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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 3055–3058

Cu(I)-catalyzed one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles via nucleophilic displacement and 1,3-dipolar cycloaddition

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Received 23 September 2005; revised 22 December 2005; accepted 1 March 2006
Available online 20 March 2006

Abstract—An efficient method is described for the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles in high yields from a variety of Baylis–Hillman acetates and terminal alkynes with sodium azide using CuI as a catalyst, in either water or polyethylene glycol (PEG). This procedure is operationally simple and environmentally benign. Polyethylene glycol (PEG) serves as an efficient reusable solvent with higher efficiency.

Multi-component reactions leading to interesting heterocyclic scaffolds are particularly useful for the synthesis of diverse chemical libraries of drug-like molecules for biological screening,[1] in particular, 1,4-disubstituted 1,2,3-triazoles exhibit a remarkably broad scope of selectivity, with a wide range of applications across a broad range of therapeutic areas.[2] Huisgen's 1,3-dipolar cycloaddition is the earliest known method for the synthesis of 1,2,3-triazoles.[3] Recently, Sharpless and co-workers developed Cu(I)-catalyzed ligation of azides with terminal alkynes.[4] Other methods include, use of Cu(I) stabilizing ligands,[5] generation of Cu(I) species from Cu nanosize powder[6] and copper nanoclusters.[7] Fokin and co-workers developed multi-component variants in both conventional[8] and microwave irradiation[9] methods. Very recently, Liang and co-workers described a CuI-catalyzed three-component reaction for the synthesis of 1,2,3-triazoles.[10]

Organic reactions in water, without the use of potentially harmful organic solvents, are of great current interest;[11] beyond being environmentally benign, the extraordinary physical properties of water are widely appreciated.[12] The two main reasons why chemists avoid water is the lack of solubility of most organic compounds in this medium and/or concerns that the high 'acid/base' reactivity will interfere with the desired reaction. Recently liquid or low melting polymers have emerged as alternative green reaction media with unique properties such as thermal stability, commercial availability, nonvolatility, immiscibility with a number of organic solvents, and recyclability. PEG is preferred over other polymers in this context since it is inexpensive, contains no halogen, is easily degradable, and of low toxicity.[13] Many organic reactions have been carried out using PEGs as solvents or co-solvents, such as Heck reactions,[14] Suzuki cross-coupling reactions,[15] oxidation of sulfides, the Wacker reaction[16] and chemoselective deprotection of 1,1-diacetates.[17]

Baylis–Hillman adducts and their acetates are useful precursors for the synthesis of a variety of heterocycles and biologically active natural products including α-alkylidene-β-lactams, α-methylene-γ-butyrolactones, mikanecic acids, frontalin as well as drugs like trimethoprim and many others.[18] Nucleophilic displacement of Baylis–Hillman acetates is one of the most straightforward reactions in organic chemistry.[18,19]

We report herein, an efficient and safe one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles using Baylis–Hillman acetates, sodium azide and terminal alkynes in either water or poly(ethylene glycol) [PEG] 400, a recyclable solvent. To the best of our knowledge, this is the first

Keywords: 1,4-Disubstituted 1,2,3-triazoles; 1,3-Dipolar cycloaddition; PEG; Water; CuI.
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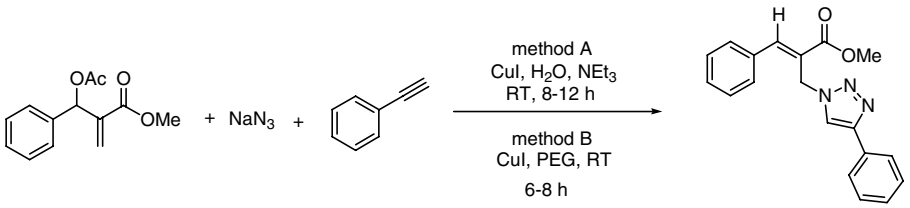
0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.03.007



Scheme 1.

Table 1. Screening of different solvents for the synthesis of 1,4-disubstituted 1,2,3-triazoles[a]

Entry	Solvent system	Isolated yield (%)
1	THF	42
2	CH_3CN	55
3	DMSO	60
4	DMSO–H_2O (3:1)	80
5	^tBuOH–H_2O (3:1)	80
6	H_2O	75
7	PEG	86[b]

[a] Reaction conditions as exemplified in the typical experimental procedure.[23]
[b] In the absence of base.

report of the use of Baylis–Hillman acetates as substrates in the synthesis of 1,4-disubstituted 1,2,3-triazoles (Scheme 1).

Preliminary experiments were performed using Baylis–Hillman acetate **1** with sodium azide and phenylacetylene **3** in the presence of triethylamine. Reactions were performed with various solvent systems viz., THF, DMSO, CH_3CN, DMSO–H_2O (3:1), ^tBuOH–H_2O (3:1) and H_2O. In all solvents except PEG, the presence of NEt_3 facilitates the formation of Cu acetylide, whereas in PEG, formation of copper acetylide occurs even in the absence of the base. The results are summarized in Table 1.

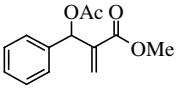
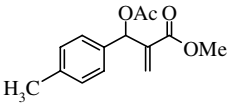
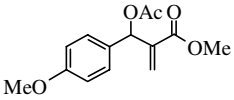
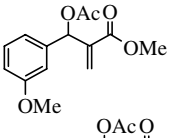
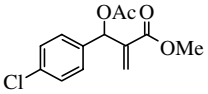
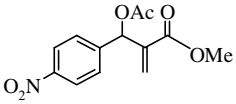
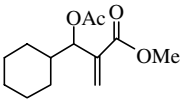
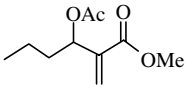
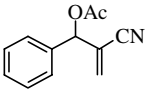
As can be seen from Table 1, THF and CH_3CN afforded lower yields (entries 1 and 2), whilst the mixed solvent systems achieved higher yields (entries 4 and 5). Although, the reaction proceeds smoothly in water (entry 6), excellent yields were obtained only when polyethylene glycol 400 (entry 7) was used as solvent. Among the copper salts screened, copper(II) salts[20] were not effective, giving the products in low yields with no regioselectivity. CuI was found to be the most effective, giving the products in high yields with 99% regioselectivity.[21]

Under the optimized reaction conditions, various aryl- and alkyl-substituted Baylis–Hillman acetates were reacted with sodium azide and phenylacetylene using copper iodide as catalyst to afford 1,4-disubstituted 1,2,3-triazoles with (*E*)-stereoselectivity both in water and PEG and the results are summarized in Table 2.

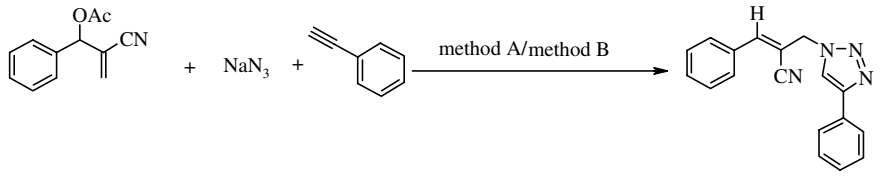
Among the substrates screened, aryl-substituted Baylis–Hillman acetates gave better yields than alkyl-substituted substrates. Structurally and electronically diverse Baylis–Hillman acetates afforded the corresponding products in good yields in PEG and required less time than those in water. It was observed that the PEG can serve as recyclable medium for this reaction, CuI in PEG was recycled for four cycles and showed consistent activity.[24]

Further, the reaction of the Baylis–Hillman acetate derived from acrylonitrile, that is, 3-acetoxy-2-methylene-3-phenylacrylonitrile (entry 9), sodium azide and phenylacetylene gave the corresponding product in

Table 2. Synthesis of 1,4-disubstituted 1,2,3-triazoles from various Baylis–Hillman acetates, sodium azide and phenylacetylene

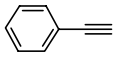
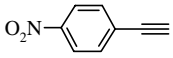
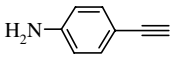
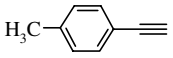
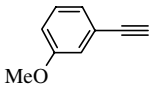
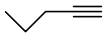
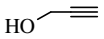
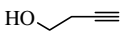
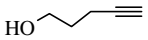
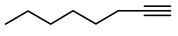
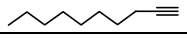
Entry	Baylis–Hillman acetate	Time (h)		Isolated yield (%)	
		H_2O	PEG	H_2O[a]	PEG[b]
1		8.0	6.0	75	86 80[c]
2		8.0	6.0	80	85
3		8.0	6.0	64	75
4		8.0	6.0	60	71
5		9.0	7.0	68	82
6		10	7.0	71	90
7		12	8.0	56	70
8		12	8.0	60	72
9		8.0	6.0	72	90[d]

[a,b] Reaction conditions as exemplified in the typical experimental procedure, method A and method B.[23]
[c] Yield after fourth cycle.[19a]
[d] Product obtained with (*Z*)-stereoselectivity.



Scheme 2.

Table 3. Synthesis of 1,4-disubstituted 1,2,3-triazoles from Baylis–Hillman acetates **1**, sodium azide and different terminal alkynes

Entry	Terminal alkyne	Time (h)		Isolated yield (%)	
		H_2O	PEG	H_2O[a]	PEG[b]
1		8	6	75	86
2		8	6	72	93
3		10	8	52	73
4		8	6	71	82
5		8	6	76	89
6		8	6	55	70
7		8	6	72	81
8		8	7	69	75
9		10	8	50	61
10		10	8	50	58
11		12	10	28	42

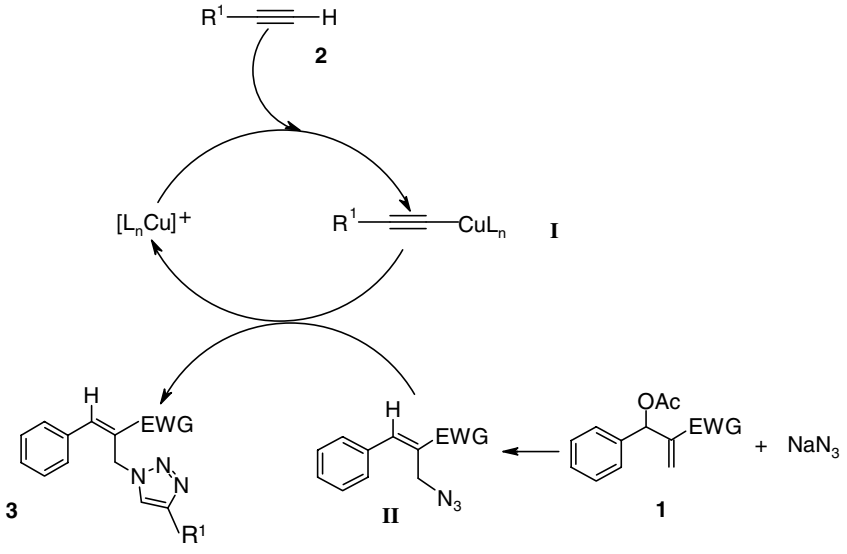
[a,b] Reaction conditions as exemplified in the typical experimental procedure, method A and method B.[23]

excellent yield with (*Z*)-stereochemistry, in agreement with the literature report[19a] (Scheme 2).

To extend the general applicability of this reaction, several terminal alkynes were reacted with Baylis–Hillman acetate **1** and sodium azide under the optimized conditions in water or PEG; the results are given in Table 3. The *p*-nitro- (entry 2) and *m*-methoxy- (entry 5) phenylacetylenes were found to be more reactive than *p*-amino- and *p*-methyl- (entries 3 and 4) phenylacetylenes. In addition, the system was applied to other aliphatic alkynes (entries 6–11). It is noteworthy that the yields of metal acetylide decreased with increase in chain length.

On the basis of these results, together with the literature reports,[3,22] we propose a plausible mechanism (Scheme 3). Formation of acetylide **I** by the reaction of terminal alkyne **2** with copper iodide, would be followed by a regioselective 1,3-dipolar cycloaddition with the azido derivative **II** of the Baylis–Hillman acetate, formed by the nucleophilic displacement of acetate in **I** by sodium azide, to give the 1,4-disubstituted 1,2,3-triazole **3**.

In conclusion, 1,4-disubstituted 1,2,3-triazoles have been synthesized for the first time directly from a variety of Baylis–Hillman acetates, terminal alkynes and sodium azide using copper iodide as catalyst at room temperature via nucleophilic displacement and 1,3-dipolar cycloaddition in either water or PEG. The method described here is simple and applicable to a wide range of substrates.



Scheme 3.

Acknowledgement

P.S.R. thanks the Director, Indian Institute of Chemical Technology, Hyderabad, for providing facilities for carrying out his M.Tech. dissertation work.

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20. $Cu(OAc)_2$, $CuCl_2$ and $Cu(acac)_2$ gave poor yields 55%, 40% and 36%, respectively.
21. By using CuI as a catalyst, 1,3-dipolar cycloaddition occurred regioselectively and the ^1H NMR spectrum of **3** revealed the olefinic proton of the triazole ring at δ 7.49 ppm as a singlet, which confirms the regioselective formation of **3**. When using Cu(II) salts, the olefinic protons signals at δ 7.42, 7.38 for 1,5- and 1,4-disubstituted 1,2,3-triazole isomers, respectively.
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23. Typical experimental procedure: Method A: A mixture of Baylis–Hillman acetate **1** (1 mmol) sodium azide (1.2 mmol, 78 mg), phenylacetylene (1.1 mmol, 112 mg), triethylamine (2.6 mmol, 262 mg) and CuI (2.5 mol %) in water (3 mL) was stirred at ambient temperature for 8 h. After completion of the reaction (as monitored by TLC) the catalyst was filtered through Celite and the product was extracted with ether (3×10 mL). After removing the solvent under vacuum, the crude product was purified by column chromatography on silica gel (hexane–ethyl acetate, 9:1) to afford pure 3-phenyl-2-(4-phenyl-1,2,3-triazol-1-ylmethyl)-acrylic acid methyl ester **3** (239 mg, 75%). Method B: A mixture of Baylis–Hillman acetate **1** (1 mmol), sodium azide (1.2 mmol, 78 mg), phenylacetylene (1.1 mmol, 112 mg) and CuI (2.5 mol %) in PEG-400 was stirred at ambient temperature for 6 h. After completion of the reaction, the reaction mixture was extracted with diethyl ether (5×10 mL), concentrated in vacuum and purified by column chromatography to afford pure 3-phenyl-2-(4-phenyl-1,2,3-triazol-1-ylmethyl)-acrylic acid methyl ester **3** (274 mg, 86%). Spectroscopic data for **3** (Table 2, entry 1): white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.83–7.81 (d, 2H, $J = 8.30$ Hz), 7.76–7.68 (d, 2H, $J = 6.79$ Hz), 7.47–7.41 (m, 4H, $J = 7.55$ Hz), 7.38 (s, 1H), 7.31–7.25 (m, 2H, 6.79 Hz), 5.40 (s, 2H) 3.86 (s, 3H); EIMS: *m/z* (%): 319 (M^+, 40%), 140 (100), 102 (15); HRMS (ES): calcd for $C_{22}H_{17}N_3O_2$, 319.3623, found: 319.3573. Anal. Calcd for $C_{22}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.45; H, 5.31; N, 13.14.
24. After extraction of the product by ether, the mother liquor was reused for the second run with the same substrates. The result of the first cycle and subsequent cycles gave the products in consistent yields (86%, 80%, 82% and 80%).