was accompanied by bromination of the isoquinoline moiety. The salts (**69**; Br in place of BF₄), (**71**), and (**73**) were obtained in 61, 72, and 79% yield.



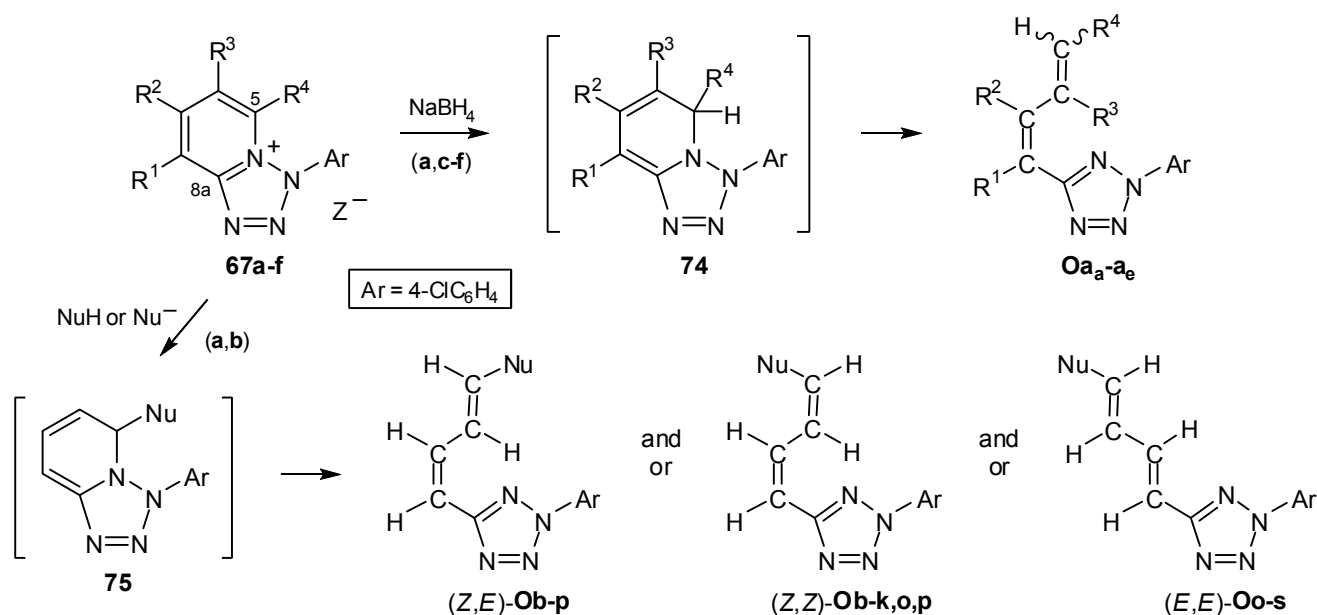
66, 67	R ¹	R ²	R ³	R ⁴	X	Z	yield (%)	ref.
a	H	H	H	H	H/MeO/Cl/Br	Br	77-89	100–102
b	H	H	H	H	F/Cl/ <i>i</i> -Pr/CO ₂ Et	BF ₄	46 [a]	103 [a], 104 [b]
c	Me	H	H	H	Cl	Br	76	101,102
d	H	Me	H	H	Cl	Br	81	101,102
e	H	H	Me	H	Cl	Br	78	101,102
f	H	H	H	Me	Cl	Br	61	101,102

[a] For X = CO₂Et. [b] For X = F/Cl/*i*-Pr (yields not reported).



Scheme 24

In principle, nucleophilic attack to the tetrazolopyridiniums (**67**) can occur at C(5) or C(8a); both modes were observed, with 2*H*-tetrazoles (**O**) arising by the former, *i.e.* via intermediates like **74** or **75**. Whilst the



O	R ¹	R ²	R ³	R ⁴	yield (%)
a_a	H	H	H	H	74
a_b	Me	H	H	H	68
a_c	H	Me	H	H	80
a_d	H	H	Me	H	34
a_e	H	H	H	Me	50 [a]

[a] Mixture of *Z,E* and *Z,Z* isomers.

O	Nu	from free amine in	yield (%): <i>E,E</i>
o [a]	morpholino	MeOH	61 [a]
p [b]	NMe ₂	MeCN	75
q	NEt ₂	MeCN	70
r	piperidino	MeCN	76
s	pyrrolidin-1-yl	MeCN	80

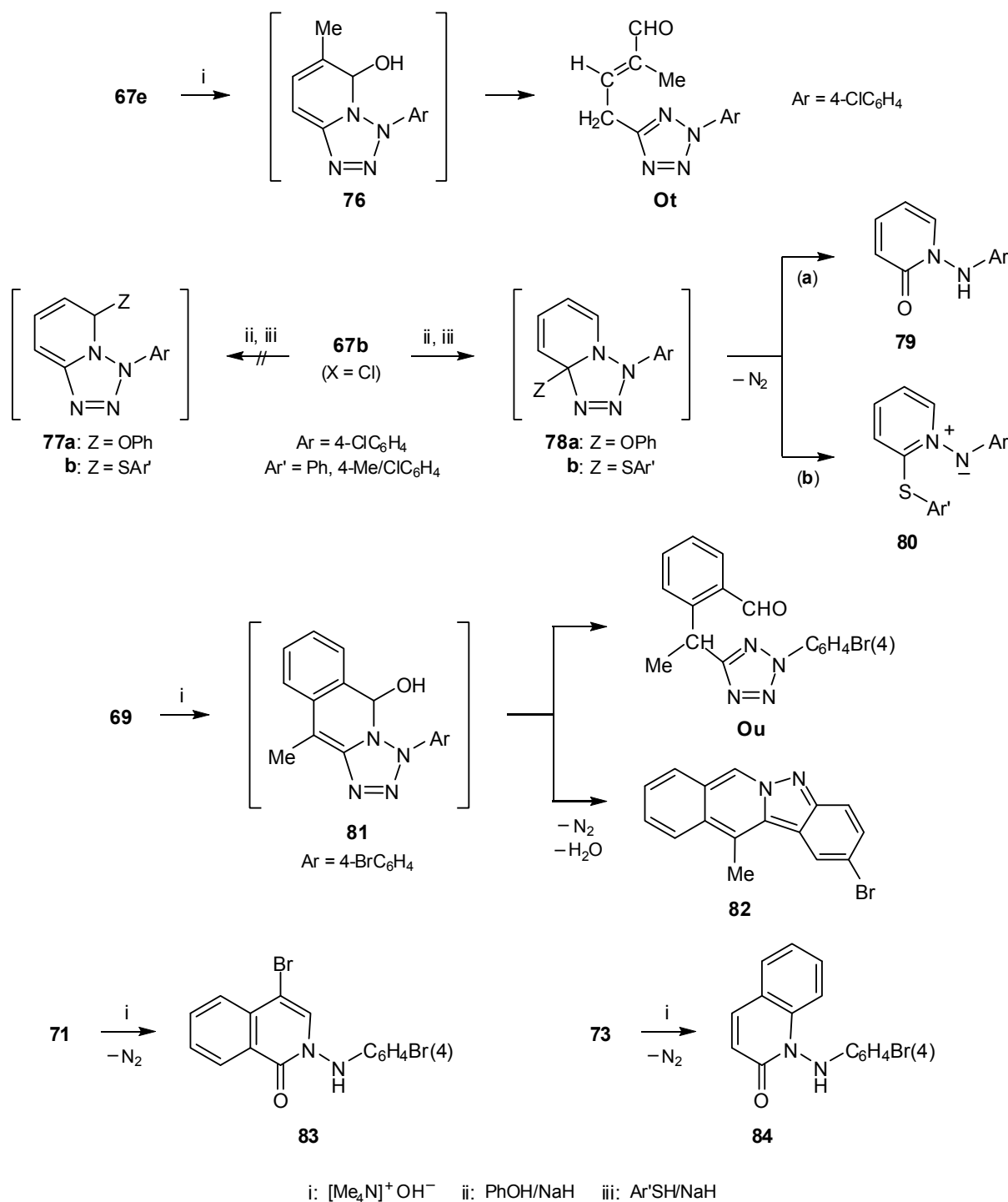
[a] Ref.¹⁰¹; with Ar = Ph and 4-MeOC₆H₄: 56 and 53%. [b] Ref.¹⁰⁸

O	Nu	from	ratio: <i>Z,E/Z,Z</i>	yield (%): <i>Z,E/Z,Z</i>
b	OMe	NuH + NaH	38/62	12/38 [a]
c	OEt	NuH + NaH	60/40	12/34
d	OPr- <i>i</i>	NuH + NaH	95/5	75/5
e	OBu- <i>t</i>	NuH + NaH	100/0	79/0
f	OCH ₂ CF ₃	NuH + NaH	20/80	21 [b,c]
g	CN	[NBu ₄]CN	8/92	15/67
h [d]	Me	MeMgI		56 [c]
i	D	NaBD ₄		65 [c]
j	aziridin-1-yl	NuH in MeCN	20/80	82 [c]
k	2-methylaziridin-1-yl	NuH in MeCN [e]	90/10	63 [c]
l	benzimidazol-1-yl	NuH + NaH		(92) 82 [f]
m	indol-1-yl	NuH + NaH		85 [f]
n	phenothiazin-10-yl	NuH + NaH		81 [f,g]
o [h]	morpholino	NuH + NaH	100/0	69/0
p [i]	NMe ₂	NuH in DMSO	74/26 [j]	

[a] 70% isolated mixture (46% with Ar = 4-FC₆H₄ or 4-*i*-PrC₆H₄). [b] Preparative run using preformed sodium alkoxide; besides 26% **79** (*cf.* Scheme 26). [c] Mixture of *Z,E* and *Z,Z* isomers. [d] Identical with **Oa_e**. [e] With addition of K₂CO₃. [f] *Z,E* isomer only. [g] For analogues with Ar = 4-MeO/EtO₂CC₆H₄ and Nu = 2-substituted phenothiazin-10-yl (yields 39-86%), see ref.¹⁰³ [h] Refs.^{106,107} [i] Ref.¹⁰⁷ [j] Observed when reaction started.

Scheme 25

stereochemistry and mechanism of this ring cleavage were studied in detail,^{106,107} the employment of a wide variety of nucleophiles demonstrated the versatility of the reaction (Scheme 25). Tetrazoles with an unsubstituted or alkyl substituted dienic chain were obtained from the reaction with sodium tetrahydroborate (\rightarrow **Oa_a-a_e**),¹⁰¹ and **Oa_e** (\equiv **Oh**) also with methylmagnesium iodide.¹⁰⁷ Of course, especially useful are ring openings that gave side chains bearing a functionality like an alkoxy or a cyano group (\rightarrow **Ob-e**,^{106,107} **Of**,¹⁰⁷



Scheme 26

Og^{106,107}), an *N*-linked heterocycle (\rightarrow **Oj,k**,¹⁰⁷ **Ol,m**,¹⁰⁶ **On**^{104,106}) or an amino group (\rightarrow **Oo**,^{101,106,107} **Op**,^{107,108} **Oq-s**¹⁰⁸). As expected, the formation of a deuterated dienic chain could be achieved too (\rightarrow **Oi**).¹⁰⁷ Ring opening of **67** with tetramethylammonium hydroxide should provide alkenals, but clean results were obtained only with a single member of this class (see Scheme 26: **67e** \rightarrow **76** \rightarrow **Ot**; 73% yield); most substrates (**67**) rapidly decomposed on exposure to that reagent.¹⁰²

Sodium methoxide¹⁰² as well as 2,2,2-trifluoroethoxide¹⁰⁷ attacked **67b** (X = Cl) at both C(5) and C(8a) to give as a side product the aminopyridone (**79**). However, phenolate and thiophenolate ions affected the bicycle at C(8a) only. The resultant species (**78a,b**) expelled nitrogen and, depending on the nucleophile used, in turn stabilized to either **79** (*via* hydrolysis) or to the pyridinium-*N*-aminide (**80**).¹⁰⁹

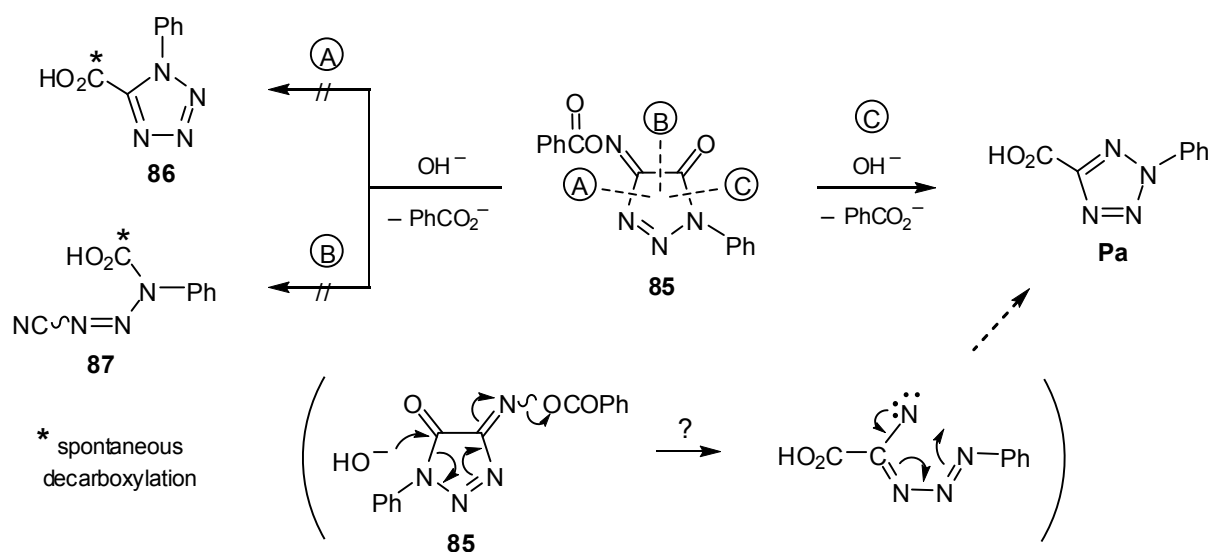
Regarding the behaviour of benzologues towards nucleophiles (*i.e.* the hydroxide ion), only in the case of linear anellation (**69**) the ring opening to a 2*H*-tetrazole could be observed (\rightarrow **Ou**; 40%); nevertheless, the respective intermediate (**81**) underwent a competing reaction to afford the indazoloisoquinoline (**82**; 35%).¹⁰⁵ In analogy to the reaction of the salt (**67e**), the angularly anellated congener (**71**) should also be capable of giving a tetrazole, but here the bridgehead carbon was attacked to form the isoquinolin-1(2*H*)-one (**83**; 74%). Similarly, the salt (**73**) was transformed into the quinolin-2(1*H*)-one (**84**; 78%) rather than the corresponding 2-aryl-5-[2-(*o*-hydroxyphenyl)vinyl]tetrazole.¹⁰² These regioselectivities, changing with the site of benzoanellation of the bicyclic substrate (**67**), were rationalized in terms of the FMO theory.¹⁰⁵

Finally, it is evident that tetrazoles of the type (**O**), in particular those having dienol ether and dienamine groupings, are desired starting materials for specifically functionalized derivatives (*cf.* refs.^{104,108,112,113}). Considering the reaction of ν -triazolodiazinium salts with nucleophiles,¹¹⁴ further series of elaborately substituted 2*H*-tetrazoles may arise from ring opening of the tetrazolo congeners. However, such bicycles have not been prepared till now.

P) 4-(Acyloxyimino)-1,2,3-triazol-5(4*H*)-one

Of ring transformations starting from the ν -triazole system, the present example stands out for its peculiar course (Scheme 27): When the process (**85** \rightarrow **Pa**) was discovered a century ago,¹¹⁵ the authors imagined a new type of Beckmann rearrangement and realized that none of the two classical modes were operative, as in those cases the isomeric tetrazole (**86**) [*via* bond scission (A)] or the nitrile (**87**) [*via* bond scission (B)] would have formed.¹¹⁶ Whilst the product (**Pa**) was shown to arise almost quantitatively (even under mild conditions), the mechanism [*via* bond scission (C)] remained open. Possibly it is the attack of hydroxide ion onto C(5) in **85** to give an intermediate which is capable of undergoing this particular conversion, since the molecule did not change in the absence of alkali. The behaviour of **85** towards acidic agents has not been

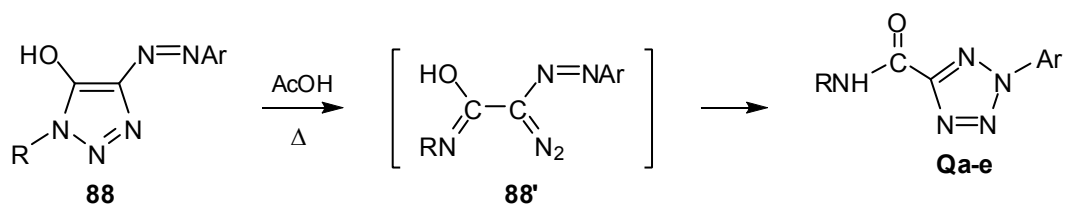
investigated, while an attempt to rearrange the corresponding oxime-type compound with benzenesulfonyl chloride/pyridine met with failure.¹¹⁵



Scheme 27

Q) 4-Arylazo-1,2,3-triazole

Allowing for the capacity of ring opening of certain *1H*-1,2,3-triazoles to α -diazoimines, the special type of substrates (**88**) can be viewed as sources of *2H*-tetrazoles (**Q**), because the diazo group of the open-chain form (**88'**) invites the arylazo unit to cyclization (Scheme 28). Indeed, this conversion, though not recognized, was encountered already in 1904: When the azo compound (**88c**) was prepared, a colourless side product occurred,¹¹⁷ and a related observation was made by others who recrystallized the derivative



88, Q	R	Ar	yield (%)
a	H	Ph	79
b	Me	Ph	77
c	Ph	Ph	78
d	PhCH ₂	Ph	63
e [a]	H ₂ NCOCH ₂	4-MeC ₆ H ₄	[b]

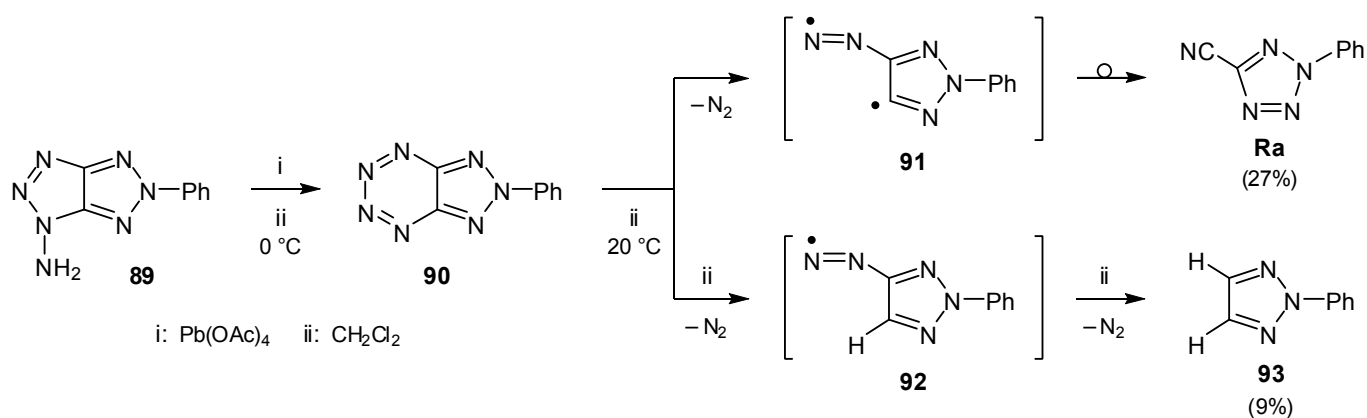
[a] Structure (**Qe**) likely by analogy, but not confirmed by an independent route. [b] Yield not reported.

Scheme 28

(**88e**) from acetic acid.¹¹⁸ The break-through came in the 1950s, when it was shown that the triazoles (**88a-d**), on heating in acetic acid, rapidly rearrange to the tetrazolecarboxanilides (**Qa-d**).¹¹⁹ In view of this finding the unknown materials of refs.^{117,118} were looked upon as the tetrazoles (**Qc**) and (**Qe**).

R) 2*H*-1,2,3-Triazolo[4,5-*e*][1,2,3,4]tetrazine

An unexpected entry to a 2*H*-tetrazole was encountered when the bicyclic system (**90**) – the first molecule showing a 1,2,3,4-tetrazine moiety [generated from the aminotriazole half-ring of **89**] – was allowed to decompose in dichloromethane (Scheme 29). The extrusion of molecular nitrogen from the labile substrate (**90**) led to the intermediary species (**91**) and (**92**), which then rearranged to the cyanotetrazole (**Ra**) and, after additional loss of nitrogen, to the 1,2,3-triazole (**93**), respectively.^{120a} These products were isolated in a ratio 3:1, whereas an NMR study showed 50% each, but when the decomposition was performed in CDCl₃, the yield of the (deuterated) triazole was distinctly lower than that of **Ra** due to the isotope effect which originated from the hydrogen-abstraction step.^{120b} While the interesting degradation pathway of **90** was studied theoretically by AM1 calculations,¹²¹ the structure of the tetrazole (**Ra**) was investigated by X-ray crystallography.¹²²



Scheme 29

CONCLUSION

The foregoing inspection of direct routes (A) – (R) to 2*H*-tetrazoles demonstrates that this kind of entry is specially suited for making two major types of derivatives (*cf.* also Table 1 overleaf): (i) representatives having aryl substituents at N(2),¹²³ and (ii) tetrazoles bearing particular functionalities at N(2) and/or C(5), the insertion of which is difficult or impossible by other methods. Beyond that, quite a number of processes reviewed here attract interest because of their mechanism. Unfortunately, no direct access to tetrazoles having simple *alkyl* groups at N(2) is available until now, evidently owing to the lack of appropriate precursors; to overcome this long-standing deficiency remains a challenge.

Table 1. 2,5-Disubstituted tetrazoles *via* routes (A)–(R)

A	2-Ar/5-Ar, 2-Ar/5-CN, 2-X [a]/5-CN, 2-CHO/5-Ar, 2-Het/5-H
B	2-Ar/5-Alk, 2-Ar/5-Ar, 2-Ar/5-Het, 2-Ar/5-CO ₂ H, 2-CONH ₂ /5-Het (?)
C	2-CH ₂ Acyl/5-Acyl, [2-C(PPh ₃) ₂ /5-PPh ₃] ²⁺ , 2-C {=C(NR ₂) ₂ } P(O)R ₂ /5-P(O)R ₂ , 2-CH ₂ Acyl/5-SiMe ₃ , 2-CH(CONR ₂) ₂ /5-SiMe ₃
D	2-SiR ₃ /5-Alk, 2-SiR ₃ /5-Ar, 2-SnR ₃ /5-Alk, 2-SnR ₃ /5-Ar, 2-SnR ₃ /5-Het, 2-SnR ₃ /5-CH ₂ N ₃ , 2-SnR ₃ /5-[CH ₂] _n SnR ₃ , 2-SnR ₃ /5-[CH ₂] _n PR ₂ , 2-(Alk-2-enyl)/5-Alk, 2-(Alk-2-enyl)/5-Ar, 2-(Alk-2-enyl)/5-Het, 2-(Alk-2-enyl)/5-(Alk-1-enyl), 2-(Alk-2-enyl)/5-X [b]
E	2-Ar/5-Ar, 2-Ar/5-Het, 2-Ar/5-(Alk-1-enyl), 2-Ar/5-CO ₂ R, 2-Het/5-Ar, 2-Het/5-Het,
F	2-Ar/5-Ar
G	2-Ar/5-Ar
H	2-Ar/5-Ar
I	2-Ar/5-Ar, 2-Ar/5-Het, 2-Het/5-Ar,
J	2-Ar/5-Alk, 2-Ar/5-Ar
K	2-Ar/5-Ar
L	2-Ar/5-Ar
M	2-Ar/5-CH ₂ Acyl, 2-Het/5-CH ₂ Acyl, 2-Het/5-C {=NOH} X [c]
N	2-Alk/5-Het, 2-Ar/5-Het
O	2-Ar/5-(4-X-Alka-1,3-dienyl) [d], 2-Ar/5-[1-(2-CHO-Ar)Alk], 2-Ar/5-(3-CHO-Alk-2-enyl)
P	2-Ar/5-CO ₂ H
Q	2-Ar/5-CONHR
R	2-Ar/5-CN

[a] X = 2,3-*O*-alkylidene- α -D-ribofuranosyl. [b] X = OR, NR₂, SO₂R. [c] X = Alk, NH₂. [d] X = H, D, Alk, Het, CN, OR, NR₂.

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