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Synthesis and Stereochemistry of N^4-Amino-1, 2, 4 -Triazoles with Unsymmetrical Substituents at 3, 5-Positions

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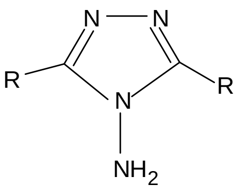
ABSTRACT

N^4-Amino-1, 2, 4 -triazoles carrying different substituents at 3, 5 - positions have been prepared by cyclocondesation of unsymmetrical N, N′-diacylhydrazines with hydrazine hydrate. The method is simple and straightforward and the yields are in most cases quantitative. The aminotriazoles are again condensed with carbonyl compounds to yield hydrazone derivatives which are interesting target molecules for stereochemical studies.

Key words : cyclocondensation, unsymmetrical aminotriazoles, stereochemical studies.

INTRODUCTION

Triazoles constitute an interesting group of heterocyclic compounds containing three 'N' atoms in a 5 - membered ring. 1, 2, 4 -Triazole and its derivatives represent some of the most biologically active classes of compounds possessing a wide spectrum of biological and pharmacological properties [1-6]. N^4 - Amino - 1, 2, 4 - triazoles with substitutions at 3, 5 - positions **1** represent a group of interesting target molecules from the point of studying their stereochemistry and their biological properties.



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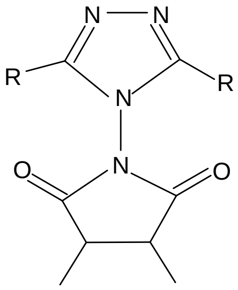

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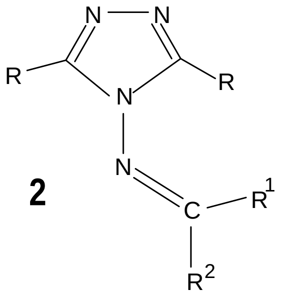

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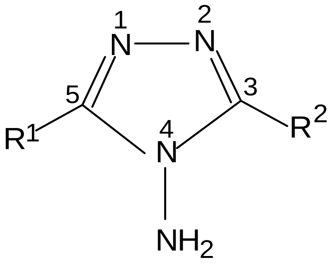
The N^4 - Amino group in **1** can be locked in some other ring system as in **2** which would provide the opportunity to study the restricted rotation about the Nsp^2-Nsp^2 single bond. In compounds of the type **2** the molecule adopts non-planar conformation about the N - N bond because of steric interactions between the substituents (R's) in the triazolyl moiety and the carbonyl groups in the imide ring system in the planar transition state.

Such non-planar conformations about the N - N bond have been illustrated[7] using asymmetric cage moieties containing the carbonyl system. An energy barrier of 87.86 $kJmol^{-1}$ hindering the rotation about the Nsp^2 - Nsp^2 single bond had been calculated on the basis of coalescence phenomena using Dynamic NMR studies. On the other hand, the terminal amino group in **1** can be consensed with carbonyl compounds to give derivatives of the type **3** which represent a group of interesting molecules for the study of stereochemistry involving restricted rotation about the Nsp^2 - Nsp^2 single bond and Nsp^2 - Csp^2 double bond together in one system[8]. The synthesis of these heterocyles are therefore of considerable interest.

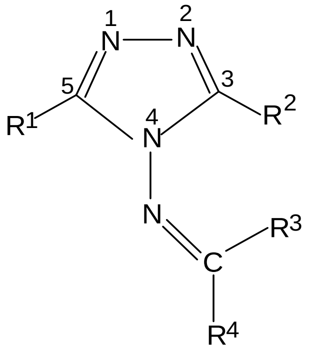
For the present studies, the following compounds 5a-5d and 6a-6e (Where $R^1 \neq R^2$) were prepared and characterised with the help of spectroscopic data.

	R^1	R^2
5a	$-C_6H_5$	$-CH_3$
5b	$-CH_2C_6H_5$	$-CH_3$
5c	$-CH_2C_6H_5$	$-C_6H_5$
5d	$-C_6H_4CH_3$(O)	$-CH_3$



5a-5d

	R^1	R^2	R^3	R^4
6a	$-C_6H_5$	$-CH_3$	$-C_6H_5$	$-C_6H_5$
6b	$-C_6H_5$	$-CH_3$	$-C_6H_5$	-H
6c	$-CH_2C_6H_5$	$-C_6H_5$	$-C_6H_5$	$-C_6H_5$
6d	$-CH_2C_6H_5$	-SH	$-C_6H_5$	-H
6e	$-CH_3$	$-C_6H_4CH_3$(*o*)	$-C_6H_5$	$-C_6H_5$



6a-6e

EXPERIMENTAL SECTION

The melting points were recorded on "VEEGO" m. p. apparatus and are uncorrected. IR spectra were recorded on a SHIMADZU FTIR 8400S spectrophotometer in KBr pellets with absorption given in cm^{-1}. ^1HNMR spectra were recorded in deuterated chloroform or deuterated dimethylsulphoxide on a Brucker ACF 300 MHz spectrophotometer or Jeol GSX 400 MHz spectrophotometer. The chemical shifts (δ) are given in ppm relative to internal tetramethyl silane (TMS). The compounds were purified by column chromatrography on silica gel using a solvent mixture of ethyl acetate and petroleum ether and by crystallization from ethanol or ethanol and diethyl ether mixture. The purity of the compounds were checked by TLC on silica gel plates using ethyl acetate and petroleum ether mixture, uv radiation or iodine were used as visualizing agent.

Preparation of compounds

Preparation of N^4 - amino - 3, 5 - disubstituted - 1, 2, 4 - triazoles (5):

An ethanolic solution of carboxylic acid was refluxed for 8 h in the presence of few drops of H_2SO_4 to yield ethyl ester. The resulting ester was then treated with hydrazine hydrate to get acid hydrazide. The hydrazide was treated with acid chloride at room temperature with constant stirring to give unsymmetrical N, N′ - diacylhydrazine. An equimolar amount of N, N′ - diacylhydrazine and hydrazine hydrate was heated under reflux for 5 - 6 h. The compound was isolated from the product by column chromatography (silica gel) using a mixture of ethyl acetate and petroleum ether as eleunt.

5a : Yield : 70%; m. p. : 102 - 04°C; Calculated for $C_9H_{10}N_4$: C, 62.05%; H, 5.79%; N, 32.16%; Found : C, 62.09%; H, 5.81%; N, 32.11%, IR (KBr) (Cm^{-1}) : 3201 (N - H), 3296 (N - H),1614(C = N), 1566 (C = N), ^{1}HNMR ($CDCl_3$) : δ 1.59(3H, s, CH_3), 4.10(2H, NH_2), 7.26 - 7.76(5H, m, Ar)

5b : Yield : 80%; m. p.: 117°C; Calculate for $C_{15}H_{14}N_4$: C, 71.98%; H, 5.64%; N, 22.38%; Found: C, 71.99%; H, 5.68%; N, 22.44%; IR(KBr) (Cm^{-1}): 3201(N - H), 3296 (N - H), 1612 (C = N), 1564 (C = N) ; ^{1}HNMR($CDCl_3$) : δ 3.59(2H, s, CH_2), 4.12(2H, s, NH_2), 6.66 - 7.77(10H, m, Ar).

5c : Yield : 70%; m. p. : 110°C; Calculated for $C_{10}H_{12}N_4$: C, 63.81%; H, 6.43%; N, 29.77%; Found : C, 63.80%; H, 6.45%; N, 29.70% ; IR(KBr) (Cm^{-1}) : 3180 (N - H), 3292(N - H), 1641(C = N), 1527(C = N) ; ^{1}HNMR($CDCl_3$): δ 1.63(3H, s, CH_3), 3.58(2H, s, CH_2), 3.89(2H, s, NH_2), 7.22 - 7.38(5H, m, Ar)

5d : Yield : 90%; m. p. : 121 - 23°C; Calculated for $C_{10}H_{12}N_4$: C, 66.64%; H, 7.46%; N, 25.90%; Found : C, 66.68%; H, 7.45%; N, 25.95% ; IR(KBr) (Cm^{-1}) : 3277 (N - H), 1609(C = N), 1594(C = N); ^{1}HNMR ($CDCl_3$): δ 1.79(3H, s, CH_3), 2.49(3H, s, CH_3), 4.15(2H, s, CH_2), 7.11 - 7.33(10H, m, Ar).

Preparation of Alkanimines (6):

An equimolar amount of compound (**5**) and carbonyl compounds in ethanol is presence of few drops of HCl or glacial acetic acid was heated under reflux for 2 h. On cooling the reaction mixture crystalline product were separated out. It was further purified by recrystallisation from aq. ethanol to get compounds (**6**).

6a : Yield : 91%; m. p. : 115°C; Calculated for $C_{22}H_{18}N_4$: C, 78.3%; H, 5.72%; N, 15.90%; Found : C, 78.35%; H, 5.68%; N, 15.85% ; 1R(KBr) (Cm^{-1}): 3023(Ar - H), 1573(C = N), 1583(C = N). ; ^{1}HNMR($CHCl_3$) : δ 1.6(3H, s, CH_3), 7.25 - 7.48(15H, m, Ar).

6b : Yield : 92%; m.p. : 210°C; Calculated for $C_{15}H_{14}N_4$: C, 73.89%; H, 5.84%; N, 20.27%; Found : C, 73.85%; H, 5.80%; N, 20.23% ; 1R(KBr)(Cm^{-1}) : 3081(Ar - H), 3032(Ar - H), 1600(C = N), 1552(C = N); ^{1}HNMR($CHCl_3$) : δ 2.50 (3H, s, CH_3), 7.48 - 7.92(10H, m, Ar), 11.89(1H, s, =C - H).

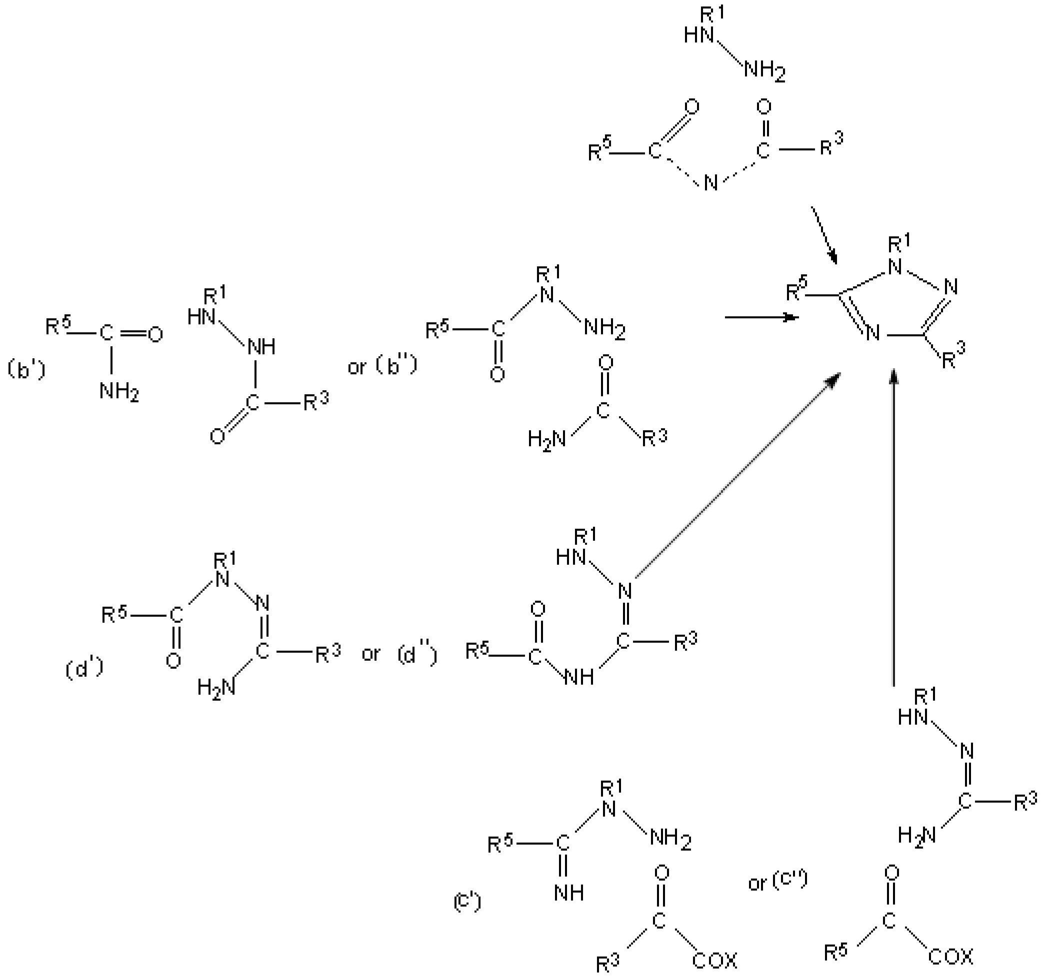
6c : Yield : 82%; m. p. : 205°C; Calculated for $C_{28}H_{22}N_4$: C, 81.28%; H, 5.65%; N, 13.07%; Found : C, 81.25%; H, 5.62%; N, 13.04%; 1R(KBr)(Cm^{-1}) : 3029 (Ar - H), 1650(C = N), 1546(C = N) ; ^{1}HNMR($CHCl_3$) : δ 1.93(2H, s, CH_2), 7.18 - 7.85(20H, m, Ar)

6d : Yield : 70%; m. p. 194°C Calculated for $C_{16}H_{14}N_4S$: C, 66.21%; H, 5.23%; N, 18.17%; S, 10.40% ; Found : C, 66.25%; H, 5.25%; N, 18.12%; S, 10.41%; 1R(KBr)(Cm^{-1}) : 3101(Ar - H), 3061(Ar - H), 2752(S - H), 1583(C = N), 1506 (C = N), 1419(C = C) ; ^{1}HNMR($CHCl_3$) : δ 4.18(2H, s, CH_2), 7.23 - 7.84(10H, m, Ar), 10.32(1H, s, =C - H), 10.78(1H, s, S - H).

6e: Yield : 75%; m. p. : 133 - 35°C; Calculated for $C_{23}H_{20}N_4$: C, 79.16%; H, 6.64%; N, 14.28%; Found : C, 79.14%; H, 6.65%; N, 14.28% ; IR(KBr)(Cm^{-1}) : 3058(Ar - H), 3026(Ar - H), 1579(C = N), 1502(C = N), 1471 (C = C); ^{1}HNMR($CHCl_3$) : δ 1.79(3H, s, CH_3), 2.45(3H, s, CH_3), 7.13 - 7.70(15H, m, Ar).

RESULTS AND DISCUSSION

To present a systematic survey of methods suitable for the preparation of 1, 2, 4 - triazole and its derivatives is rather difficult. Usually the triazole ring is obtained either by synthesis from acyclic compounds or by transformation of other cyclic systems. In the former case analysis of the number and nature of bonds formed is a convenient, systematic way to approach triazole synthesis but it may be misleading to the extent of obstructing progress.

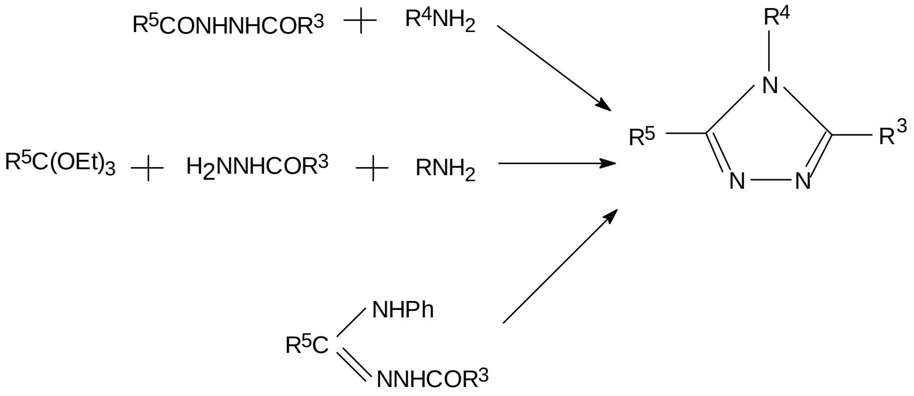


Scheme 1

Since only few synthesis of 1, 2, 4 - triazoles have had their mechanism studied and most of such studies had been carried out without the benifit of powerful modern methods, convenience of classification may not be the best guide to the choice of conditions and most reactive starting materials.

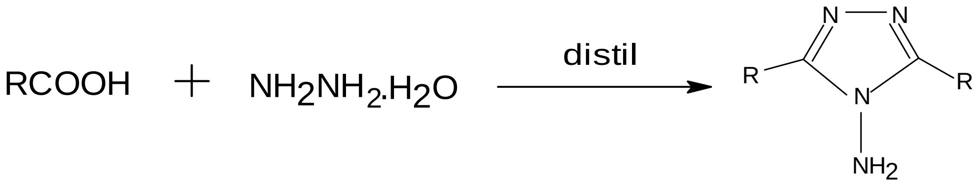
The relative ease of forming C - N and C = N bonds as compared with the difficulty of N - N bond formation practically leads to the use of hydrazines in the synthesis of 1, 2, 4 - triazoles. The possible synthetic methods are given in **Scheme 1**[9], describing the use of one of the following (a) hydrazine (b) an acylhydrazine (c) amidrazone or (d) acylamidrazone. The dotted lines leave the presence or absence of a bond open, X-stands for a suitable leaving group, usually OH, H_2O.

Synthesis of 1, 2, 4 - triazoles with substituents at N^4, proceeding from or through hydrazidines, amidrazones or acylimidrazones is presented in **Scheme 2**. It is assumed that all such reactions proceed through amidrazone or acylimidrazone intermediates[10], also that the formation of these is the rate determining step in these reactions. Although this generalization has not been well established, it is supported by the popularity of preparation starting from amidrazones or acylamidrazones, the success of other synthesis being limited by their suitability for the formation of these reactive intermediates.



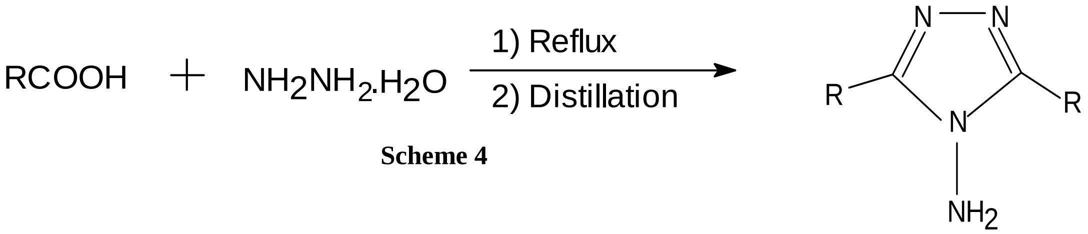
Scheme 2

One convenient synthesis of N^4 - Amino - 1, 2, 4 - triazoles with substituents at 3, 5 - positions compatible with green protocol is the direct distillation of the corresponding carboxylic acids with hydrazine hydrate [11] (**Scheme 3**).



Scheme 3

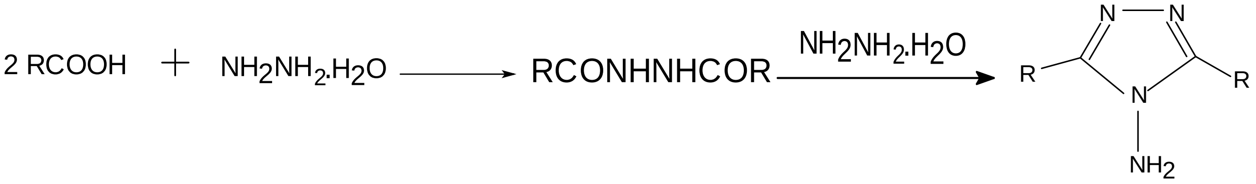
However, in practice, it has been found that direct distillation gives poor yields of the N^4 - Amino triazoles. The yield can be improved quantitatively by refluxing the corresponding acids with hydrazine for 3 - 4 hours followed by slow distillation [8] (S**cheme 4**).



Scheme 4

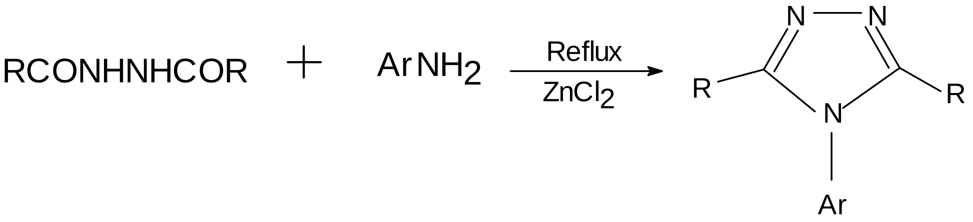
In fact, these procedures would give only the N^4 - Aminotriazoles with similar substitutions at 3, 5 - positions. N^4 - Aminotriazoles with unsymmetrical substitutions at 3, 5 - positions will be interesting from the point of stereochemical studies and will be interesting precursors for target compounds of the type **3**. To introduce dissimilar substitutions, a different synthetic strategy has to be adopted.

The synthesis of **1** by scheme **3** or scheme **4** probably proceeds through the formation of N, N′-diacylhydrazine which undergoes cyclocondensation with another molecule of hydrazine hydrate to give **1** (S**cheme 5**).



Scheme 5

The involvement of N, N′-diacylhydrazines as intermediate in triazole synthesis is supported by the fact that N^4 - arylsubstituted - 1, 2, 4 - triazoles **4** have been synthesized by the reaction of the corresponding diacylhydrazines with arylamines[12] (S**cheme 6**). These reactions are catalysed by $ZnCl_2$.



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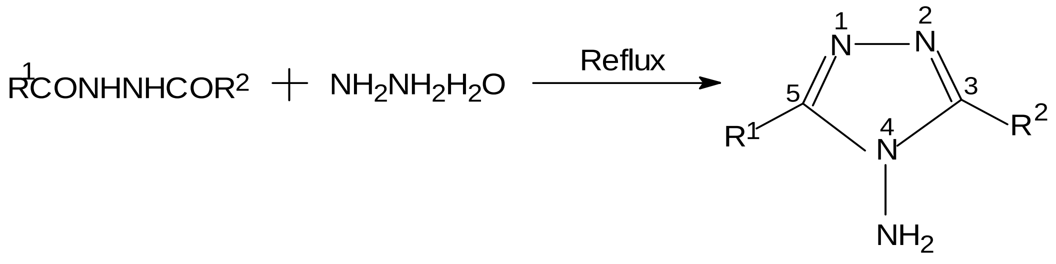
S**cheme 6**

Once it has been established that these triazoles can be obtained from cyclocondensation of N, N′-diacylhydrazines with another molecule of hydrazine, the question of introducing different substituents at 3, 5 - positions can be achieved by starting with unsymmetrical diacylhydrazines. The target compounds **5** have been synthesized from unsymmetrical diacylhydrazines following the reaction (**Scheme 7)**.

$$R^1COOH + C_2H_5OH \xrightarrow[\text{Reflux}]{\text{Conc. } H_2SO_4} \underset{\text{Ethyl carboxylate}}{R^1COOC_2H_5}$$

$$R^1COOC_2H_5 + NH_2NH_2.H_2O \xrightarrow[\text{Reflux}]{C_2H_5OH} \underset{\text{Acid hydrazide}}{R^1CONHNH_2}$$

$$R^1CONHNH_2 + R^2COCl \xrightarrow[\text{R.T.,stirred}]{\text{5\% NaOH}} \underset{\text{N,N'-Diacylhydrazine}}{R^1CONH\text{-}NHCOR^2}$$



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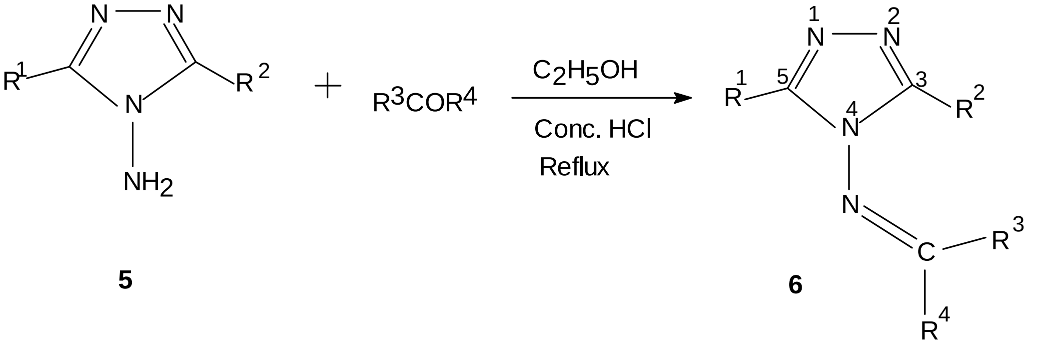
Scheme 7

These unsymmetrical triazoles **5** can be converted to hydrazone of the type **6** by condensation with carbonyl compounds (**Scheme 8**).



Scheme 8

In the hydrazones of the type **6**, the terminal nitrogen atom is locked in an ortho- substituted aromatic system (triazolyl ring), which prevents the inversion on the terminal nitrogen. These compounds **6** are interesting target molecules for stereochemical investigations regarding the restricted rotation about the Nsp^2 - Nsp^2 single bond and N = C double bond together in one system.

CONCLUSION

The synthesis of N^4-amino-1, 2, 4 –triazoles with unsymmetrical substituents at 3,5- positions proceeds through the formation of the intermediate unsymmetrical N,N′-diacyl hydrazines. The N^4-amino-1, 2, 4 –triazoles can be condensed with carbonyl compounds to give a type of sterically crowded hydrazones where the terminal nitrogen of the hydrazone is locked in a ring system which represent a group of interesting compounds for stereochemical studies.

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