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Transition-Metal-Free Catalytic Synthesis of 1,5-Diaryl-1,2,3-triazoles

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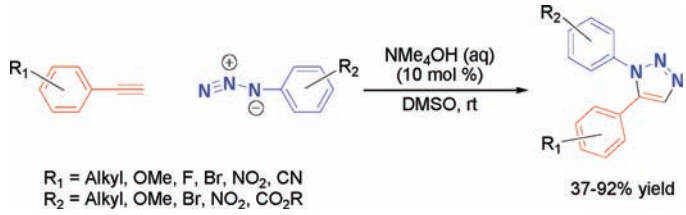
ABSTRACT



1,5-Diarylsubstituted 1,2,3-triazoles are formed in high yield from aryl azides and terminal alkynes in DMSO in the presence of catalytic tetraalkylammonium hydroxide. The reaction is experimentally simple, does not require a transition-metal catalyst, and is not sensitive to atmospheric oxygen and moisture.

The copper(I)-catalyzed azide−alkyne cycloaddition (CuAAC) is a reliable means for the synthesis of 1,4-disubstituted-1*H*-1,2,3-triazoles.[1] The exceptional stability of 1,2,3-triazoles and the availability of a reliable synthesis leading to these heterocycles have enabled widespread applications of this previously underutilized class of azoles in medicinal chemistry, chemical biology, and materials science.[2]

In contrast to the 1,4-disubstituted-1*H*-1,2,3-triazoles, general and regioselective routes leading to the 1,5-regioisomers are not as well developed.[3−8] Although syntheses relying on the nucleophilic attack by the acetylide at the electrophilic terminal nitrogen of the azide are known,[9] the requirement for the stoichiometric lithium or magnesium acetylide reagent imposes obvious limitations on the range of functional groups that are compatible with these processes. Reported here is a mild and experimentally simple catalytic method for the generation of the reactive acetylides which readily react with organic azides resulting in the exclusive formation of 1,5-disubstituted triazoles.

We envisioned that the high acidity of aryl acetylenes in dimethylsulfoxide[10−12] should allow formation of the reac-

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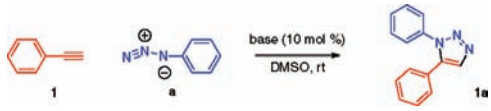
tive acetylide species by treatment of the alkyne with a hydroxide or alkoxide base in this solvent. In fact, formation of acetylide intermediates has been proposed by Ishikawa and co-workers in their studies of the alkynylation of ketones.[13] Screening of various hydroxides and alkoxides confirmed this hypothesis, revealing that anhydrous sodium, potassium, cesium hydroxides, and aqueous tetramethylammonium and benzyl-trimethylammonium hydroxides catalyze formation of 1,5-diaryl-substituted-1*H*-1,2,3-triazoles in DMSO at room temperature (Table 1).

Table 1. Performance of Selected Hydroxide Bases in Catalytic Synthesis of 1,2,3-Triazoles



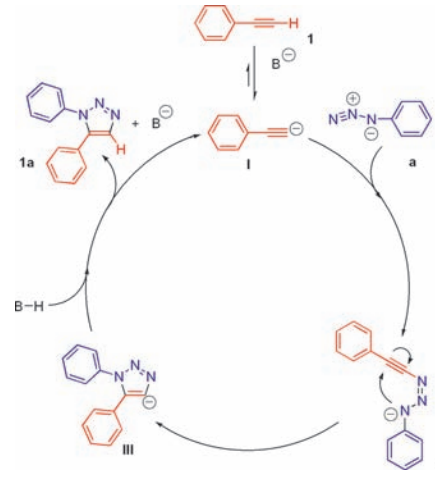
base	KOH (powder)	KOH[c] (aq)	$BnNMe_3OH$ (aq)	NMe_4OH (aq)
yield (%)[a]	91	86	81	86
time (h)[b]	>10	>10	5	5

[a] Base (0.42 mmol) was added to a solution of phenylacetylene (461 μL, 4.2 mmol) and azidobenzene (500 mg, 4.2 mmol) in DMSO (16.8 mL) at room temperature and stirred under a CO_2-free atmosphere. Product was isolated by vacuum filtration after addition of water. [b] Reaction progress was monitored by LC-MS. [c] 2.6 M aqueous solution of KOH (160 μL, 0.42 mmol) was added to the reaction mixture.

Dry DMSO and less nucleophilic bases such as potassium *tert*-butoxide can also be used to minimize hydrolysis of substrates which contain base-sensitive functionalities. In many cases, the desired products precipitated upon addition of 5−20× volume of ice-cold water and were isolated by simple filtration. Reactions in DMSO afforded higher isolated yields than in DMF on larger scale and at higher concentration. Although tetraalkylammonium hydroxides resulted in the slightly diminished yields of the products compared to powdered KOH, the shorter reaction times and the experimental convenience of using aqueous base solutions make tetraalkylammonium hydroxides advantageous catalysts for practical reasons.

While our mechanistic studies of this hydroxide-catalyzed synthesis of triazoles in DMSO are not complete, we offer in Scheme 1 a general proposal for 1,5-triazole formation from acetylides and organic azides. Reversible deprotonation of the terminal alkyne **1** generates an aryl acetylide **I**, which acts as a nucleophile to attack the terminal nitrogen of aryl azide **a**. The triazenide intermediate **II** then undergoes either 6π-electrocyclization or 5-*endo*-dig cyclization to form 1,5-disubstituted-1,2,3-triazolyl anion **III** which completes the catalytic cycle by deprotonation of a molecule of DMSO, terminal alkyne, or water. That DMSO is likely deprotonated

Scheme 1. Proposed Intermediates in the Base-Catalyzed Synthesis of 1,5-Disubstituted-1,2,3-Triazoles



under the reaction conditions is evidenced by the incorporation of deuterium into the product when the reaction is performed in d_6-DMSO with potassium *tert*-butoxide (0.2 equiv). This finding suggests that in addition to stabilizing the anionic intermediates (**II** and **III**) DMSO participates in the various necessary proton-relay events. Observation of a trace amount of 4-triazenyl triazole byproduct, the formation of which can be rationalized by the nucleophilic attack of triazolyl anion **III** on another molecule of aryl azide, lends further support to the involvement of triazolyl anion **III**.

The scope of this process was examined as illustrated by the examples in Table 2. Most aryl and heteroaryl azides and terminal alkynes readily participate in this 1,5-diaryl-substituted-1,2,3-triazole synthesis. It is noteworthy that base-labile functionalities (entries 6 and 9) were tolerated. Aryl azides with sterically demanding *ortho*-substituents gave slightly lower yields, possibly due to interference with the ring closure of the triazenide intermediate (Table 2, entries 2, 4, and 15). Electronic properties of both reactants significantly influence the outcome of the reaction. For example, very electron-deficient 4-nitrophenyl azide produced the triazole in moderate 62% yield (entry 3), likely due to the less efficient triazenide cyclization step. Similarly, 4-nitrophenyl acetylene produced the desired triazole product in only 37% yield (entry 12), which could be a consequence of the reduced nucleophilicity of the acetylide anion. Alkyl acetylenes failed to react under the current conditions, probably due to their lower acidity.[14]

The results described above demonstrate that sufficiently nucleophilic and reactive acetylides can be prepared from terminal alkynes without involving aggressive lithium or magnesium reagents. Such acetylides react selectively with even modestly electrophilic organic azides, producing 1,5-

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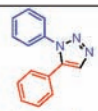
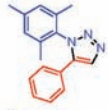
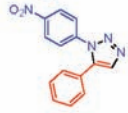
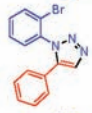
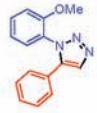
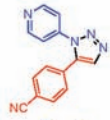
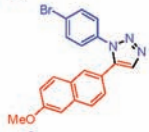
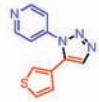
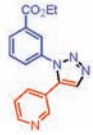
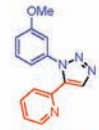
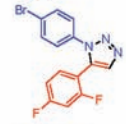
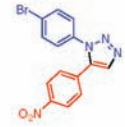
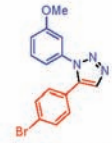
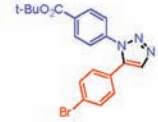
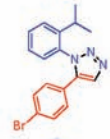
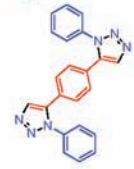
Table 2. Scope of the Base-Catalyzed Synthesis of 1,2,3-Triazoles

entry	product	yield[a] (%)	mp (°C)
1	 1a	86	113–114
2	 1b	60[c]	100–102
3	 1c	62[c]	164.5–165.5
4	 1d	64[c]	95–97
5	 1e	79[c]	105–107
6	 2f	70[b,c]	170–171
7	 3g	56[c]	152–153
8	 4f	69[b]	184–185
9	 5h	79[b,c]	75.5–77.5
10	 6i	92[c]	oil
11	 7g	83	120–122
12	 8g	37[c]	172–173
13	 9i	92[c]	148–149
14	 9j	76[b]	153–156
15	 9k	70[c]	Oil
16	 10a	85	267–269

[a] Unless stated otherwise, method A (base = aq NMe_4OH) was used, and the product was isolated by filtration. [b] Method B (base = *t*-BuOK) was used. [c] Isolated yield after flash column chromatography.

disubstituted triazoles under mild, transition-metal-free conditions. Experimental simplicity, ease of product isolation, low cost, and ready availability of reagents should make this method immediately useful for the synthesis of these heterocycles.

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Supporting Information Available: Experimental procedures, characterization data, and copies of ^1H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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