APPROACHES TO THE SYNTHESIS OF 1-SUBSTITUTED 1,2,4-TRIAZOLES

Marudai Balasubramanian, James G. Keay, and Eric F.V. Scriven*

Reilly Industries, Inc., 1500 S. Tibbs Avenue, Indianapolis, Indiana, IN 46242, USA.

Navayath Shobana

Department of Chemistry, University of Florida, Gainesville, Florida, FL 32611-2406, USA.

Abstract- *This review summarizes the main methods currently available for the synthesis of 1-substituted 1,2,4-triazoles.*

CONTENTS

Dedicated to Dr. Alan R. Katritzky with appreciation on the occasion of his 65th birthday.

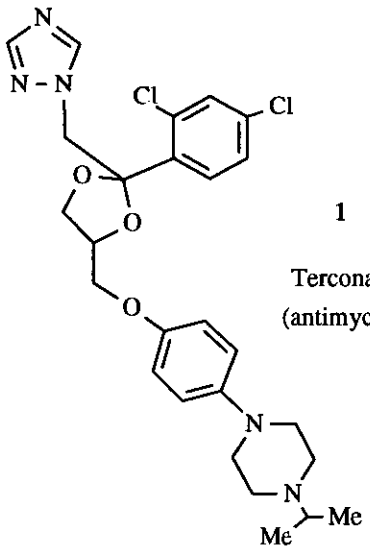
1. INTRODUCTION

Two major reviews are available that cover all aspects of 1,2,4-triazole chemistry. One by Temple[1] covers the period to 1981 and the other by Polya[2] to 1984. This brief review is focussed on recent methods that have been used to achieve regiospecific 1-alkylation chiefly of the parent system. Much of the work in this area has been driven by the need to synthesize 1-substituted 1,2,4-triazoles which are of interest for their biological activity.

The alkylation of a specific ring nitrogen atom in the 1,2,4-triazole system continues to pose a challenge to the heterocyclic chemist. This difficulty can in principle be circumvented by introduction of an alkyl group before ring closure, however few convenient routes are known. Direct alkylation of 1,2,4-triazole usually affords a mixture of isomeric products.[1,2] Ratios vary with the nature of the alkylating agent and the conditions employed, but range from 70:30 to 90:10.[3] The separation of 1- from 4-substituted 1,2,4-triazoles is important as usually only the 1-isomer is desired for its biological activity.

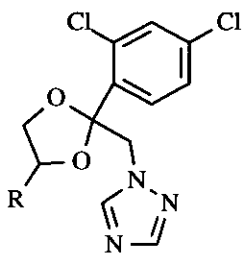
Many 1-substituted 1,2,4-triazoles have found use[4] as antimycotic agents, agricultural fungicides, plant growth regulators or aromatase inhibitors. As fungicides and antimycotics they have set new standards in medicine and agriculture with respect to efficacy and range of disease control. The primary mode of action is by supression of cytochrome P-450 activity which is required in the demethylation of 14α-methylsterols to ergosterol biosynthesis.[5] These materials are termed Ergosterol Biosynthesis Inhibitors (EBI). The 1-isomer is much more active than the 4-isomer.

Examples of some biologically active molecules containing the 1,2,4-triazole moiety are given (Scheme 1).



1

Terconazole
(antimycotic)

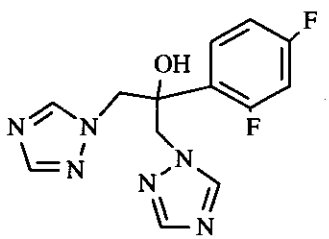


2

R= Et, Etaconazole

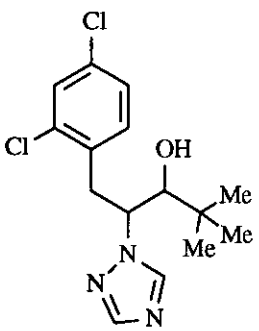
R= Pr, Propiconazole

(fungicides)



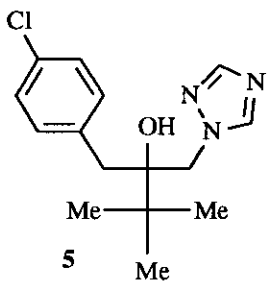
3

Fluconazole
(antimycotic)



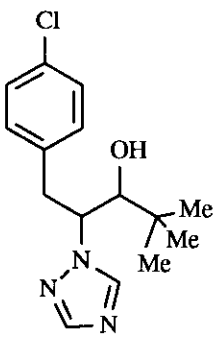
4

Dichlorobutrazole
(fungicide)



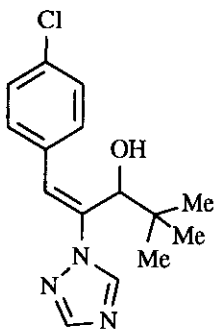
5

Vibunazole
(fungicide)



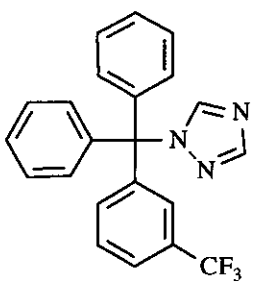
6

Paclobutrazole
(plant growth regulators)



7

Uniconazole
(fungicide)



8

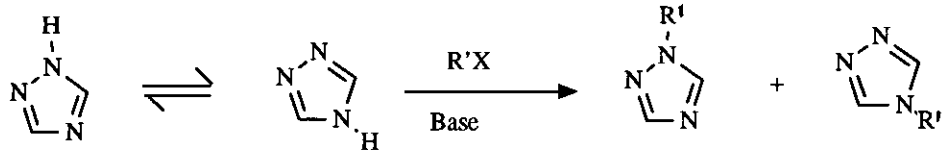
Fluotrimazole
(fungicide)

Scheme 1

2. METHODS OF SYNTHESIS

2.1. Direct Alkylation of 1,2,4-Triazole

2.1.1. With Alkyl/Aryl Halides: In many instances the synthesis of 1-alkyl-1,2,4-triazoles has been accomplished by the direct alkylation of 1,2,4-triazole (Scheme 2). Invariably the 1-isomer is accompanied by the undesired 4-isomer (0 - 30%). The exact ratio depends on the nature of the alkylating agent and the conditions employed (Table 1). Usually bases such as sodium ethoxide[6,7] and sodium hydroxide[8,9] are used to form triazolyl anions before reaction with alkylating agents, usually alkyl or aryl halides. 1-Methyl-1,2,4-triazoles[8] can be isolated in 65% yield from 1,2,4-triazole and methyl iodide in the presence of sodium methoxide. Nmr measurements showed 6.5 : 1 mixture of the 1- : 4-isomer.[8] On the other hand, use of trimethyloxonium fluoroborate[8] in nitromethane, for the alkylation of triazole yielded 1-methyl- (16%), 4-methyl- (31%) and unreacted 1,2,4-triazole. Various research groups[10 - 13] have attempted the alkylation of 1,2,4-triazole using activated aryl halides. Conditions (Table 1) include the Ullmann reaction in the presence of CuO/potassium carbonate and heating[11, 12] in an autoclave at 180 to 190 °C. Unactivated aryl halides failed to arylate 1,2,4-triazole under Ullmann conditions. Katritzky and coworkers[14] have exploited the use of sodium hydroxide in DMF as a base for the alkylation of 1,2,4-triazole. This procedure affords superior yields when compared to those reported from procedures using sodium alkoxide or sodium hydride. Mainly 1-substituted triazoles were obtained except in alkylations involving benzyl bromide and chlorotriphenylmethane, where a mixture of 1- and 4-substituted products was formed.



9 **10** **11**

Scheme 2

Table 1. Alkylation and Arylation of 1,2,4-Triazole.

Entry	Conditions	Alkylating Agent	% Alkyltriazole (yield)	Ratio 1- :4-	Ref.
1	Na, MeOH, 120 °C	MeI	78[a]	-	6
2	Na, EtOH, 1 h, reflux	$C_6H_5CH_2Cl$(excess)	70[a]	-	7
3	K_2CO_3, CuO, Py reflux, 16 h	1-Cl-2-NO_2-benzene	68[a]	-	10
4	K_2CO_3, CuO, Py, reflux, 165 h	1-Cl-2-NO_2-benzene	10[a]	-	10
5	autoclave, 190 °C	2-Cl-pyridine	6[a]	-	11
6	NaOH/DMF, 25 °C	PrI	65	100 : 0	14
7	NaOH/DMF, 25 °C	$C_6H_5CH_2Cl$	88	94 : 6	14
8	K_2CO_3, EtOAc, reflux, 5 h, 18-C-6	BuBr	99[a]	-	16
9	K_2CO_3, EtOAc, 5 h reflux, PEG 600	*sec*-C_4H_9Br	27[a]	-	16
10	n-$Bu_4N^+Br^-$, KOH, K_2CO_3, 20 h, reflux	$PhCH_2Cl$	88	85 : 15	15
11	-do-	$(Ph)_3CCl$	57	100 : 0	15
12	KOH, ultrasound, BBDECl	4-F-1-NO_2-benzene	53[a]	4 : 1	18

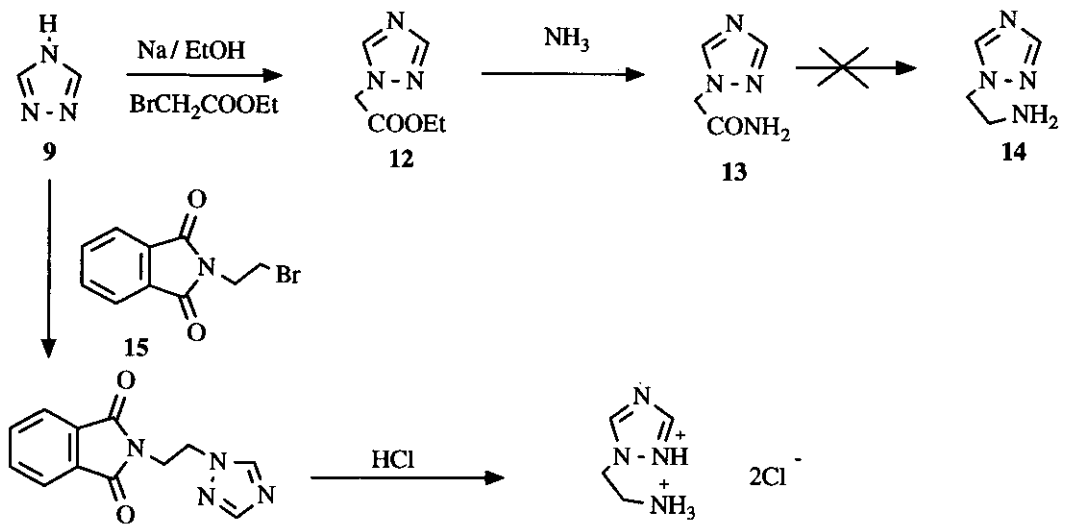
a = isolated yield.

The use[15 - 17] of phase transfer catalysts (liquid-liquid or solid-solid) has made available another procedure for synthesis (Entries 8 - 12, Table 1). The most commonly used phase transfer catalysts are

tetrabutylammonium bromide and bisulfate (xylene solvent), poyethylene glycol (PEG) in the presence of potassium carbonate, as acid binding agent and 18-Crown-6. Studies indicate that 18-Crown-6 is the best catalyst. However, this technique is not suitable for alkyl halides with side chains. Recently, Elguero and coworkers[18] claimed the use of phase transfer catalysts such as TBAB (tetrabutylammonium bromide), TDA-1 [tris(3,6-dioxaheptyl)amine] and BBDECl [1,5-bis-(*N*-benzyl-*N*,*N*-diethylammonium)diethyl ether dichloride] without solvent for the arylation of 1,2,4-triazole (Entry 12, Table 1).

It should be noted that where high temperature conditions were employed (Table 1) some interconversion of 4- to 1-substituted triazoles may have occurred (see Section 2.4).

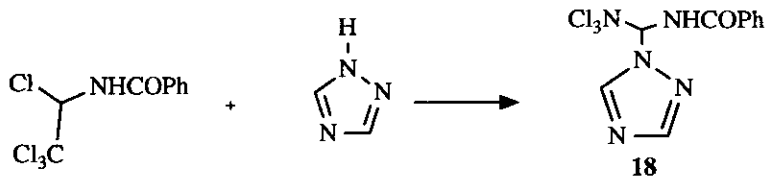
The quarternary ammonium salt (**17**) of one of the interesting[19] 1-substituted triazoles, 1β-aminoethyl-1,2,4-triazole (**14**), which was speculated to have biological activity, was synthesized from 1,2,4-triazole and 2-bromoethylphthalimide (**15**, Scheme 3). An attempt to synthesize the compound (**14**) from 1,2,4-triazole and ethyl bromoacetate failed, as the amide (**13**) could not be reduced to the amine (**14**).



9 **12** **13** **14** **15** **16** **17**

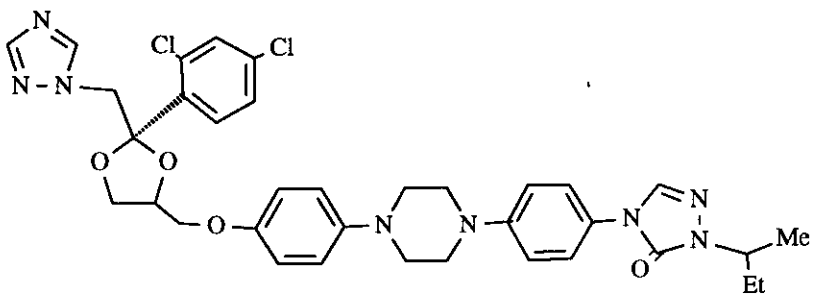
Scheme 3

N-(1-Triazol-1-yl-2,2,2-trichloroethyl)benzamide (**18**) was synthesized[20] by stirring *N*-(1,2,2,2-tetrachloroethyl)-2-chlorobenzamide with 1,2,4-triazole in benzene at room temperature.



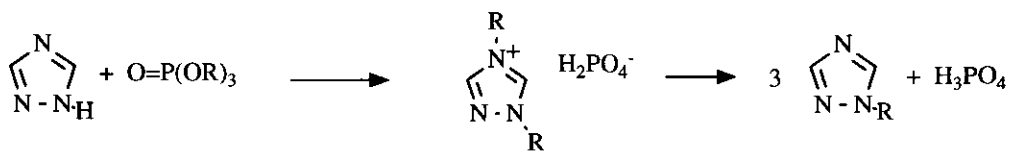
18

The bactericide and medicinal fungicide (**19**) was prepared[21] by the alkylation of 1,2,4-triazole with a 2-bromomethyl-1,3-dioxolane derivative in the presence of potassium carbonate.



19

2.1.2. With Alkyl Phosphates: A new method [22] for *N*-alkylation of 1,2,4-triazole consists of the use of trialkyl phosphates as alkylating agents (Scheme 4). Trimethyl, triethyl and tributyl phosphates are effective for alkylation, though the activity decreases in the order, methyl> ethyl > butyl. The yields ranged from 45 - 90%, with the N-1 isomer predominant. A by-product of this reacton was speculated to be a quarternary salt (**20**), which could not be isolated due to its oily and hygroscopic nature. The yield of the *N*-1 isomer increased considerably when the reaction was carried out in the presence of a tertiary amine, probably because the added base was effective in suppressing the formation of the salt (**20**).

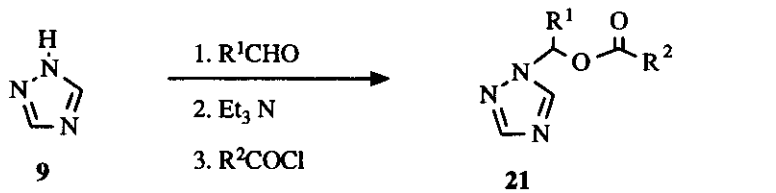


20

Scheme 4

2.1.3. With Aldehydes and Derivatives: A recently discovered[23] general and regiospecific approach to the synthesis of 1-substituted 1,2,4-triazoles (**21**) involves the reaction of 1,2,4-triazoles with aldehydes and

various acid chlorides (Scheme 5). Alkylation could be accomplished with a wide variety of aliphatic aldehydes, including sterically hindered ones. It was also found to work with aromatic aldehydes. Acylating agents such as pivaloyl chloride and benzoyl chloride could be used as trapping agents.

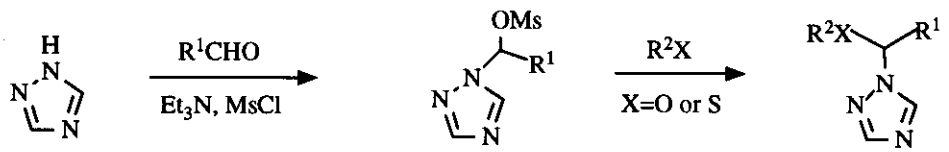


9 **21**

21a: R^1=Ph, R^2=Me (46%)
21b: R^2=R^1=Me (82%)
21c: R^1=Et, R^2=Me (72%)

Scheme 5

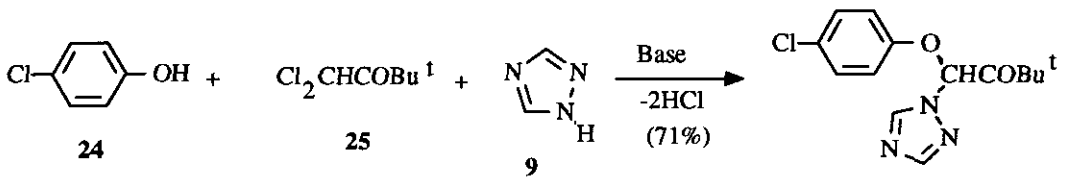
The same group has very recently found[24] that further reaction at the functionalized α-position of **22** led to a regiospecific synthesis of **23** (Scheme 6). The reaction between aliphatic aldehydes or glyoxals and 1,2,4-triazole followed by addition of mesyl chloride gives α-mesylates of 1-alkyl-1,2,4-triazole (**22**) regiospecifically. Mesylate ion is readily displaced by alkoxide, aryloxide, alkylthiolate or arylthiolate nucleophiles to give the corresponding α-functionalised 1-alkyl-1,2,4-triazoles (**23**) in good yield. In the case of **23** (R^1=Et, XR^2=SPh), ^{1}H and ^{13}C nmr spectra confirmed the regiochemical purity of the biologically active substituted 1,2,4-triazole isomers obtained. There was no evidence for the presence of the inactive 4-isomer.



9 **22** **23**

Scheme 6

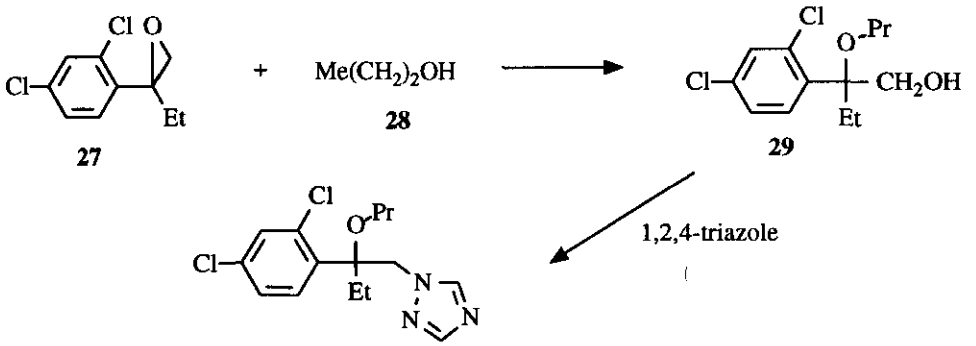
2.1.4. With α-Haloketones: The synthesis of 1,2,4-triazolyl-1-phenoxyacylmethane (**26**) by reaction of a dihaloketone (**25**), 1,2,4-triazole and a phenol *(24)* in the presence of a base (Scheme 7) has been claimed for a large number of phenols.[25, 26]



24 25 9 26

Scheme 7

2.1.5. With Oxiranes: 1-Triazolylethyl ether derivatives[27,28] such as **30** have been synthesized conveniently in moderate yield (Scheme 8) by reaction of an oxirane *(27)* at temperatures of *ca.* 100 ^{0}C, in the presence of an acid condensation agent, with an alcohol (**28**) to give a glycol monoether (**29**), which is subsequently reacted with 1,2,4-triazole in the presence of methane sulfonyl chloride.

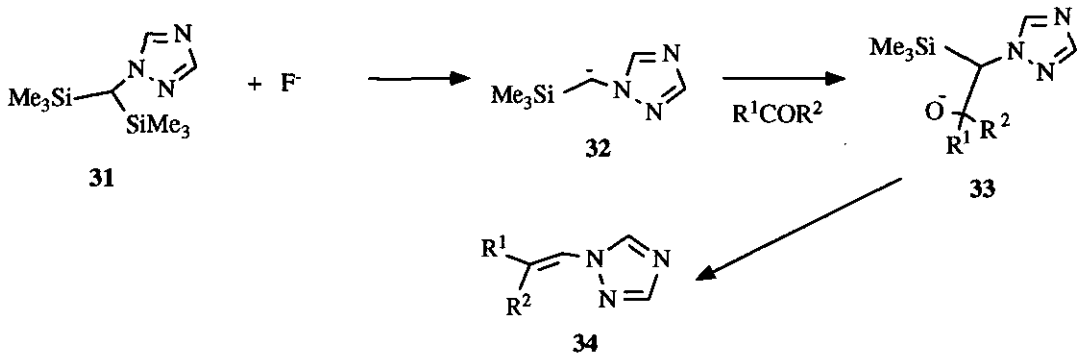


27 28 29 30 (54.8%)

Scheme 8

2.2 Vinylation of 1,2,4-Triazole

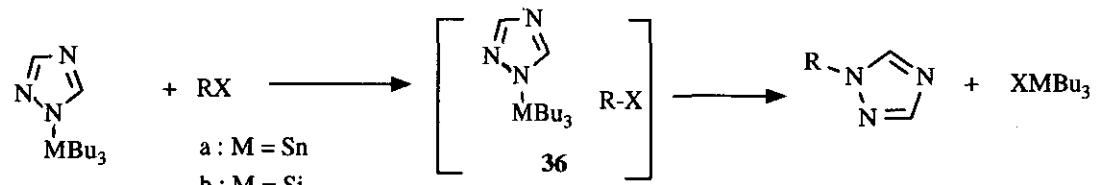
The synthesis of 1-vinyl-1,2,4-triazoles (in 95.5% yield) may be achieved by heating 1,2,4-triazole with acetylene at 180 - 220 ^{0}C both in the absence and presence of a strong base.[28, 29] A novel route to 1-vinyl-1,2,4-triazoles (**34**) has been established[30] by the fluoride-catalyzed Peterson reaction of 1-[bis{trimethylsilyl}methyl]-1,2,4-triazole (**31**) with carbonyl compounds (Scheme 9). The reaction occurs with aromatic aldehydes and ketones and yields of vinyl triazoles (**34**) range between 80 - 90%. In the case of β-tetralone, which has the most enolizable carbonyl group, no product was obtained and β-tetralone was recovered (97.5%) due to the formation of the enolate anion by proton transfer to the anion *(32)*.



Scheme 9

2.3 Alkylation of a Substituted Triazole

2.3.1. By Substitution of 1-Substituted 1,2,4-Triazole: The regiospecific synthesis of 1-alkylated 1,2,4-triazoles has attracted a lot of attention in the recent years. 1-Trimethylsilyl- and trimethylstannyltriazoles readily undergo alkylation at the carbon adjacent to the silicon and tin functions[31] which are then eliminated. Trimethylstannyl compounds are usually less reactive than the corresponding silicon derivatives.[32] The reactivities of organostannylamines[33] and organosilicylamines[34] of 1,2,4-triazoles towards alkyl and acyl halides permits a highly regiospecific method for the synthesis of 1-alkyl- and 1-acyl-1,2,4-triazoles (Scheme 10). Primary halides give the *N*-alkylated heterocycles in quantitative yield. Reactivity decreases with secondary and tertiary halides (Table 2).

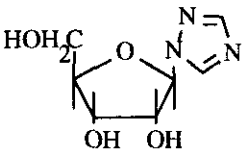


Scheme 10

Table 2. Reaction of trimethylstannyl- and trimethylsilyltriazoles with alkyl halides.

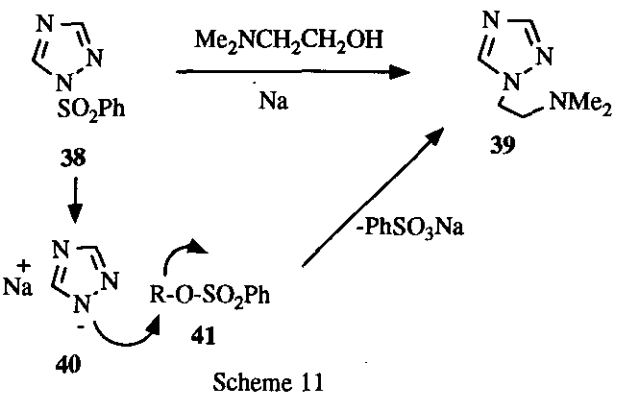
Entry	Starting Material **35**	Alkylating/ Acylating Agent	Condition Temp/Time (°C, h)	% 1-Substituted triazole	Ref.
1	a	$C_6H_5CH_2Br$	100, 3	97	33
2	a	CH_2=CH-CH_2Br	120, 4	87	33
3	a	BuBr	100, 12	94	33
4	a	EtCH(Br)Me	110, 18	35	33
5	a	*i*-PrBr	100, 24	12	33
6	b	$C_6H_5CH_2Br$	120, 10	92	34
7	b	CH_2=$CHCH_2Br$	120, 10	92	34
8	b	EtCH(Br)Me	100, 45	34	34
9	b	AcCl	distillation	95	34
10	b	$MeCOCH_2Cl$	100, 1	100	34

The trimethylsilyl derivative of *s*-triazole (**35**) has been made use[35] of for the synthesis of *o*-benzoyl derivative of 1-(β-D-ribofuranosyl)-1,2,4-triazole (**37**) by reaction with 2,3,4-tri-*o*-benzoyl-D-ribofuranosyl-bromide.



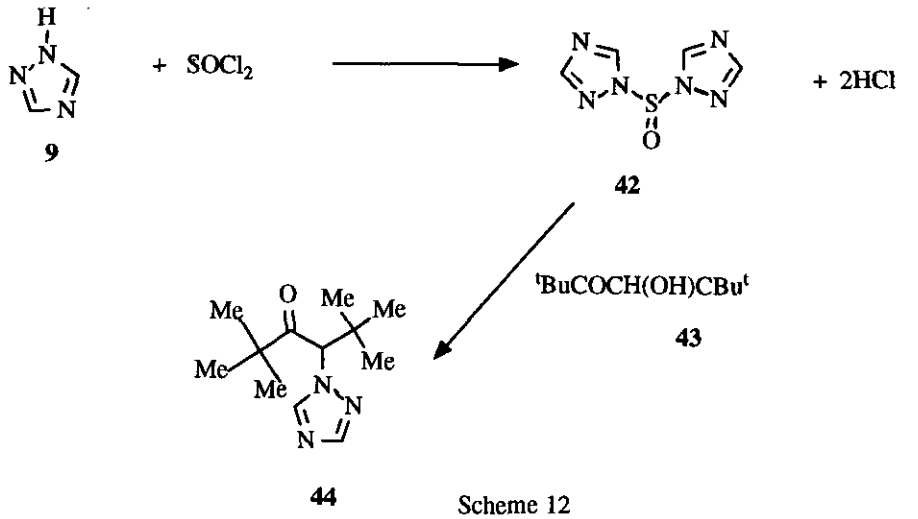
37

1-Benzenesulfonyl-1,2,4-triazole (**38**) recently has been found[36] with sodium salts of alcohols to give 1-alkyl-1,2,4-triazoles (**39**). The mechanism (Scheme 11) involves a nucleophilic attack by the alkoxide on the sulfur atom of **38** leading to alkyl benzenesulfonate (**41**), which further undergoes nucleophilic substitution by sodium triazolate (**40**) to give the alkylated triazole (**39**).



Scheme 11

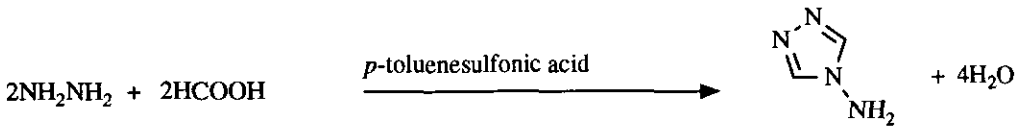
1-Substituted triazoles such as **44**, have been synthesized[26] from sulfonyl derivative (**42**) by reaction with bis-*tert*-butylacyloin (**43**, Scheme 12).



Scheme 12

2.3.2. From Alkylation of 4-Substituted 1,2,4-Triazole: Over the years several modifications have been attempted in order to synthesize regiospecifically the 1-substituted 1,2,4-triazoles. One idea was to block the 4-position of 1,2,4-triazole to bring about a regiospecific 1-alkylation. The amino group was considered to be best suited for this purpose as 4-amino-1,2,4-triazole (**45**) can easily be prepared[37] from hydrazine and

derivatives of formic acid (Scheme 13). There has been several papers[38 - 41] in the literature devoted to this concept.



45 (93%)

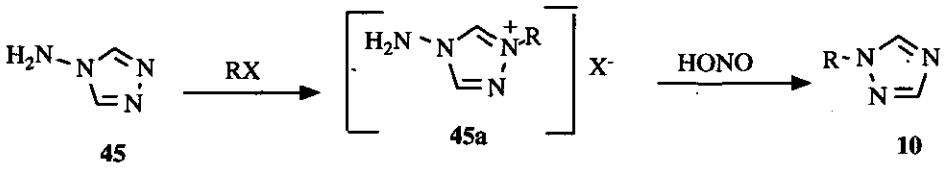
Scheme 13

4-Amino-1,2,4-triazole (**45**) readily reacts with alkyl halides to form quarternary salts, which on subsequent deamination with nitrous acid yield exclusively the 1-substituted product (Table 3). Calculations show that the electron density on the 4-amino group is so greatly reduced by the strongly electrophilic triazole ring that alkylation occurs on one of the amidine nitrogen atoms. Timpe *et al.*[38] have alkylated a number of triazoles using this technique. They followed a two-step procedure in which the triazolium salts (**45a**) were first isolated and then later on treated with nitrous acid for deamination. This procedure has been made[39] use of, for the synthesis of *N*-chloroethyl-1,2,4-triazole (Table 3, Entry 2).

Table 3.

Entry	Alkylating Agent		Two-step Yield		One pot yield	Ref.
	R	X	**45a**	**10**	**10**	
1	Me	OTs	88	72	-	38
2	$ClCH_2CH_2$	Cl	-	-	52	40
3	$PhCOCH_2$	Cl	76	89	76	40
4	*sec*-Bu	Br	59	85	84	40

The above procedure may be carried out by performing the alkylation and deamination reactions in one pot in good yield without isolating the aminotriazolium salt (**45a**) (Scheme 14).[39 - 41]



45 45a 10

Scheme 14

This reaction sequence is useful for alkylating agents as unreactive as primary alkyl chlorides as well as for more reactive benzylic and phenacyl halides. The mild non basic conditions employed are particularly suited to alkylating agents that bear base sensitive groups, which contrast with the strongly basic conditions used in direct alkylations. This work provides the first example of a fairly general high yield regiospecific one-pot synthesis of 1-substituted 1,2,4-triazoles from 4-amino-1,2,4-triazole. In the case of phenacyl triazole[41] [Table 3, Entry 3], the use of too great an excess of nitrous acid led to reaction at an active methylene group and therefore other methods of deamination[41] (such as reductive deamination and oxidative deamination) were investigated.

2.4. Alkylation Involving Rearrangement

Lately the isomerisation[42 - 46] of 4-substituted 1,2,4-triazoles (**11**) to 1-substituted 1,2,4-triazoles (**10**) has become an important method of synthesis of 1-substituted 1,2,4-triazoles. Rearrangements occur when:

1) 4*H*-isomers such as 4-benzyl- and 4-phenacyl-1,2,4-triazoles are heated to temperatures above 150 ^{0}C in the presence of a catalytic amount of the corresponding alkyl halides (Table 4).[42 - 45]

2) Alcohols such as **46** are heated in the presence of a base such as sodium hydroxide and essentially in the absence of a polar aprotic solvent.[44, 46]

In the former isomerization[42 - 45] the mechanism is speculated to involve the formation of a quarternary ammonium salt (**45a**) that undergoes elimination of the alkyl group from the 4-position (Scheme 14).

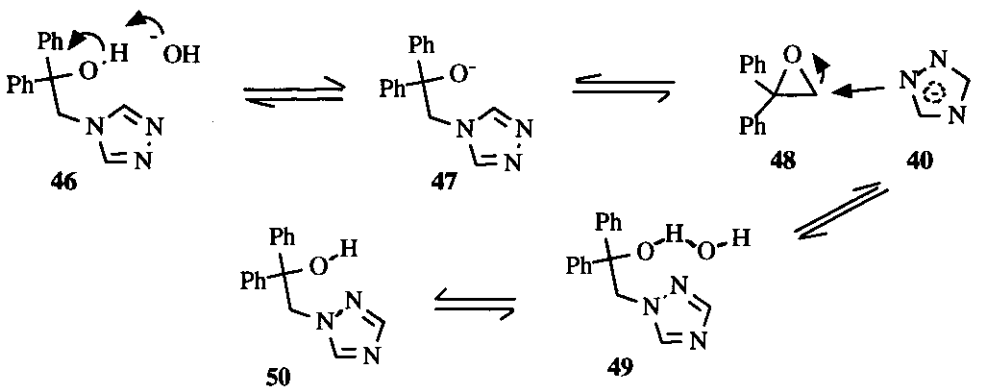
Table 4. Isomerization of 4-substituted 1,2,4-triazoles.

Entry	4*H*-triazole R	Alkylating Agent	Conditions Temp, Time °C, h	Conversion to 1H isomer	Ref.
1	$PhCH_2$	$PhCH_2Br$	180, 5	>98 : <2	43,45
2	PhCHMe	PhCH(Br)Me	160, 22	>97 : <3	45
3	$4\text{-}BrC_6H_4COCH_2$	$4\text{-}BrC_6H_4COCH_2Br$	160, 3	>99 : <1	45

The isomerization may be performed in the presence of the isomeric 1*H*-substituted 1,2,4-triazole, which generally being more thermodynamically stable than the 4*H*-isomer, remains unchanged in the reaction mixture. This technique is of value in converting the relatively minor proportion, generally around 15% or below, of the less desirable 4*H*-substituted 1,2,4-triazole, which accompanies the 1*H*-isomer during alkylation of 1,2,4-triazole.

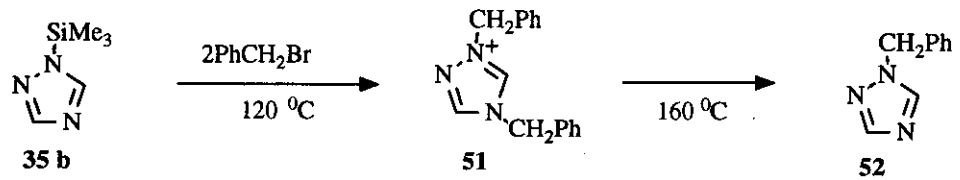
Alternatively, the 1*H* isomer can be obtained regiospecifically by direct alkylation of 1,2,4-triazole at elevated temperatures with a slight excess of the alkylating agent.

The transformation[44, 46] of a 4*H*-β-hydroxyethyl-1,2,4-triazole derivative (**46**) into the 1*H* isomer (**49**) has been explained as involving a nucleophilic attack of the base such as hydroxide ion, with the formation of an oxirane intermediate (**48**) and triazole anion (**40**).[46] The nucleophilic ring opening of the oxirane (**48**) by the triazole anion (**40**) leads to the 1-isomer (**50**, Scheme 15).



Scheme 15

According to a literature[34] report, treatment of 1-trimethylsilyl-1,2,4-triazole (**35b**) with benzyl bromide at 120 ^{0}C after 10 h, gives 1-benzyl-1,2,4-triazole (**52**). Repetition of this reaction[45] by Smith *et al.*, yielded only 20% of the expected triazole (**52**). The major product was the quarternary salt (**51**) (Scheme 16).



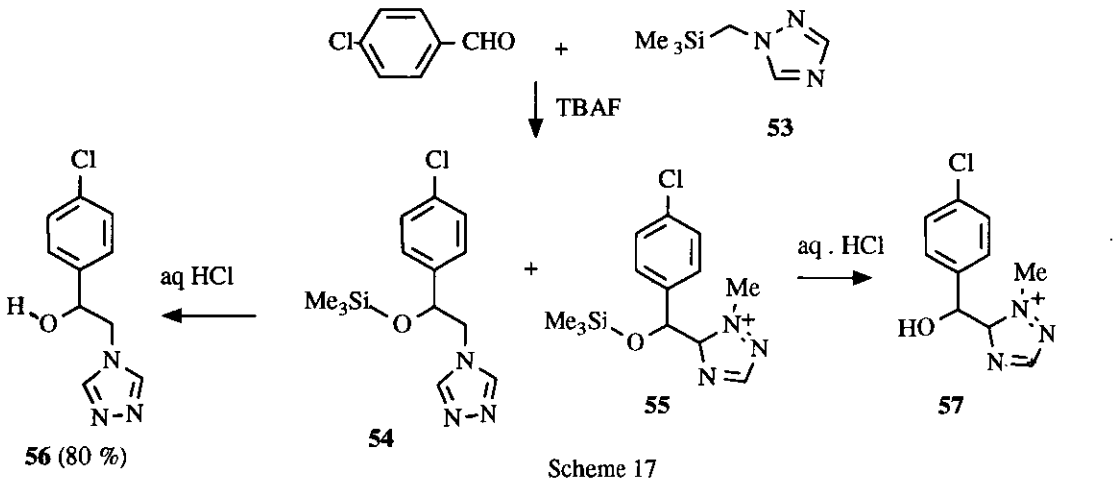
Scheme 16

The authors[34] isolated the 1-benzyl product (**52**) from the mixture by distillation, which was responsibile for the conversion of the salt (**51**) to the desired benzyl derivative (**52**). Smith *et al.*[45] found that the same benzyl derivative (**52**) could be obtained by merely heating 1,2,4-triazole and benzyl bromide at 110^{0}C obviating the necessity for involvement of the trimethylsilyl group.

2.5. Substituent Modification

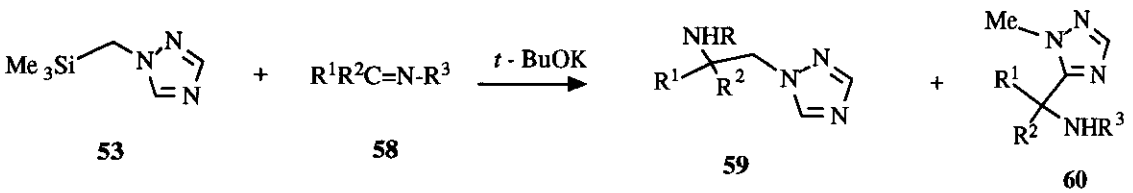
Sometimes a substituent already attached to the 1-position of a substituted 1,2,4-triazole is subjected to modification with a view to synthesize new 1-alkylated 1,2,4-triazoles. One versatile intermediate that has attracted[47, 48] considerable attention is 1-(trimethylsilylmethyl)1,2,4-triazole (**53**). Fluoride or alkoxide induced reaction[47] of **53** with carbonyl compounds has provided synthetic routes to (1,2,4-triazol-1-yl)ethanols (**56**) which may or may not be accompanied by small quantities of

(1-methyl-1,2,4-triazol-5-yl)methanols (**57**) after acid catalyzed hydrolysis (Scheme 17).



Scheme 17

Extension[48] of this method to include the potassium *tert*-butoxide induced reaction of 1-[trimethylsilylmethyl]-1,2,4-triazole (**53**) with imine (**58**) to yield (triazol-1-yl)ethylamine (**59**) (Scheme 18) was explored. The byproduct of this reaction is the isomeric triazole derivative (**60**).

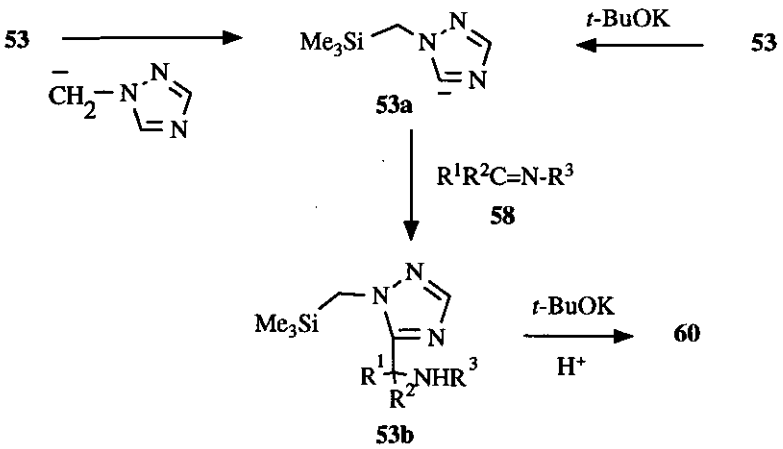


a : R^1 = 4-F-C_6H_3,, R^2 = H, R^3 = 2,4Cl_2 -C_6H_3 **59a** (49%) + **60 a** (10%)

b : $R^1 = R^2 = R^3$ = 4-ClC_6H_4 **59b** (5%) + **60b** (53%)

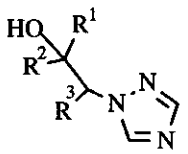
Scheme 18

The formation of isomeric triazole derivative (**60b**) (53%) may be explained as due to the weaker reactivity of ketimine (**58b**) when compared to **58a**. In this case the methyl anion generated, acts as a base rather than a nucleophile to remove the proton from position 5 of the triazole ring in **53** and the resulting triazol-5-yl anion (**53a**) reacts with imine (**58**) yielding triazolylmethylamine (**60**) after subsequent desilylation (Scheme 19).



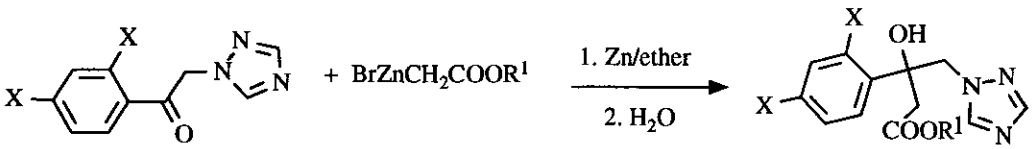
Scheme 19

According to another possible mechanism, the triazol-5-yl anion (**53a**) may be generated directly from **53** by a deprotonation at the 5-carbon of **53** by *t*-BuOK (Scheme 19). By a mechanism similar to the previous one[47, 48] phenylthio-, methylthio- and methoxy-substituted silylmethyl-1,2,4-triazoles which act as substituted *N*-azolylmethylanion equivalents,[49] were prepared and made to react with carbonyl compounds in the presence of flouride anion to obtain 2-phenylthio-, 2-methylthio and 2-methoxy substituted (1,2,4-triazol-1-yl)ethanols (**61**).



61: R^3 = SPh, SMe or OMe

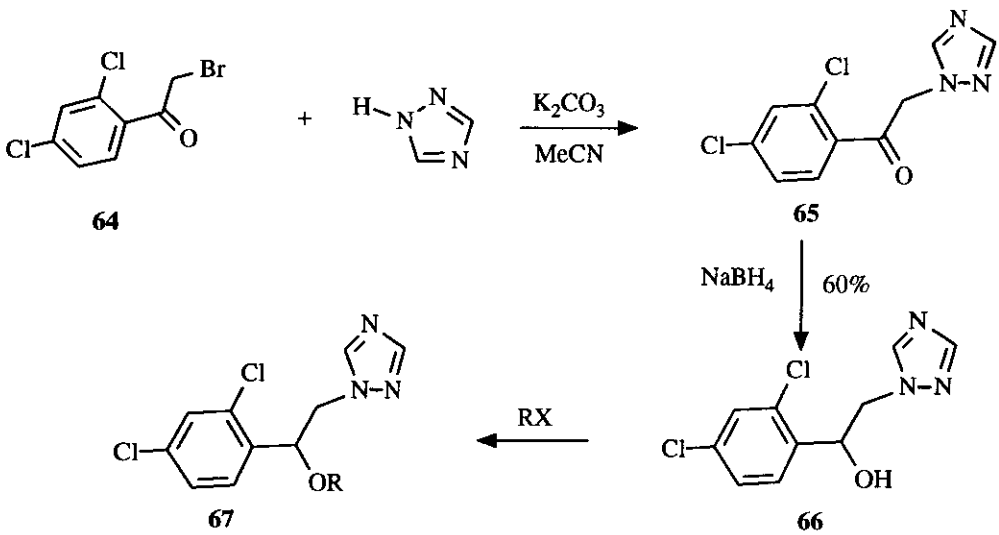
The most convenient synthesis[50] of 1-alkyl-1-aryl-2-triazolylethanols (**63**) (with long chain alkyl groups) is to react carbonyl derivatives of 1,2,4-triazole (**62**) and bromo esters $BrCH_2COOR'$ (R'=nC_8H_{17}, $nC_{12}H_{25}$) in ether in the presence of activated zinc (Reformatsky reaction) (Scheme 20). The yields of **63** range from 50 - 83%.



62 63

Scheme 20

1-(2,4-Dichlorophenyl)-2-(1,2,4-triazol-1-yl)ethyl ether (**67**) has been synthesized[51] (Scheme 21) from the appropriate triazolyl alcohols (**66**) by reaction with alkyl halides. The alcohol (**66**) is synthesized from 1,2,4-triazole by reaction with α-bromoketones (**64**) in the presence of a base, followed by subsequent reduction with $NaBH_4$.



64 65 66 67

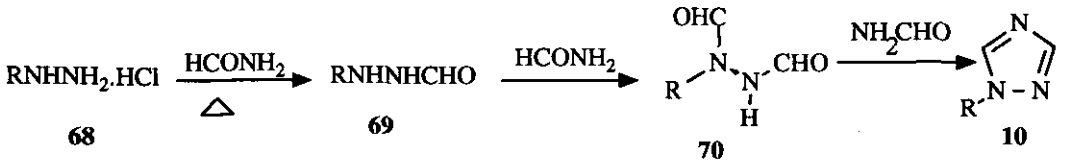
RX = 2,4-dichlorophenylmethyl chloride

RX = allyl bromide

Scheme 21

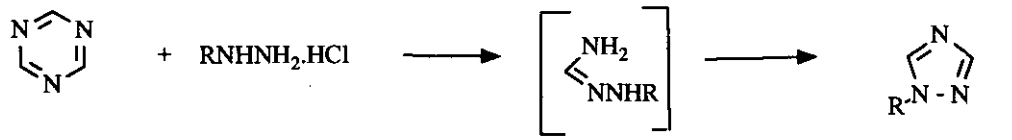
2.6. Ring Synthesis

One of the oldest methods of synthesis[52, 53] of 1-alkyl (**10**) (R = alkyl) and 1-aryl-1,2,4-triazoles(**10**)(R = aryl) the Pellizari reaction, involves the reaction of either 1-substituted hydrazines (**68**) or the corresponding formyl derivatives (**69**) with formamide at high temperatures (>200°C) (Scheme 22). The products are generally isolated in low yields because separation of the by-product is often difficult.



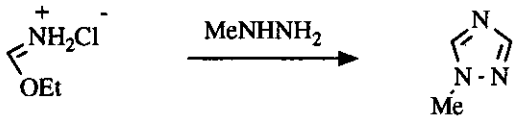
Scheme 22

An amidrazone intermediate[54] (**72**) is thought to be involved in the acid catalysed condensation of the appropriate hydrazine (**68**) with *s*-triazine (**71**) in ethanol at reflux (Scheme 23). 1-Methyl- and 1-phenyl-triazole are formed in high yields (>80%) by this method.



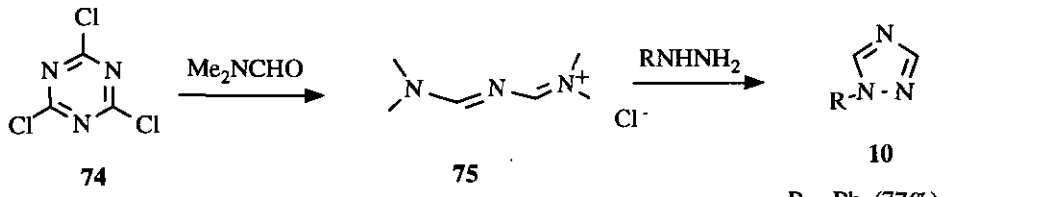
Scheme 23

The reaction of the imino ether (**73**)[55] and methyl hydrazine in ether to give a mixture of dihydrotetrazine (38%) and 1-methyl-1,2,4-triazole (27%) was also found to involve an amidrazone intermediate (Scheme 24).



Scheme 24

Another example of ring synthesis[56, 57] is the treatment of 2,4,6-trichloro-*s*-triazine (**74**) with DMF to give the reactive "Gold's Reagent" (**75**), which is condensed with substituted hydrazines to give good yields of 1-substituted triazoles (**10**) (Scheme 25).



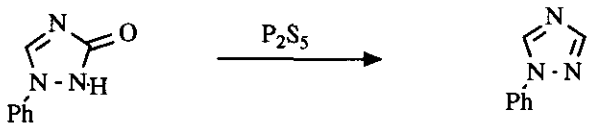
74 75 10

R = Ph (77%)
R = $HOCH_2CH_2$ (62%)
R = $Et_2NCH_2CH_2$ (50%)

Scheme 25

2.7. Miscellaneous

Another method[58, 59] for the preparation of 1-aryl-1,2,4-triazole is illustrated by the treatment of the triazolinone (**76**) with P_2S_5 to remove the oxo function (Scheme 26).



76 **10**

Scheme 26

Apparently this reaction is limited to N-aryltriazoles and N-unsubstituted triazoles since removal of both the oxo and 1-methyl groups in 1-methyltriazolinone has been reported.

3. Choice of Synthetic Reagents

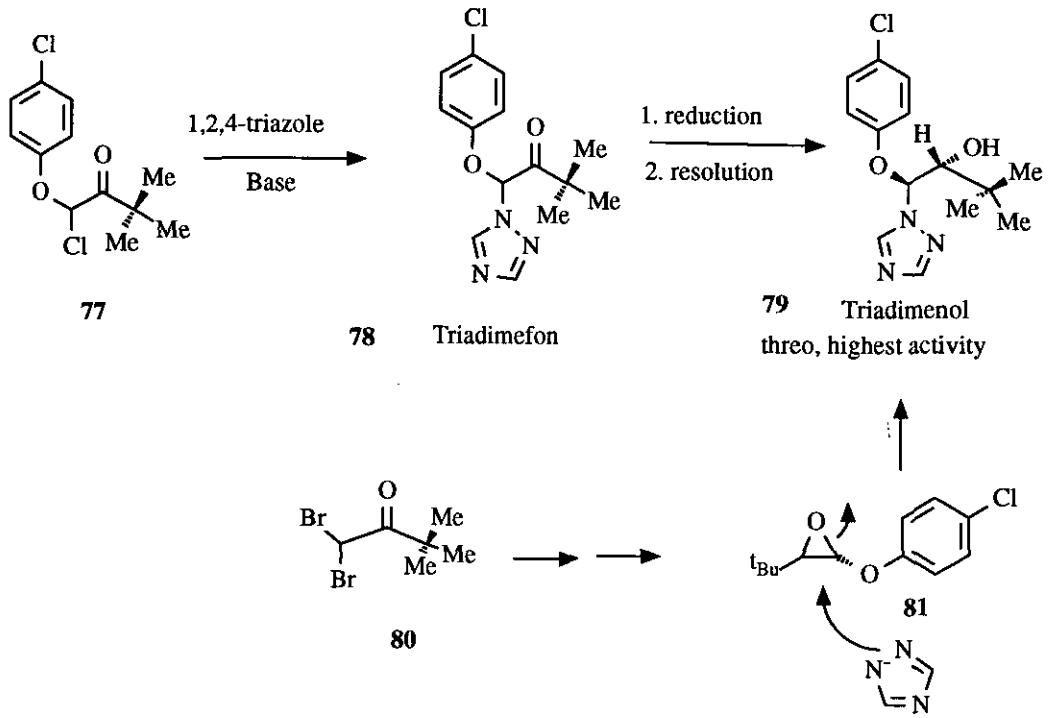
From the above it can be seen that a number of methods have been utilized for the synthesis of 1-substituted 1,2,4-triazoles. The method of choice, however, will depend upon a number of factors including the complexity and sensitivity of the molecule to be synthesized.

In the case of simple primary alkyl triazoles eg. 1-benzyl-1,2,4-triazole merely heating (typically, in the range 150-180 ^{0}C) 1,2,4-triazole with a slight excess of alkyl halide will produce a high yield of the desired product. Mechanistically, this may involve rearrangement of the concomitantly produced 4-isomer under the conditions of the reaction or during the purification procedure.[45] With secondary alkyl halides elimination

products will typically be formed in addition to the desired product.

4-Amino-1,2,4-triazole, a protected, directing synthetic equivalent of 1,2,4-triazole can be utilized[38-41] in cases where regiospecificity under mild conditions is required. Deamination of the intermediate triazolium salt may be achieved readily with nitrous acid.

Alkylation with epoxides[60, 61] has been used when the introduction of chirality or a hydroxyalkyl function is required. The reaction of 1,2,4-triazole with a specific hindered epoxide has been utilised to give rise to specific enantiomers of biological active racemates (Scheme 27).



Scheme 27

REFERENCES

1. C. Temple, Jr., "*The Chemistry of Heterocyclic Compounds*", Vol. 37, (ed., J.A. Montgomery, A.S. Weissberger and E.C. Taylor, Wiley, New York, 1981; K.T. Potts, *Chem. Rev.*, 1961, **61**, 87.

2. J.B. Polya, "*Comprehensive Heterocyclic Chemistry*", (Vol.5, eds. A.R. Katritzky and C.W. Rees), Pergamon, Oxford, 1984, p. 733.
3. C.F. Kroger and W. Freiberg, *Chimia*, 1967, **21**, 161.
4. M.B. Green and D.A. Spilker "*Fungicide Chemistry, Advances and Practical Applications*", ACS Symposium Series 304, 1986; "Synthesis and Chemistry of Agrochemicals, (eds. D.R. Baker, J.G. Fenyes, W.K. Moberg and B. Cross), ACS Symposium Series 355, 1987; K. Richardson and M.S. Marriott, *Ann. Rep. Med. Chem.*, 1987, **22**, 159; S. Massa, R. Di Santo, A. Retico, M. Artico, N. Simonetti, G. Fabrizi, and D. Lamba, *Eur. J. Med. Chem.*, 1992, **27**, 495; M. Ogata, H. Matsumoto, S. Shimizu, S. Kida, M. Shiro, and K. Tawara, *Eur.J. Med. Chem.*, 1989, **24**, 137; P. Ph. Tozzolino, *Speciality Chemicals*, 1993, **13**, 54.
5. W.E. Dismukes, *Ann. Intern. Med.*, 1988, **109**, 177.
6. M.R. Atkinson and J.B. Polya, *J. Chem. Soc.*, 1954, 141.
7. R.G. Jones and C. Ainsworth, *J. Am. Chem. Soc.*, 1955, **77**, 1538.
8. R.A. Olofson and R.V. Kendall, *J. Org. Chem.*, 1970, **35**, 2246.
9. H. Hoffmann and R. Pooth, *Arch. Pharm.*, 1982, **315**, 422.
10. M.A. Khan and J.B. Polya, *J. Chem. Soc.(C)*, 1970, 85.
11. T. Kauffmann, J. Legler, E. Ludorff, and H. Fischer, *Angew. Chem., Int. Ed. Engl.*, 1972, **11**, 846.
12. R. Jacquier, M.L. Roumestant, and P. Viallefont, *Bull. Soc. Chim. Fr.*, 1967, 2634.
13. A.N. Terpigorev, M.B. Shcherbinin, A.G. Bazanov, *and* I.V. Tselinskii, *Zh. Org. Khim.*, 1982, **18**, 463 (*Chem. Abstr.*, 1982, **96**, 181213x).
14. A.R. Katritzky, W. Kuzmierkiewicz, and J.V. Greenhill, *Recl. Trav. Chim. Pays-Bas.*, 1991, **110**, 369.
15. R.M. Claramunt, J. Elguero, and R. Garceran, *Heterocycles*, 1985, **23**, 2895.
16. H. Zhang, L. Liao, and Q. Guo, *Youji Huaxue*, 1986, **2**, 108 (*Chem. Abstr.*, 1986, **105**, 226456b).
17. H. Zhang, L. Liao, and Q.Guo, *Faming Zhuanli Shenqing Gongkai Shuomingshu* CN 85,102,995 (*Chem. Abstr.*, 1988, **109**, 211055d).
18. M.L. Cerrada, J. Elguero, J. de la Fuente, C. Pardo, and M. Ramos, *Syn. Commun.*, 1993, **23**, 1947.
19. C. Ainsworth and R.G. Jones, *J. Am. Chem. Soc.*, 1955, **77**, 621.
20. Kureha Chemical Industry Co., Ltd., *Jpn. Kokai Tokkyo Koho JP* 82 77,678 (*Chem. Abstr.*, 1982, **97**, 182424z).
21. S.A. Inke, *Span. ES* 548,092; (*Chem. Abstr.*, 1987, **106**, 67321f).

22. K. Yamauchi and M. Kinoshita, *J. Chem. Soc., Perkin Trans. I*, 1973, 2506.

23. K. Smith, M.E.W. Hammond, D.M. James, I.J. Ellison, and M.G. Hutchings, *Chem. Lett.*, 1990, 351.

24. K. Smith, A. Small, and M.G. Hutchings, *SynLett.*, 1991, 485.

25. C. Stoelzer, W. Kraemer, K.H. Büchel,and W. Meiser, *Ger. Offen.*, 2,406,665 (*Chem. Abstr.*, 1975, **83**, 206289y) [equivalent *US Patent* 4,013,677].

26. H. Timmler; W. Kramer, K.H. Büchel, H. Kaspers, and W. Brandes, *Ger. Offen.*, 2,431,407, (*Chem. Abstr.*, 1976, **84**, 150636k) [equivalent *US Patent* 4,582,843].

27. R. Nyfeler, H. Zondler, and E. Sturm, *European patent* EP 126,430 (*Chem. Abstr.*, 1985, **103**, 71319s) [equivalent *US Patent* 4,945,100].

28. A. Kotone, M. Hoda, and T. Fujita, *Japan Kokai*, 75 04,074 (*Chem. Abstr.*, 1975, **83**, 114414g).

29. L.P. Makhno, T.G. Ermakova, E.S. Damnina, L.A. Tatarova, G.G. Skvortsova, and V.A. Lopyrev, *USSR patent* 464,584 (*Chem. Abstr.*, 1975, **83**, 114416j).

30. S. Shimizu and M. Ogata, *J. Org. Chem.*, 1987, **52**, 2314.

31. V.N. Torocheshnikov, N.M. Sergeyev, N.A. Viktorov, G.S. Goldin, V.G. Poddubny, and A.N. Koltsova, *J. Organometal. Chem.*, 1974, **70**, 347.

32. J.G.A. Luijten, M.J. Janssen, and G.J.M. Van der Kerk, *Recl. Trav. Chim. Pays-Bas*, 1962, **81**, 202.

33. R. Gassend, J.C. Maire, and J.C. Pommier, *J. Organomet. Chem.*, 1977, **133**, 169.

34. J.P. Gasparini, R. Gassend, J.C. Maire, and J. Elguero, *J. Organomet. Chem.*, 1980, **188**, 141.

35. H.G.O. Becker, L. Krahnert, G. Rasch, W. Riediger, and J. Witthauer, *J. Prakt. Chem.*, 1969, **311**, 477 (*Chem. Abstr.*, 1969, **71**, 388675s).

36. A.R. Katritzky, G.F. Zhang, J. Pernak, and W.Q. Fan, *Heterocycles*, 1993, **36**, 1253.

37. C.F.H. Allen and A. Bell, *Org. Syn.*, 1944, **24**, 12; G.L. Goe, E.F.V. Scriven, J.G. Keay, and L.M. Huckstep, *European Patent* EP 269,308 (*Chem. Abstr.*, 1988, **109**, 211058g) [equivalent *US Patent* 5,099,028].

38. H.G.O. Becker, H. Boettcher, T. Roethling, and H.J. Timpe, *Z. Chem.*, 1966, **8**, 22 (Chem. Abstr., 1966, **64**, 19596d)

39. A. Kotone, M. Hoda, and T. Fujita, *Jpn. Kokai. Tokkyo. Koho.*, 1974, SHO 49-117470.

40. B.A. Astleford, G.L. Goe, J.G. Keay, and E.F.V. Scriven, *J. Org. Chem.*, 1989, **54**, 731.

41. J.G. Keay and E.F.V. Scriven, *Chemical Specialities USA 91 Symposium.*, 1991, 21.

42. C.S. Barnum, R.E. Olson, and W.K. Moberg, *European Patent* EP 296,745 (*Chem. Abstr.*, 1989, **110**, 173241x).

43. M.G. Hutchings, A. Small, and K. Smith, Brit. *UK Patent* GB 2,198,436 (*Chem. Abstr.*, 1989, **110**, 212823k).

44. R.V.H. Jones, *European Patent* EP 326,241 (*Chem. Abstr.*, 1990, **112**, 55882a), [equivalent *US Patent* 4,966,976].

45. K. Smith, A. Small, and M.G. Hutchings, *Chem. Lett.*, 1990, 347.

46. T.W. Bentley, L.M. Howle, P.J. Wareham, and R.V.H. Jones, *Tetrahedron*, 1992, **48**, 7869.

47. S. Shimizu and M. Ogata, *J. Org. Chem.*, 1986, **51**, 3897

48. S. Shimizu and M. Ogata, *Syn. Commun.*, 1989, **19**, 2219.

49. S. Shimizu and M. Ogata, *Tetrahedron*, 1989, **45**, 637.

50. J. F. Chollet, L. Miginiac, G. Picotin, and P. Miginiac, *Syn. Commun.*, 1989, **19**, 2167.

51. H. Timmler, K. Buchel, W. Brandes, P.E. Frohberger, and H. Scheinpflug, *Ger. Offen.*, 2,547,954 (*Chem. Abstr.*, 1977, 87, 53317m), [equivalent *US Patent* 4,327,104].

52. G. Pellizari and A. Soldi, *Gazz. Chim. Ital.*, 1905, **35**, 373.

53. C. Ainsworth, N.R. Easton, M. Livezey, D.E. Morrison, and W.R. Gibson, *J. Med. Pharm. Chem.*, 1962, **5**, 383.

54. C. Grundmann and R. Ratz, *J. Org. Chem.*, 1956, **21**, 1037.

55. H. Kohn and R.A. Olofson, *J. Org. Chem.*, 1972, **37**, 3504.

56. H. Gold, *Angew. Chem.*, 1960, **72**, 956 (*Chem. Abstr.*, 1960, **55**, 14478b).

57. M.A. Khan and J.B. Polya, *Rev. Latinoamer. Quim.*, 1972, **3**, 119; S. Somasekhara, R.K. Thakkar, and G.F. Shah, *J. Indian. Chem. Soc.*, 1972, **49**, 1057.

58. O. Widman, *Ber.*, 1893, **26**, 2612.

59. G. Young and W.H. Oates, *J. Chem. Soc.*, 1901, **79**, 659.

60. H. Arold, H.L. Elbe, E. Kranz, W. Kraemer, J. Stetter, and C. Stoelzer, *Ger. Offen.* 2,713,777 (*Chem. Abstr.*, 1979, **90**, 38931a).

61. V.A. Prasad, *US Patent* 4,970,320 (*Chem. Abstr.*, 1991, **114**, 122385x); J. Gasteiger and K. Kaufmann, *Tetrahedron Lett.*, 1985, **26**, 4341.

Received, 27th September, 1993