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Review

1,3-Dipolar Cycloaddition Reactions of Substituted Benzyl Azides with Acetylenic Compounds

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Abstract: We review in this article some of our work which has been published over the last fifteen years in the area of 1,3-dipolar cycloaddition reactions of substituted benzyl azides with acetylenic compounds to form the corresponding 1,2-3-triazoles. Several triazole derivatives were transformed into triazolopyridazine and triazolo-1,3,4-oxadiazole derivatives upon their reactions with hydrazine.

Keywords: Azides, 1,2,3-triazole, triazolopyridazine, triazolo-1,3,4-oxadiazole, 1,3-dipolar cycloaddition reactions.

Introduction

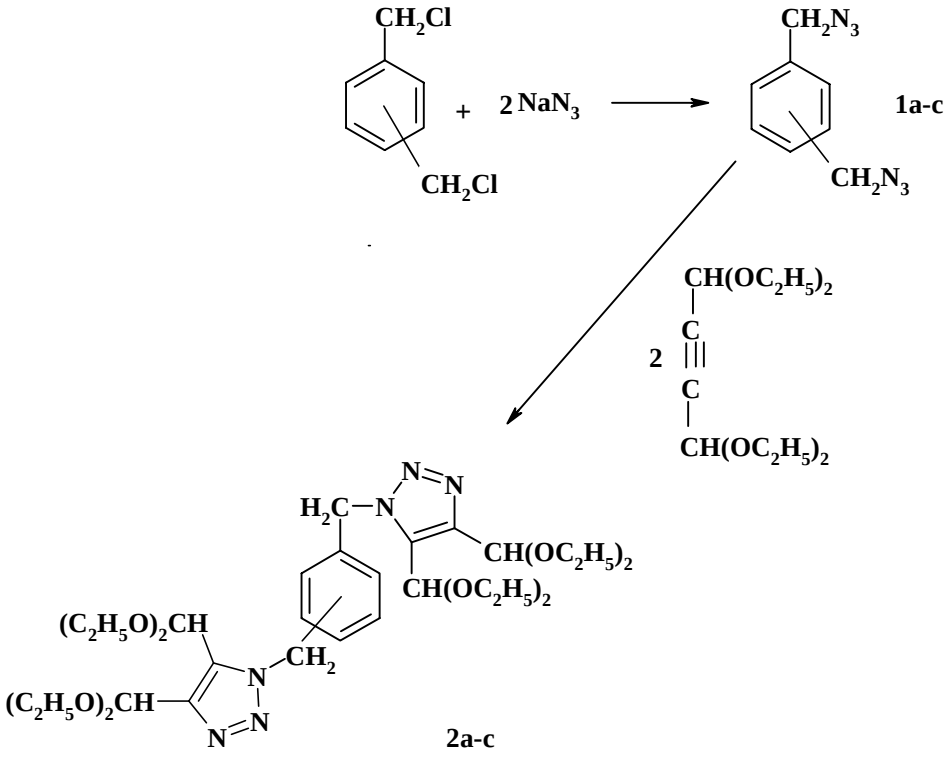
Azides are considered very important compounds due to both their industrial as well as biological applications [1]. Azide derivatives have been used in rubber vulcanization, polymer crosslinking, dyes, tire cored adhesives, foaming of plastics, pharmaceuticals, pesticides and herbicides [1]. Many azide compounds show mutagenic activities [2-4].

The chemistry of azides has thus attracted the attention of many chemists, since many of these compounds play an important role in organic chemistry [5-7]. One of the more useful synthetic applications of azides is the preparation of 1,2,3-triazoles via 1,3-dipolar cycloaddition reactions of azides with substituted acetylene compounds [8-13].

The chemistry of 1,2,3-triazoles has also received much attention because of their wide range of applications. They have been used as fungicides, herbicides, light stabilizers, fluorescent whiteners, optical brightening agents, and corrosion retardants [14-16]. Moreover 1,2,3-triazole derivatives show significant antimicrobial, cytostatic, virostatic, and anti-inflamatory activities [17].

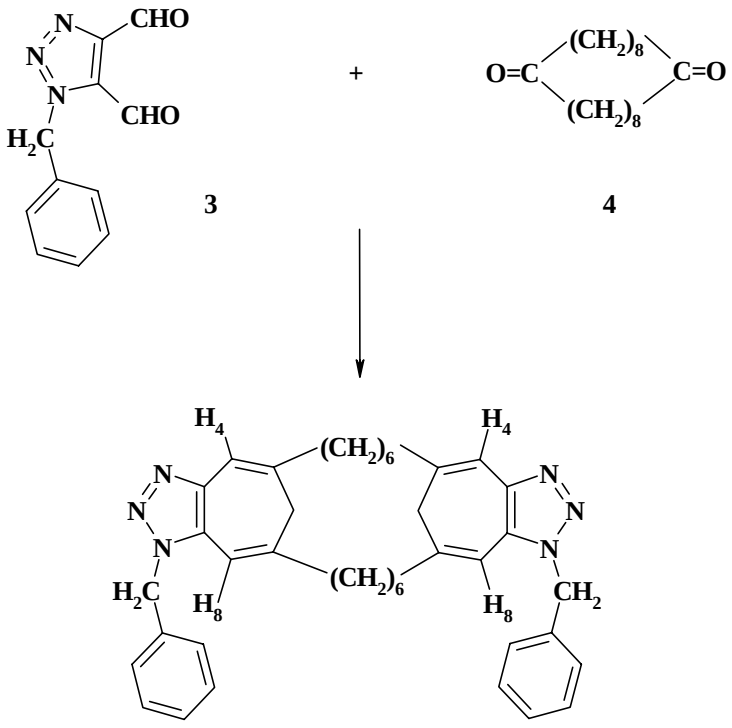
Over the last fifteen years we have contributed extensively to this field. Thus, in 1986 we reported the preparation of bis(azidomethyl)benzenes **1a-c** and their reaction with acetylendicarboxaldehyde bisdiethylacetal to form the phenylenebis(methylene)bis(triazole-4,5-dicarboxaldehyde)tetrakis(ethyl acetals) **2a-c** as shown in Scheme 1 [18].

Scheme 1



The same year we reported the synthesis of the novel ring system, 1,1′-dibenzyl-5,5′,7,7′-bis(hexamethyleno)bis[6(2H)-cycloheptatriazolone] (**5**) from the condensation reaction of 2 moles of 1-benzyl-*1H*-triazole-4,5-dicarboxaldehyde (**3**) with 1,10-cyclooctadecanedione (**4**) as shown in Scheme 2 [19]. The aim of this synthesis was to study the effect of a polymethylene bridge on the aromaticity and planarity of a system containing two triazoletropone systems within the same molecule [19].

Scheme 2



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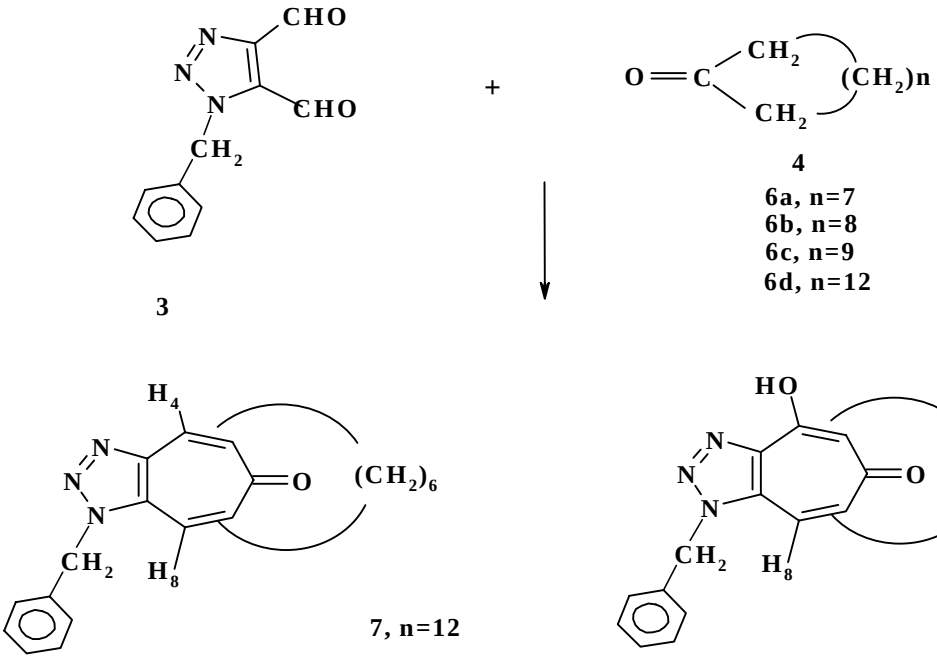
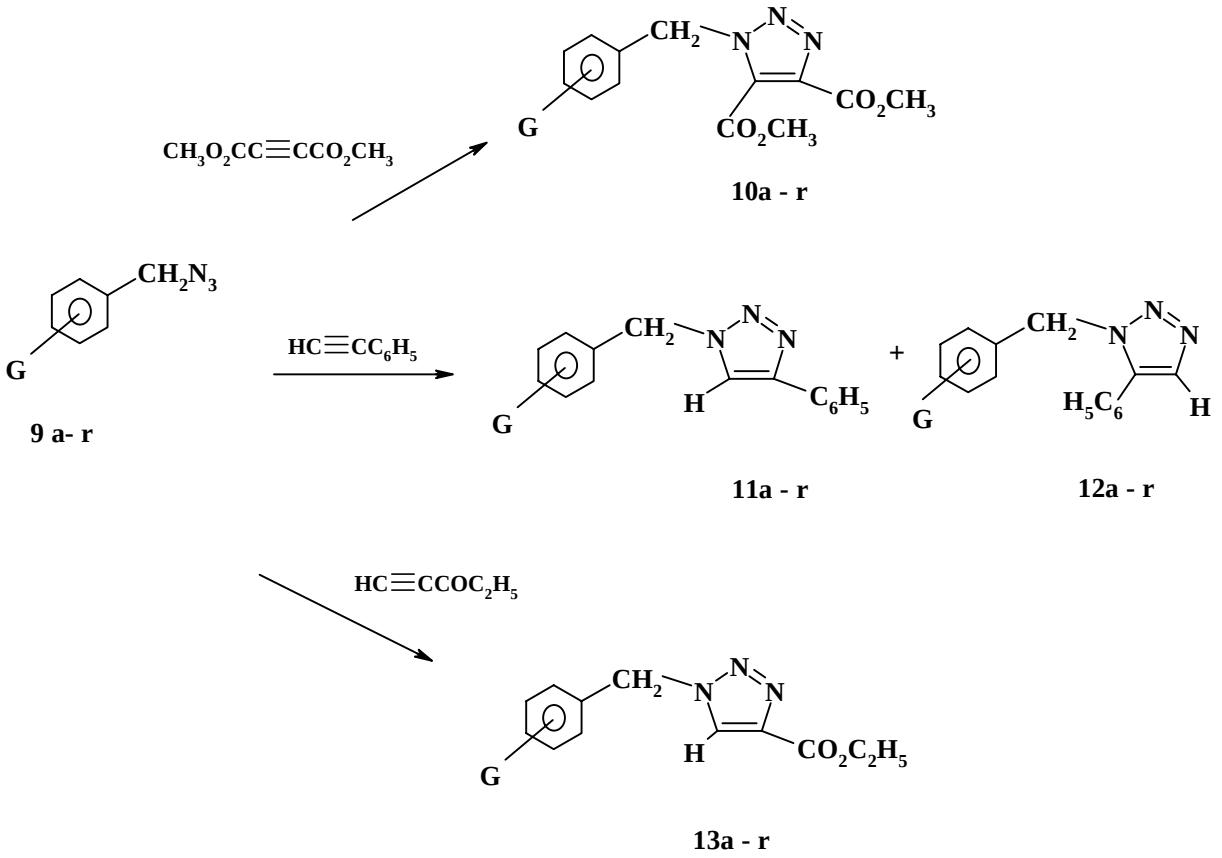
A year later we reported the condensation reaction of 1-benzyl-*1H*-triazole-4,5-dicarboxaldehyde (**3**) with cyclic ketones **6a-d** to form 1-benzyl-5,7-polymethyleno-6-(2H)-cyclo-heptatriazolone (**7)** or 4-hydroxy-1-benzyl-4,5-dihydro-5,7-polymethyleno-6-(2H)-cycloheptatriazol-ones (**8a-c**) as shown in Scheme 3 [20].

Scheme 3



In 1988, we described the interaction of synthetic organic azides with highly purified camel gluathione S-transferase in an attempt to elucidate the role of these enzymes in the detoxification of organic azides [21]. A year later our group described the reaction of substituted benzyl azides with some acetylenic esters and with phenylacetylene [22]. Thus, substituted benzyl azides **9a-r** were reacted with dimethyl acetylenedicarboxylate in boiling ethanol to give the corresponding triazoles **10a-r** in more than 80% yield as shown in Scheme 4.

Scheme 4



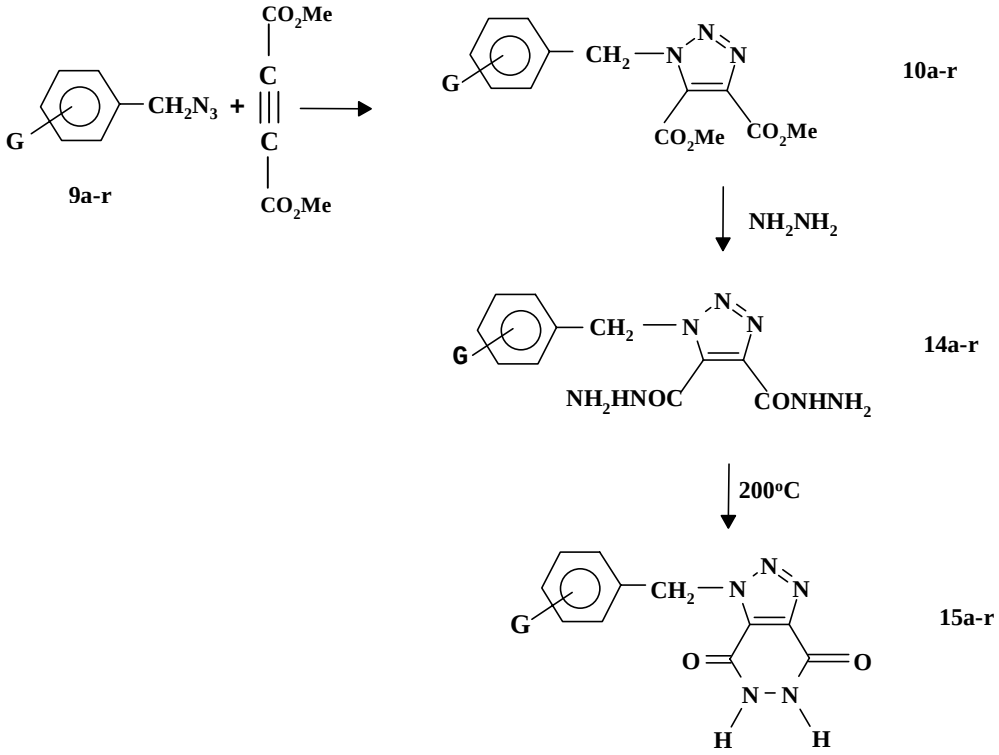
On the other hand, the reactions of azides **9a-r** with phenylacetylene afforded, as expected and revealed by thin layer chromatography, a mixture of two isomeric products in over 85% overall yield. The isomeric triazoles **11a-r**, **12a-r** are shown in Scheme 4. The product mixtures were separated by preparative thin layer chromatography using silica gel and a toluene-ethyl acetate mixture as eluent. The relative ratios of the two isomeric products was found to be in the range of 10:90 to 40:60. Surprisingly, the isomers separated in each reaction gave identical IR and ^{1}H-NMR spectral data and melting points. This might be due to the similarity of the chemical environment of the protons in either position 4 or 5 in the triazole ring. The less hindered triazoles **11a-r** are believed to be the major products on the basis of steric considerations. This assignment is quite compatible with the reported results of Tsypin and Mihelcic and their co-workers on the addition of heterocyclic and aliphatic azides

to phenylacetylene [23-24]. Unlike the reactions with phenylacetylene, the reactions of azides **9a-r** with ethyl propiolate were found to be completely regiospecific. Thin layer chromatography using different solvent systems confirmed the presence of a single product in each reaction. These products are believed to be triazoles **13a-r** as depicted in Scheme 4.

Reactions of **10a-r** with excess hydrazine hydrated under reflux conditions gave the corresponding bis (hydrazinocarbonyl) derivatives **14a-r**. Heating compounds **14a-r** at 200 °C for about 4-5 hrs was found to be a convenient method for the synthesis of 1-substituted benzyl-1H-1,2,3-triazolo [4,5-d] pyridazidine-4,7-diones **15a-r** as shown in Scheme 5 [25].

Scheme 5

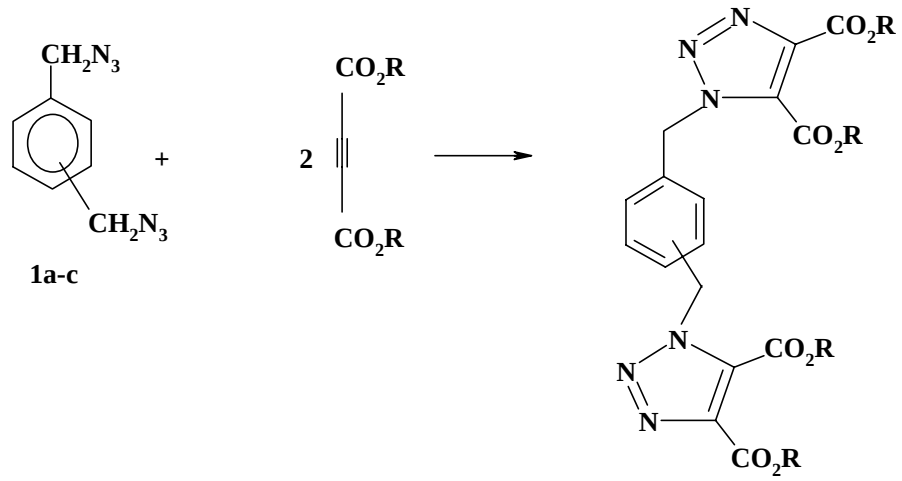
Compound	G
a	H
b	4-CH_3
c	3-CH_3
d	2-CH_3
e	4-OCH_3
f	3-OCH_3
g	4-NO_2
h	3-NO_2
i	2-NO_2
j	2-Cl
k	3-Cl
l	4-Cl
m	4-Br
n	3-Br
o	2-Br
p	2-F
q	3-F
r	4-F



In 1991, we reported the reactions of bis(azidomethyl) benzenes **1a-c** with several substituted acetylenes that formed the corresponding bistriazoles [26]. Thus 1,2-, 1,3- and 1,4-bis (azidomethyl) benzenes (**1a-c**) underwent cycloaddition reactions with dimethyl-, diethyl- and di-*tert*-butyl acetylenedicarboxylate, respectively, in methanol or ethanol at reflux temperature to form the corresponding tetramethyl, tetraethyl and tetra-*tert*-butyl 1,1′-(phenylenedimethylene) bis-1*H*-1,2,3-triazole-4,5-dicarboxylates **16a-c**, **17a-c** and **18a-c**, respectively, in quantitative yields as shown in

Scheme 6. The completion of the reaction was monitored by the disappearance of the azide IR absorption in the range 2170-2220 cm^{-1}.

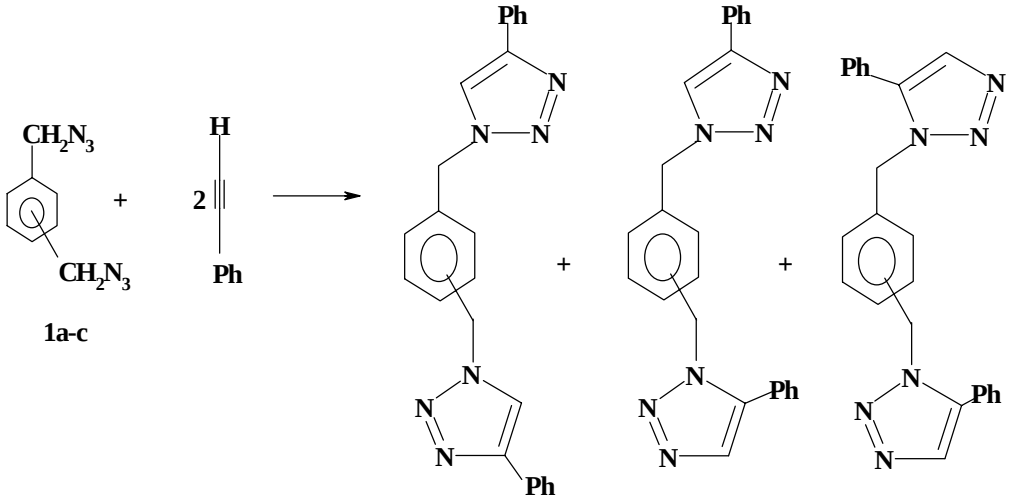
Scheme 6



a, *ortho*	**R=CH_3**	**16 a-c, R=CH_3**
b, *meta*	**R=C_2H_5**	**17 a-c, R=C_2H_5**
c, *para*	**R=$(CH_3)_3$**	**18 a-c, R=$(CH_3)_3$**

Likewise, bis-azides **1a-c** reacted with phenylacetylene to give a mixture of two isomeric products as revealed by thin-layer chromatography, although three isomeric products are theoretically possible as shown in Scheme 7.

Scheme 7

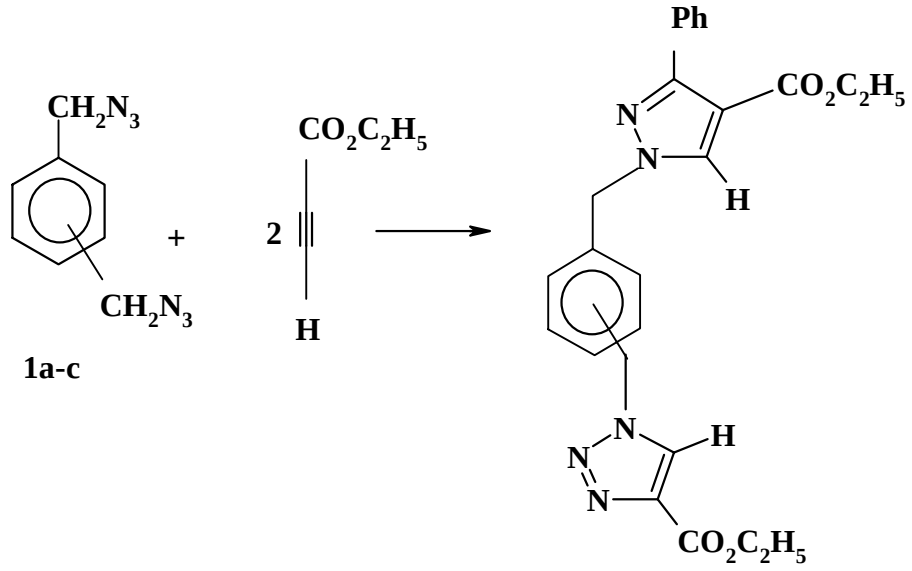


a, *ortho*
b, *meta* **19a-c** **20a-c** **21a-c**
c, *para*

^{1}H-NMR spectroscopy did not differentiate between the two isomeric bistriazoles. Thus, the four benzylic protons in the product mixture appeared as a sharp singlet in the range 5.52-5.70 ppm. This is quite consistent with our previously reported results on the reactions of monoazides with phenylacetylene [22]. Although the two products were not separated, it is believed that the major products are the less sterically hindered 1,1′- (phenylendimethylene) bis-[4-phenyl-*1H*-1,2,3-triazoles] **19a-c** while the minor products should be the isomers **20a-c** on the basis of steric and statistical considerations. The isomeric bistriazoles **21a-c** are excluded on the same basis. This regiochemical assignment is compatible with the literature reports, one of the recent reports being published by Fouli and co-workers [27].

In great contrast with the latter reactions, the reactions of bis-azides **1a-c** with ethyl propiolate, have displayed complete regiospecificity under similar conditions. Only one product was obtained in a high yield, again, this result is consistent with our previous findings [22]. In addition, on the basis of steric and electronic factors, the products are assigned structures **22a-c** as shown in Scheme 8. The remarkable difference in the reactivities of the three bis-azides **1a-c** is worthy of comment. The trend is quite clear. The 1,4-isomer **1c** is the most reactive whereas the 1,2-isomer **1a** is the least reactive. indeed, the decisive factor is the steric hindrance which is lowest in the 1,4-bis-azide **1c** and highest in the 1,2-isomer **1a** [26].

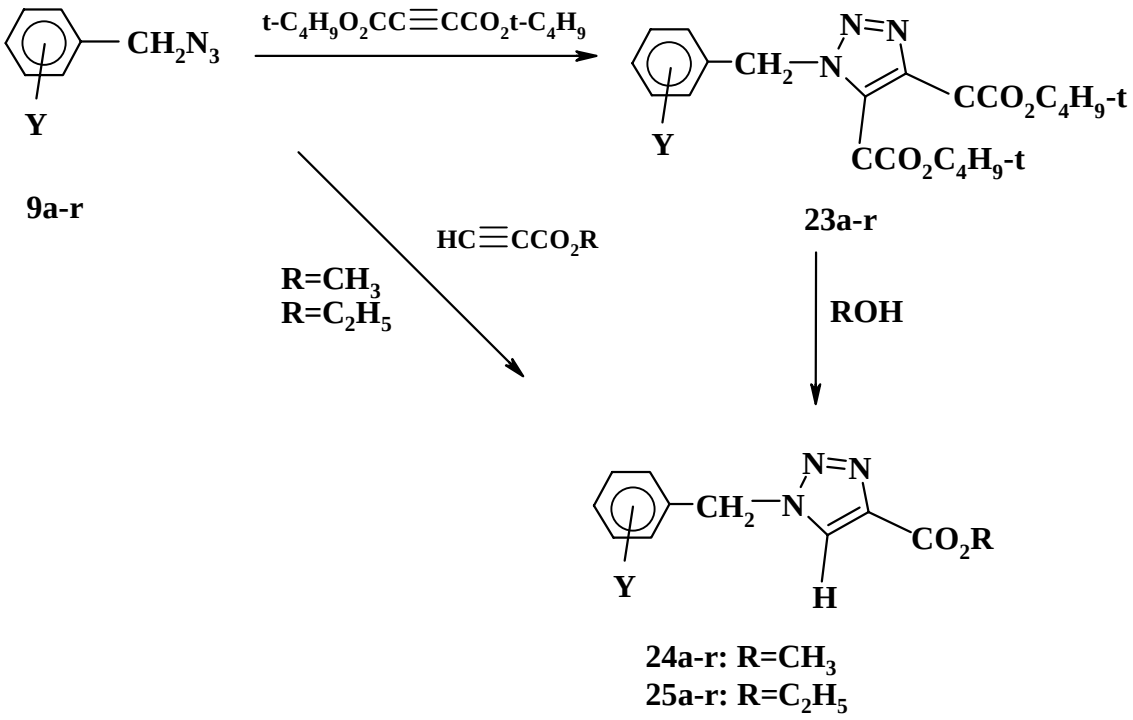
Scheme 8



Moreover, we have studied the effect of solvent and reaction time on the products of the 1,3-dipolar cycloaddition of substituted benzyl azides with di-*tert*-butyl acetylenedicarboxylate [28]. Substituted benzyl azides **9a-r** underwent cycloaddition reactions with di-*tert*-butyl acetylenedicarboxylate, in refluxing methanol or ethanol for 3-20 hrs producing di-*tert*-butyl 1-

(substituted benzyl)-1*H*-1,2,3-triazole-4,5-dicarboxylates **23a-r** in 73-94% yield, as shown in Scheme 9.

Scheme 9

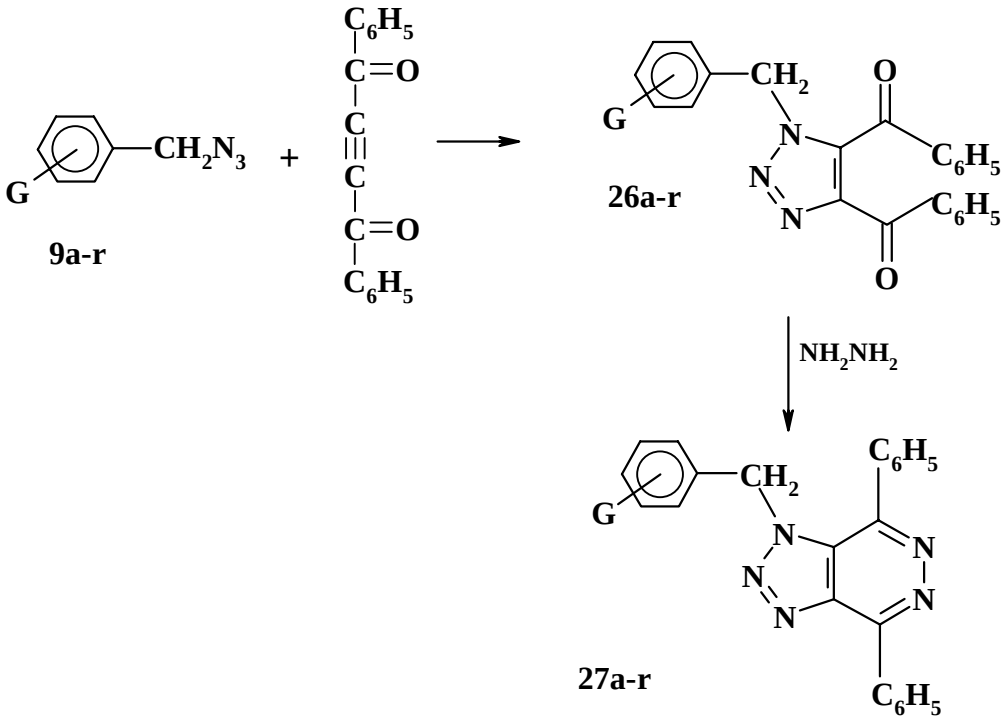


24a-r: R=CH_3
25a-r: R=C_2H_5

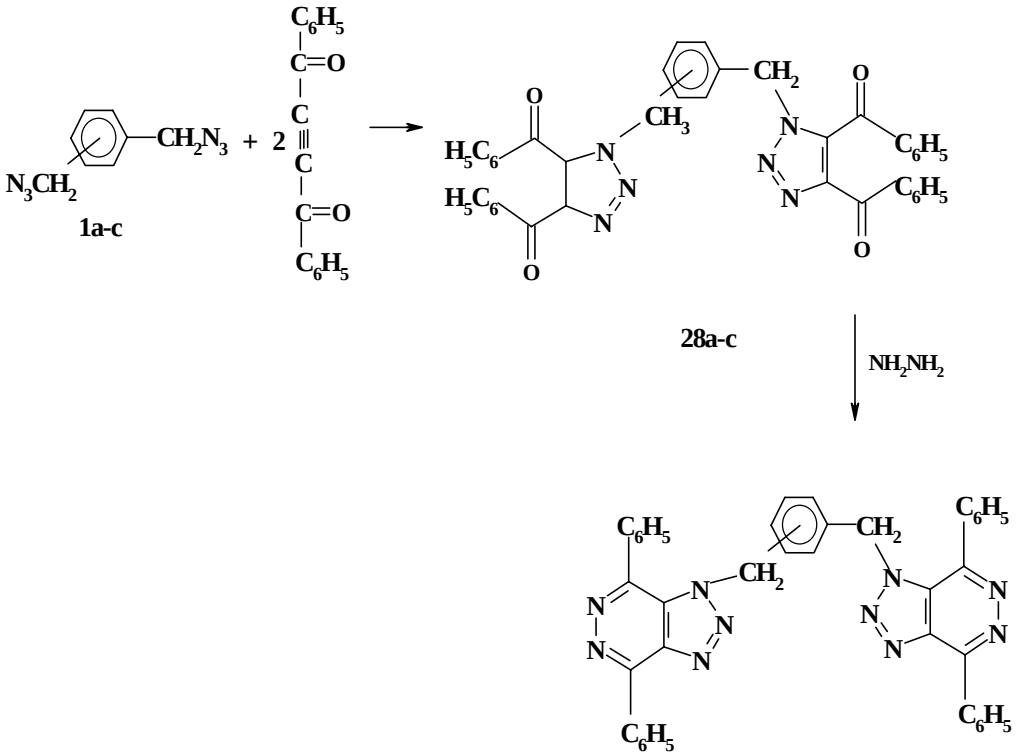
The reactions of azides **9a-r** with di-*tert*-butyl acetylenedicarboxylate, however, was found to be sensitive to the nature of the solvent being used and the type of the substituents on the phenyl ring. Thus prolonged reflux (2-3 days) of azides **9e-r** in protic solvents such as methanol or ethanol resulted in the formation of the triazole monoesters, methyl 1-(substituted benzyl)-*1H*-1,2,3-triazole-4-carboxylates **24e-r** and ethyl 1-(substituted benzyl)-*1H*- 1,2,3-triazole-4-carboxylates **25e-r**, respectively. Unexpectedly, the reaction of azides **9a-d** with di-*tert*-butyl acetylenedicarboxylate did not show the same trend under the same conditions since the triazole diesters **23a-d** were the only products obtained [28].

Recently, we have investigated the 1,3-dipolar cycloaddition reactions of substituted benzyl azides **9a-r** and bis (azdiomethyl) benzenes **1a-c** with dibenzoylacetylene to afford the corresponding 1H-1,2,3-triazole derivatives **26a-r** and **28a-c** respectively. Reaction of these triazoles **26a-r** and **28a-c** with hydrazine hydrated in ethanolic solution was found to produce in high yield the corresponding triazolopyridazine and bis (triazolopyridazine) derivatives **27a-r** and **29a-c,** respectively, as shown in Schemes 10 and 11 [29]. The inhibition effect of some of these 1-substituted benzyl-4,5-dibenzoyl-1,2,3-triazoles **26a-r** on the corrosion activity of mild steel in acid media has been investigated recently and it was found that these triazoles can be used as corrosion inhibitors [16,30,31].

Scheme 10

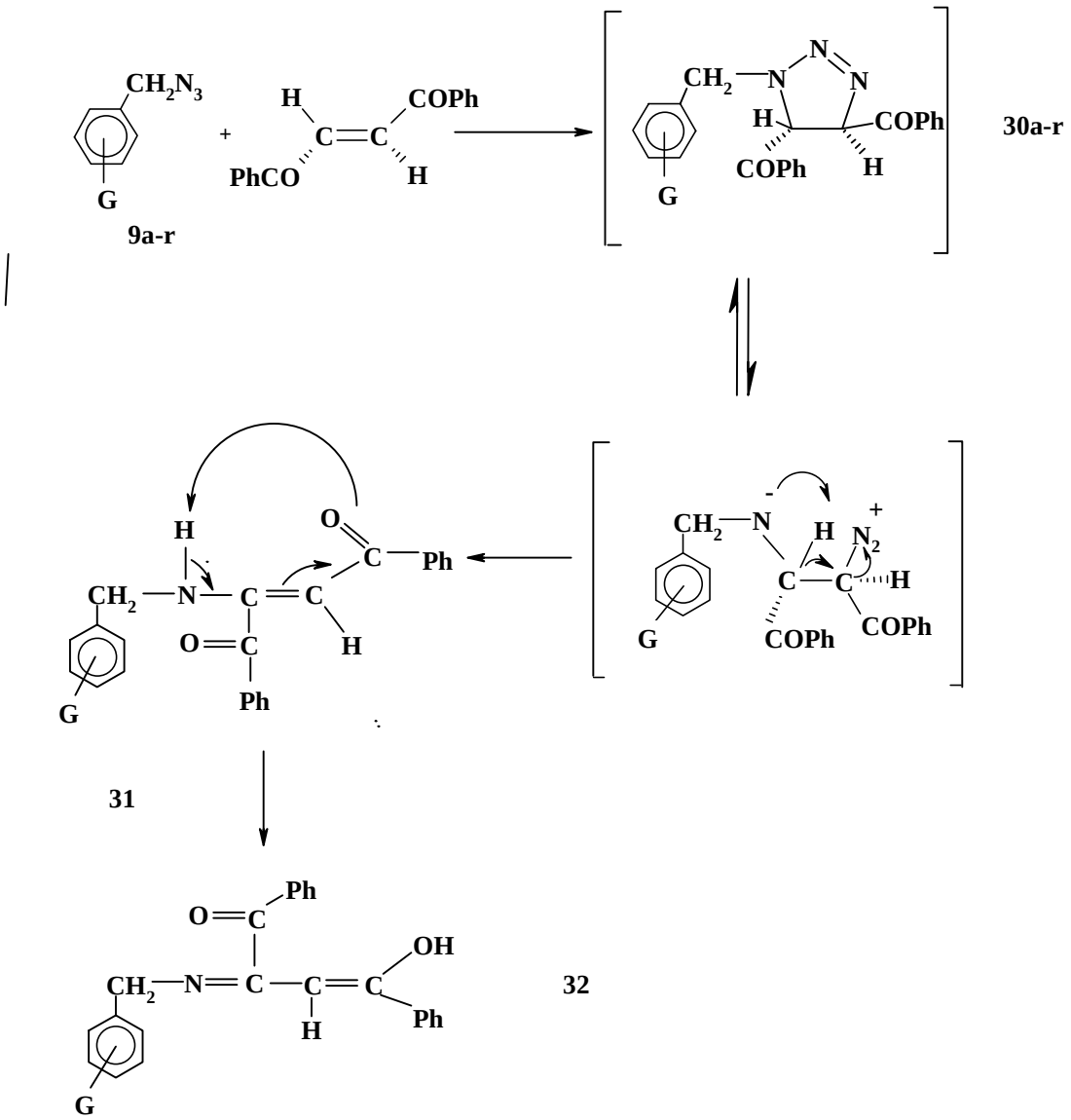


Scheme 11

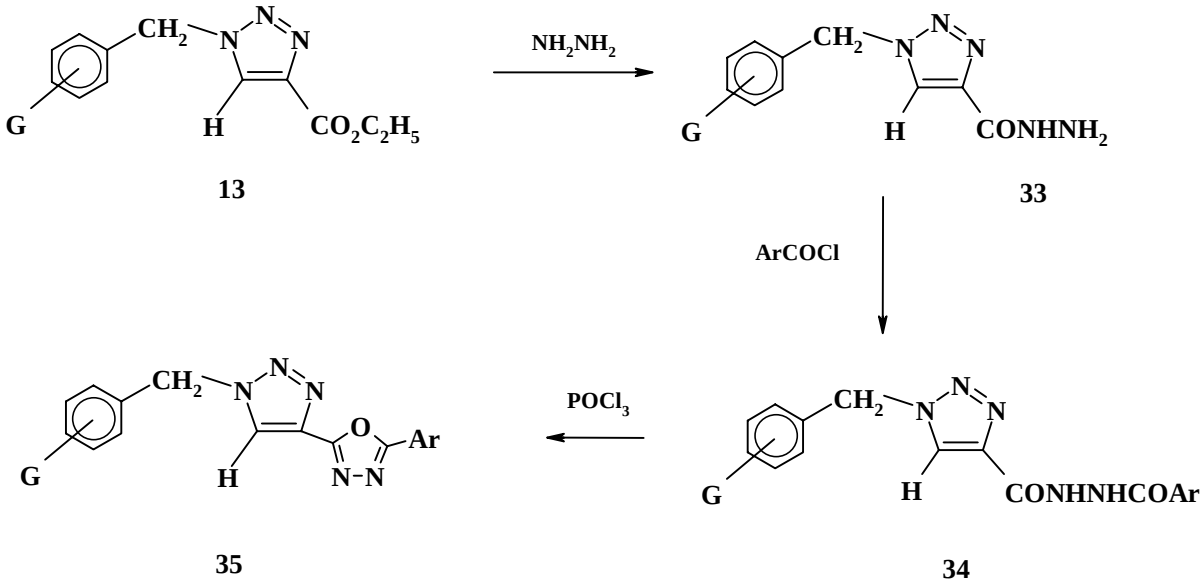


In the last few years, we have studied the cycloaddition reactions of substituted benzyl azides **9a-r** with trans-1,2-dibenzoylethylene. This study presented another good example of the drastic difference in the final products due to the difference in thermal stability of theadducts resulting from the cycloaddition process, namely triazoles and triazolines [32-34]. Thus, when azides **9a-r** reacted with trans-1,2-dibenzoylethylene in boiling ethanol, the enamines **31i-k,n-q** and enolimines **32a-h,l,m,r** were formed unexpectedly. The formation of enamines **31** and enolimines **32** might be explained by the formation of the corresponding thermally unstable triazoline **30a-r**, followed by ring cleavage and loss of a nitrogen molecule to afford the final products as keto-enol tautomers **31** and **32** as shown in Scheme 12 [32-34]. In 1999, we succeeded in the preparation of a series of 2-[1-benzyl-1,2,3-triazolo-4]-5-aryl-1,3,4-oxadiazole compounds **35** from ethyl 1-substituted benzyl-1,2,3-triazole-4-carboxylate **13** as shown in Scheme 13 [35].

Scheme 12



Scheme 13



G= H, Cl, CH_3, OCH_3

Ar= C_6H_5, pCH_3-C_6H_4, pCH_3O-C_6H_4, 2-furyl, 2-thienyl

The same year, we synthesized a series of 4,5-bis [5-aryl-1,3,4-oxadiazol-2-yl]-1-substituted benzyl-1,2,3-triazole compounds **38** from the reactions of dimethyl-1-substituted benzyl-1,2,3-triazole-4,5-dicarboxylate (**10**) with hydrazine, followed with addition of aroyl chlorides in aqueous THF in the presence of K_2CO_3 which resulted in dehydration and cyclization as shown in Scheme 14 [36].

Scheme 14

Acknowledgements

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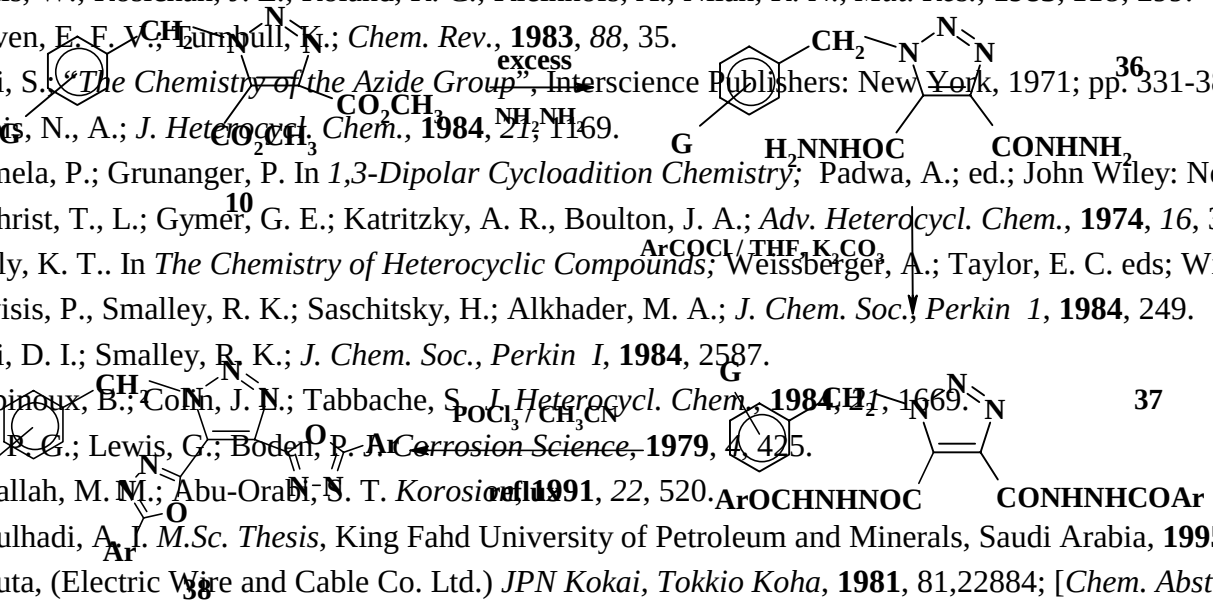

G=H,Cl, CH_3, CH_3O, NO_2, 2,6-Dichloro

Ar= C_6H_5, 4-$CH_3C_6H_4$, 2-furyl, 2-thienyl

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