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1,2,3-TRIAZOLE FORMATION UNDER MILD CONDITIONS *VIA* 1,3-DIPOLAR CYCLOADDITION OF ACETYLENES WITH AZIDES

Alan R. Katritzky,* Yuming Zhang, and Sandeep K. Singh

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, FL 32611-7200, USA

Abstract – 1,3-Dipolar cycloaddition of azides to various electron-withdrawing group substituted acetylenes leading to triazole formation under mild conditions (reaction temperature around 55 °C or below) are reviewed. Furthermore, our efforts to lower the reaction temperature of cycloaddition of acetylenic amides with azides have also been discussed.

INTRODUCTION

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1,2,3-Triazoles are important: (i) for their therapeutic value as cytostatic,[1] virostatic,[2] antiproliferative agents,[3] and GABA-antagonists;[4a,4b] (ii) as synthetic intermediates for antibiotics,[5a,5b,5c] antihistaminic agents,[6] muscarinic agonists for the treatment of Alzheimer's disease,[7] nucleosides,[8a,8b] rotaxanes,[9] chemiluminescent compounds[10a,10b] and polyheterocyclic compounds with neuroleptic activity;[11] (iii) industrially as insecticides,[12] fungicides,[13] plant growth regulators,[14,15] optical brighteners,[16] corrosion inhibitors,[17a,17b] photostabilizers for fibers, plastics or dyes,[18] and uv-screens for the protection of human skin.[19] Macromolecules with poly-1,2,3-triazoles, which have been synthesized by 1,3-dipolar cycloaddition reaction of polyazides with acetylenedicarboxylic esters, could be used for the complexation of metalions because of the high local density of nitrogen atoms.[20a,20b] Poly-1,2,3-triazoles, polymerized by (i) azidoacetylenes;[21a,21b] (ii) bisacetylenes with bisazide;[22a,22b] or (iii) keto-stabilized bisalkylidenephosphoranes with bisazides,[23] show great thermostability. The literature reports no exothermic decomposition below 320 ^{o}C.

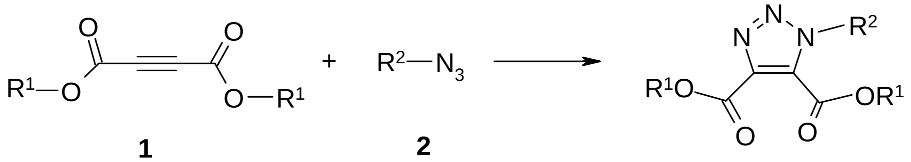
Many 1,2,3-triazoles have been prepared by 1,3-dipolar cycloadditions of acetylenes with azides. This reaction and its mechanism have been studied extensively. Under appropriate conditions, 1,3-dipolar cycloadditions of azides to acetylenes succeed with all possible combinations of substituent types. Generally, for a given azide, the more electron-withdrawing the substituents on the acetylene, the easier the cycloaddition reactions. Electron-withdrawing substituents on azides have the opposite effect. Bulky substituents hinder the reaction rate, but lead to better selectivity. The cycloadditions of an acetylene with an azide are typically carried out in toluene, ethanol or benzene, but labile molecules may not survive these conditions. The present literature review concentrates on examples of triazole formation at temperatures around 55 °C or below. We first discuss the 1,3-dipolar cycloaddition of the widely studied ester-substituted acetylenes followed by less common carboxy- and acyl-substituted acetylenes. Rare examples from the literature on acetylenecarboxylic amides and our preliminary results with these substituents are also discussed.

1. LOW-TEMPERATURE 1,3-DIPOLAR CYCLOADDITION OF ESTER SUBSTITUTED ACETYLENES

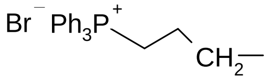
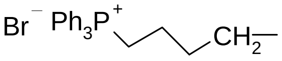
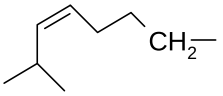
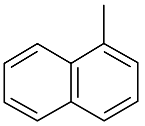
1.1 Ester-ester substituted acetylenes.

Acetylenedicarboxylic esters, in which the triple bonds are activated by two strong electron-withdrawing groups, are probably the most reactive acetylenes. Treatment of dimethyl acetylenedicarboxylate with phenyl, vinyl or alkyl azide in ether or methylene chloride gives the corresponding triazole (**3**) in good yields (Scheme 1).[24a,24b,24c,24d] Even the cycloaddition of sterically hindered di(*t*-butyl) acetylenedicarboxylate with azides can afford high yields of triazoles under mild conditions.[25a,25b]

Scheme 1



1 **2** **3**

Entry	R^1	R^2	Yield (%)	Entry	R^1	R^2	Yield (%)
a	Me	*p*-MeOC_6H_4—	94[a]	**e**	Me		80[e]
b	Me	≡—CH_2—	67[b]	**f**	Me		90[e]
c	Me	C_6H_5—	73[c]	**g**	*t*-Bu	o-BrC_6H_4—	73[f]
d	Me		62[d]	**h**	*t*-Bu		87[g]

a: In dioxane, 20 °C for 10 days; b: In ether, at 0 °C for 6 weeks;

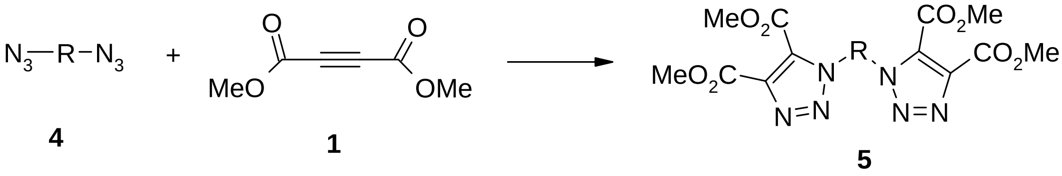
c: In refluxing ether for 66 h; d: In CH_2Cl_2, at ambient temperature for 3 h;

e: In CH_2Cl_2, at ambient temperature for 4 h; f: Heated in methanol for 3 h;

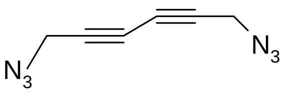
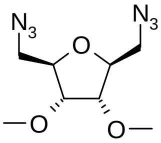
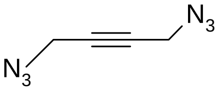
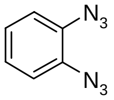
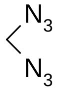
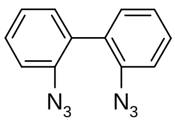
g: Reacted in large excess acetylene at rt for 2 weeks.

Similarly, bistriazoles (**5**) can also be prepared by cycloaddition of dimethyl acetylenedicarboxylate with diazides (**4**) under mild conditions. Sterically hindered azides in mild conditions sometimes give a mixture of bistriazoles and monotriazoles (Scheme 2).[24b,26a,26b,26c]

Scheme 2



4 + 1 → 5

5	N_3–R–N_3	Yield(%)	5	N_3–R–N_3	Yield(%)
a		87[a]	**d**		68[c]
b		90[a]	**e**		65[d]
c		Not available[b]	**f**		70[d]

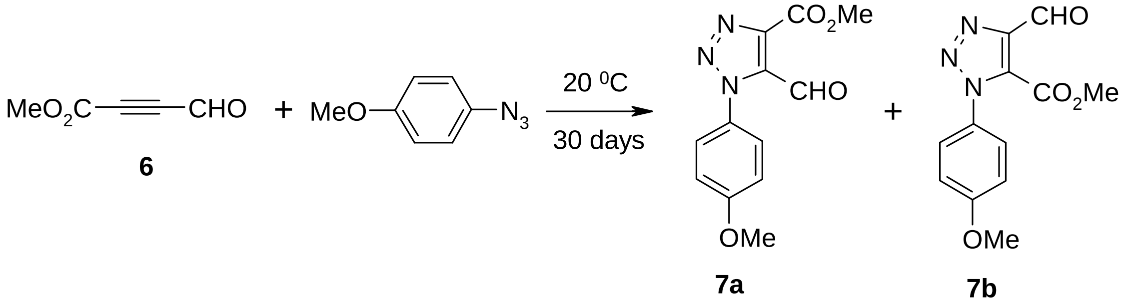
a: In ether at 0 °C for 6 weeks; *b*: In CH_2Cl_2 at rt for 3 days;

c: In acetone at rt for 2 days; *d*: In dry ether kept at rt for 24 h.

1.2 Ester-aldehyde substituted acetylenes

Low steric hindrance and the high electron-withdrawing effect of the aldehyde group have a favorable effect. Until now, only one example has been reported; reaction of ester-aldehyde disubstituted acetylene (**6**) with 4-methoxyphenyl azide at 20 °C for 30 days gives a mixture of regioisomers (**7a**) and (**7b**) in 95% yield (Scheme 3).[27]

Scheme 3

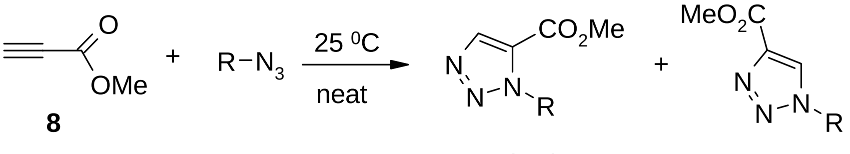


6 + 4-methoxyphenyl azide → 7a + 7b

1.3 Propiolic esters

An acetylenic triple bond activated by just one electron-withdrawing group is also very reactive. Methyl propiolate (**8**) reacts with vinyl azides at room temperature without solvent to afford the regioisomeric triazoles (**9a**) and (**9b**) (Scheme 4).[28]

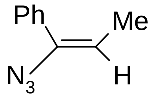
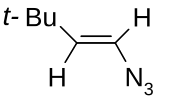
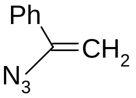
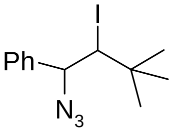
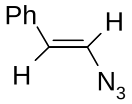
Scheme 4



8

9a (1,5)

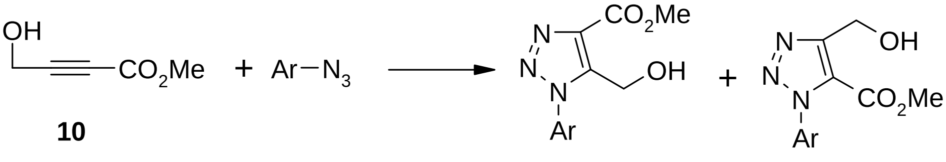
9b (1,4)

RN$_3$	Yield (%)		RN$_3$	Yield (%)	
	1,4	1,5		1,4	1,5
	80	20		67	0
	62	0		90	10
	44	0			

1.4 Substituted ethynylcarboxylate esters

Sterically less hindered methyl 4-hydroxyl-2-butynoate (**10**) reacts with aryl azides under mild conditions. Reaction of **10** with phenyl azide at 55 °C in toluene for 7 days yields triazole (**11a**) (49%) as the major product, together with triazole (**11a′**) (8%).[29] Treatment of **10** with *p*-methyoxyphenyl azide at 20 °C for 60 days gives regioisomers (**11b**) and (**11b′**) in 90% yield (Scheme 5).[27]

Scheme 5



10

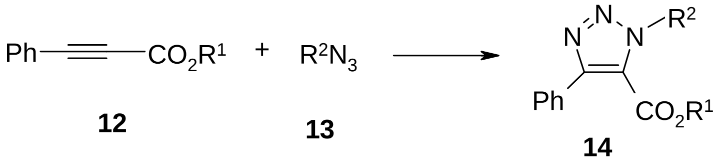
11

11'

a: Ar = Ph
b: Ar = *p*-MeOC$_6$H$_4$

On the other hand, 1,3-dipolar cycloaddition of ethyl phenylpropiolate (**12a**) with 4-methoxybenzyl azide at 95 °C requires 6 hours.[30a] Reaction of substituted acetylene (**12b**) with methyl azide at 60 °C in benzene requires 8 days to complete the reaction (Scheme 6).[30b]

Scheme 6



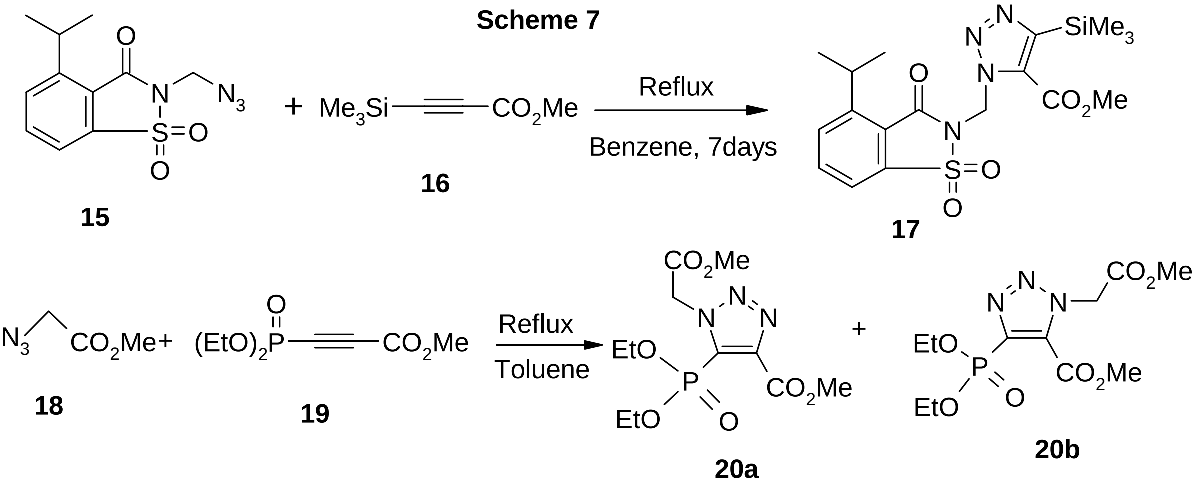
	R^1	R^2	**14** Yield (%)
a	Et	p-$MeOC_6H_4CH_2$	68[a]
b	Me	Me	100[b]

a: Reacted at 95 °C without solvent for 6 h

b: In benzene at 60 °C for 8 days

1,3-Dipolar cycloaddition of trimethylsilyl- and diethoxyphosphoryl-substituted ethynylcarboxylates with azides also requires a higher temperature. Treatment of methyl (trimethylsilyl)propiolate (**16**) with *N*-(azidomethyl)benzisothiazolone (**15**) in refluxing benzene for 7 days regioselectively gives the azide (**17**) in 68% yield.[31] Reaction of methyl azidoacetate (**18**) with ethyl (diethyoxyphosphinyl)propynoate (**19**) in refluxing toluene gives a 7 : 4 ratio of the triazoles (**20a**) and (**20b**) (Scheme 7).[32]

Scheme 7

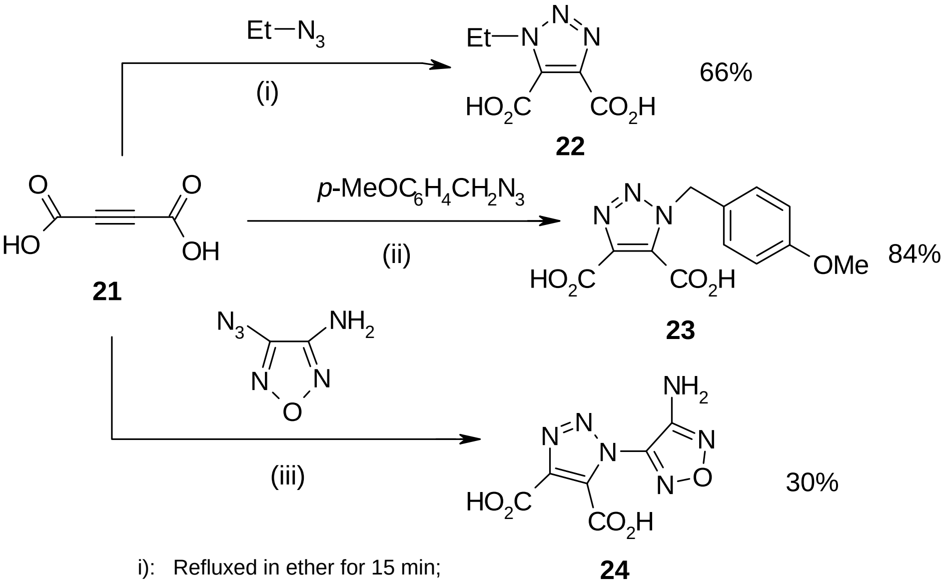


Compared to the hydroxymethyl substituent in **10**, Ph-, Me_3Si- and $(EtO)_2P(O)$- substituents in **12**, **16** and **19** are more electron-withdrawing, but to overcome the steric hindrance due to these groups, a higher reaction temperature is required for 1,3-dipolar cycloaddition.

2. LOW-TEMPERATURE 1,3-DIPOLAR CYCLOADDITION OF CARBOXYLIC ACID SUBSTITUTED ACETYLENES

Acetylenedicarboxylic acid (**21**) is also very reactive and it reacts with various azides in refluxing ether or acetone to give the corresponding 4,5-dicarboxylic acid substituted triazoles (Scheme 8).[33a,33b,33c]

Scheme 8



i): Refluxed in ether for 15 min;

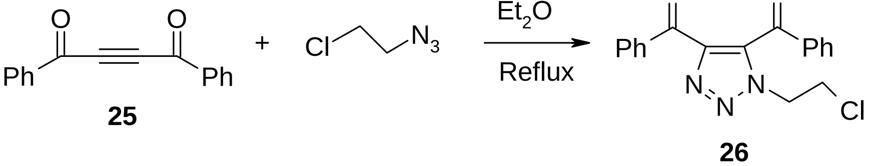
ii): Refluxed in acetone for 36 h;

iii): Refluxed in ether

3. LOW-TEMPERATURE 1,3-DIPOLAR CYCLOADDITION OF ACYL- SUBSTITUTED ACETYLENES

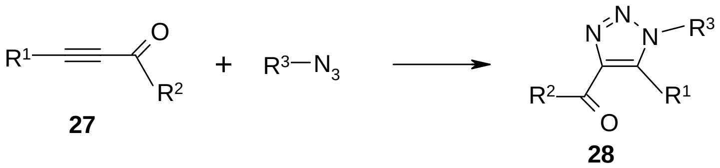
The acetylenic diketone, 1,4-diphenyl-but-2-yne-1,4-dione (**25**) reacts with 1-azido-2-chloroethane in refluxing ether to afford the corresponding triazole (**26**) in 86% yield (Scheme 9).[34]

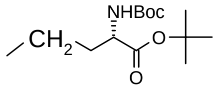
Scheme 9



Terminal acetylenic ketones are almost as reactive as propiolic esters. Reactions of the terminal acetylenic ketones (**27a-c**) with aromatic or aliphatic azides in refluxing diethyl ether afford triazoles (**28a-c**) in good yields[34,35a] while reaction of the more sterically hindered phenylethynyl ketone with *p*-chlorophenyl azide needs refluxing in toluene for 7 days to give the triazole (**28d**) in 81% yield (Scheme 10).[35b]

Scheme 10



Entry	R^1	R^2	R^3	yield(%)
a	H		Ph—	91^a
b	H	Ph—	p-$NO_2C_6H_4$—	43^a
c	H	Ph—	n-Bu—	51^a
d	Ph	p-ClC_6H_4—	p-ClC_6H_4—	81^b

a: In refluxing ether;

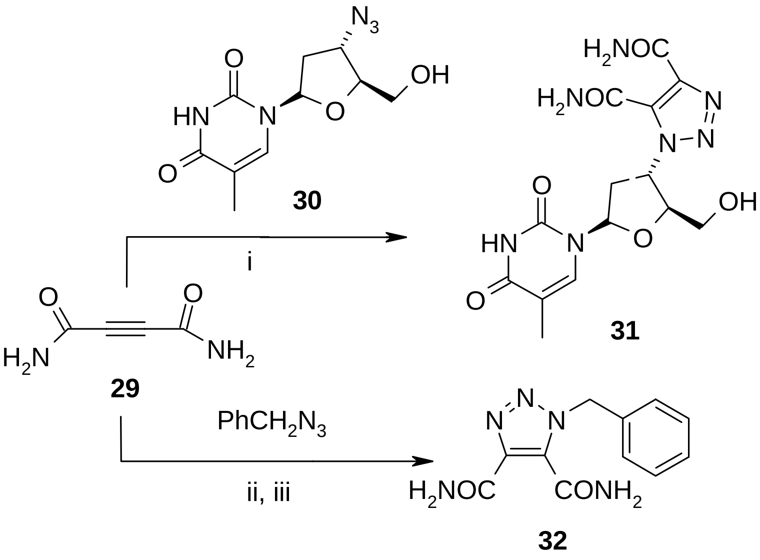
b: In refluxing toluene for 7 days

4. LOW-TEMPERATURE 1,3-DIPOLAR CYCLOADDITION OF ACETYLENECARBOXYLIC AMIDES

4.1 Acetylenedicarboxylic amide

Compared to acetylenedicarboxylates (**1**), acetylenedicarboxylic amide (**29**) is much less reactive. Cycloaddition of 5'-azido-5'-deoxythymidine (**30**) with acetylenedicarboxylamide (**29**) in DMF at 110 °C for 3 hours gives azide (**31**) in 84% yield.[36] In our laboratory,[37] reactions of acetylenedicarboxylic amide

Scheme 11



i): In DMF at 110 °C for 3 h; ii): In DMF at 110 °C for 2 h, yield 73%;

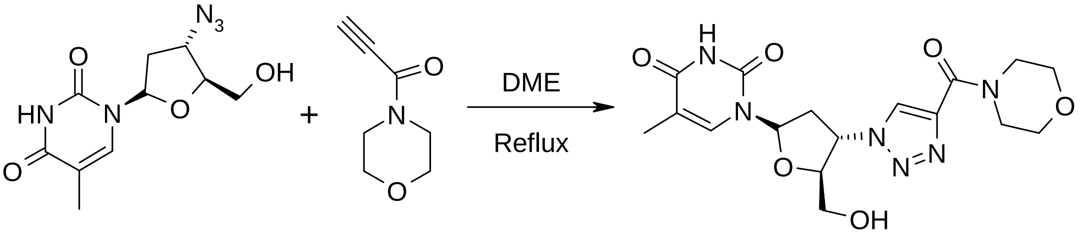
iii): In DMF at 85 °C under microwave irradiation for 30 min, yield 65%.

with benzyl azide at 110 °C in DMF for 2 hours gave 73% of triazole (**32**). Under thermal conditions, attempts to lower the reaction temperature to 85 °C or 55 °C were unsuccessful and the starting materials were recovered. Microwave heating has emerged as a useful technique in organic synthesis. It can shorten reaction time and lower reaction temperature. Treatment of acetylenedicarboxylic amide and benzyl azide at 85 °C under microwave irradiation for 30 min gives 65% yield of the corresponding triazole (**32**). However, on further lowering the reaction temperature to 55 °C, microwave radiation fails to induce reaction (Scheme 11).[37]

4.2 Propiolic amides

Propiolic amides are more reactive than acetylenedicarboxylic amides. Reaction of acetylenecarboxamide (**33**) with 5'-azido-5'-deoxythymidine (**30**) in refluxing DME for 24 hours gives triazole (**34**) in 82% yield (Scheme 12).[36]

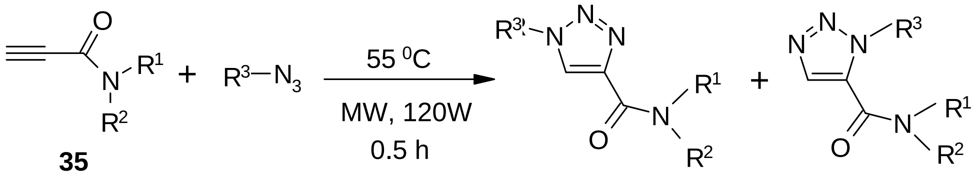
Scheme 12



30 **33** **34**

Initial attempts made by our group to lower the reaction temperature below 55 °C failed, but recently we found that under microwave irradiation, terminal acetylenecarboxamides (**35**) react with azides at 55 °C without solvent for 30 min to give a mixture of regioisomers (**36**) in high yields (Scheme 13).[37]

Scheme 13



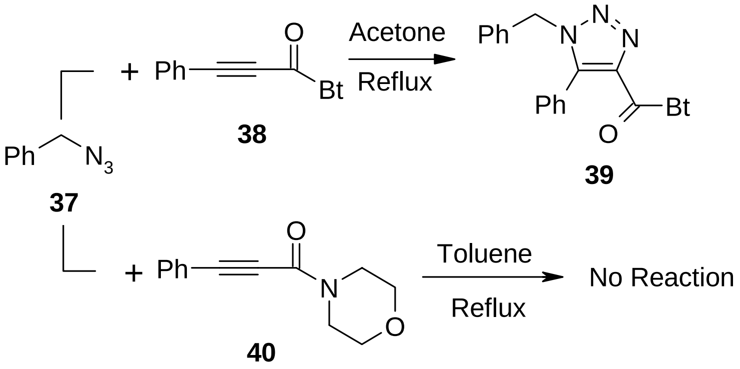
35 **36a** **36b**

Entry	R^1	R^2	R^3	Yield(%)
a	H	$PhCH_2$	$PhCH_2$	95
b	H	$PhCH_2$	$Ph(CH_2)_3$	92
c	piperidinyl		$PhCH_2$	90
d	piperidinyl		$Ph(CH_2)_3$	88

4.3 Substituted ethynylcarboxamides

1,3-Dipolar cycloadditions of substituted ethynylcarboxamides with azides have not been reported. Interestingly, we have found that refluxing of 1-(1*H*-1,2,3-benzotriazol-1-yl)-3-phenyl-2-propyn-1-one (**38**) with benzyl azide in acetone gives the corresponding triazole (**39)** in 30% yield. However, cycloaddition of 3-phenyl-2-propynamide (**40**) with benzyl azide fails even in refluxing toluene (Scheme 14).[37]

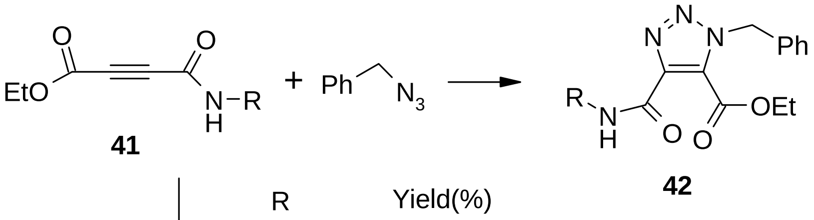
Scheme 14



Bt = Benzotriazol-1-yl

As discussed before, a phenyl group can sterically hinder cycloaddition. At the same time we have also found that a carboxylic ester substituent can facilitate the reaction. Amide-ester substituted acetylenes were synthesized by lithiation of ethyl propiolate and subsequently reaction with isocyanates[38] to examine their reactivity. Thus, reactions of ethyl 4-amido-4-oxo-2-butynoates (**41a,b**) and benzyl azide in refluxing acetone for 20 hours or under microwave irradiation at 55 °C for 30 min. gave triazoles (**42a,b**) in good yields. (Scheme 15).[37]

Scheme 15



	R	Yield(%)
a	C_6H_5	78 [a]
b	*p*-MeC_6H_4	73 [b]

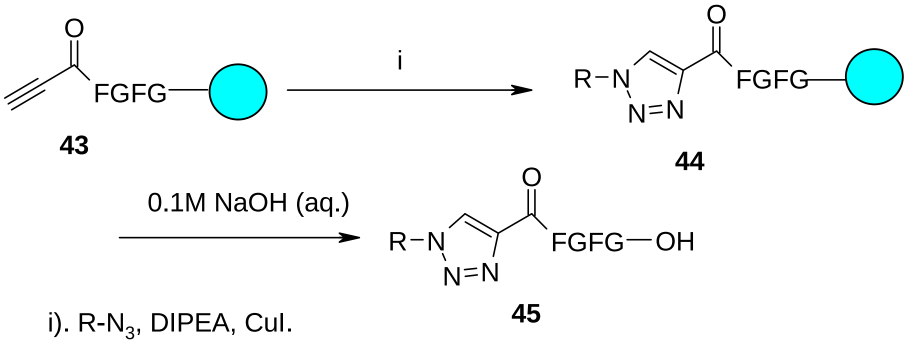
a: In refluxing acetone for 20 h

b: Under microwave irradiation at 55 °C for 30 min.

5. COPPER(I)-CATALYZED 1,3-DIPOLAR CYCLOADDITIONS OF TERMINAL ACETYLENES TO AZIDES

Recently, copper(I)-catalyzed 1,3-dipolar cycloaddition of terminal acetylene to azides on solid supports has been reported as an efficient method for preparing [1,2,3]-triazoles.[39] The resin-bound copper acetylide was reacted with primary, secondary, and tertiary alkyl azides, aryl azides and azido sugar at 25 °C for 16 hours, affording diversely 1,4-substituted 1*H*-[1,2,3]-triazoles (**44**) with quantitative conversions and purities ranging from 75% to 99%. The cycloaddition is supposed to proceed through a preformed copper-acetylide complex followed by a stepwise or concerted addition to an azide (Scheme 16).

Scheme 16



i). R-N_3, DIPEA, CuI.

FGFG: Phe-Gly-Phe-Gly.

R: $C(Me)_2CO_2H$, $C(Me)(Et)CO_2H$, $C(Et)_2CO_2H$, $C(n\text{-}Pr)_2CO_2H$,

$C(Ph)_2CO_2H$, CH_2CO_2H, $CH(n\text{-}Bu)CO_2H$, $CH(n\text{-}C_{14}H_{29})CO_2H$, 4-$C_4H_6NH_2$,

2-amino-5-guanidinopentyl, $CH_2CH(CH_2CH_2SCH_3)NH_2$, $(CH_2)_2NH_2$,

$CH_2CH(CH_2CO_2H)NH_2$, $CH_2CH(Ph)NH_2$, 1-adamantyl, 2-(2-deoxy)-Gal-SPh, H.

6. CYCLOADDITION OF AZIDOACETYLENES

Intramolecular 1,3-dipolar cycloaddition of azidoacetylenes have attracted an increasing attention due to their versatile potential in syntheses of polyheterocyclic systems such as pyrrolo[1,2-c][1,2,3]triazoles;[40a,b] tetraazabenzo[e]azulenes;[41] [1,2,3]triazolo[5,1-*c*][1,4]benzoxazines;[42] benzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]thiazines;[43] [1,2,3]triazolo[1,5-*a*]quinoxalines.[44] These reactions are always carried out at high temperatures (refluxed in benzene or toluene) because the starting material azidoacetylenes are usually sterically hindered.

1,3-Dipolar cycloadditions polymerization of azidoacetylenes have also been studied extensively. Compared to the polymerization of bisazide with bisacetylene,[22a,b] polymerization of azidoacetylene takes place at a lower temperature.[21a,b] Polymerization of 1-azido-1-propyne (**46a**) proceeds at a moderate rate even at room temperature. Neat 2-propynyl azidoacetate (**46b**) polymerizes at 60 °C in one hour; heating a benzene solution of *p*-azidophenyl acetylene (**46c**) at 60 °C also gives the desired poly[1,2,3]triazole (**47c**).[21b]

Scheme 17

$$\equiv\!-R-N_3 \xrightarrow{\hspace{3em}} \text{Poly [1,2,3]-triazole}$$

46 **47**

46	R	Polymerization		
		Time (h)	solvent	Temp (°C)
a	CH_2	0.5	neat	rt
b	$CH_2OC(O)CH_2$	1.0	neat	60 °C
c	1,4-C_6H_4	16	benzene	60 °C

7. CONCLUSION

In conclusion, 1,2,3-triazole formation *via* 1,3-dipolar cycloaddition of acetylenes with azides takes place under mild conditions when acetylenes are substituted by low steric hindrance and electron-withdrawing groups such as esters, carboxylic acids, aldehydes, ketones. Acetylenecarboxamides react with azides under microwave irradiation or in the presence of CuI catalyst.

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place at a lower temperature.[21a,b] Polymerization of 1-azido-1-propyne (**46a**) proceeds at a moderate rate even at room temperature. Neat 2-propynyl azidoacetate (**46b**) polymerizes at 60 °C in one hour; heating a benzene solution of *p*-azidophenyl acetylene (**46c**) at 60 °C also gives the desired poly[1,2,3]triazole (**47c**).[21b]

Scheme 17

$$\underset{\mathbf{46}}{\equiv\!\!-R-N_3} \xrightarrow{\hspace{2em}} \underset{\mathbf{47}}{\text{Poly [1,2,3]-triazole}}$$

46	R	Polymerization		
		Time (h)	solvent	Temp (°C)
a	CH_2	0.5	neat	r.t
b	$CH_2OC(O)CH_2$	1.0	neat	60 °C
c	1,4-C_6H_4	16	benzene	60 °C

7. CONCLUSION

In conclusion, 1,2,3-triazole formation *via* 1,3-dipolar cycloaddition of acetylenes with azides takes place under mild conditions when acetylenes are substituted by low steric hindrance and electron-withdrawing groups such as esters, carboxylic acids, aldehydes, ketones. Acetylenecarboxamides react with azides under microwave irradiation or in the presence of CuI catalyst.

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