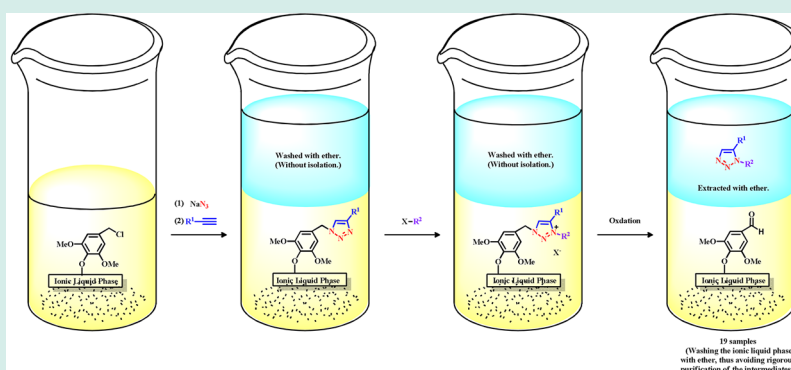


## Ionic Liquid-Phase Synthesis of 1,5-Disubstituted 1,2,3-Triazoles

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## Supporting Information



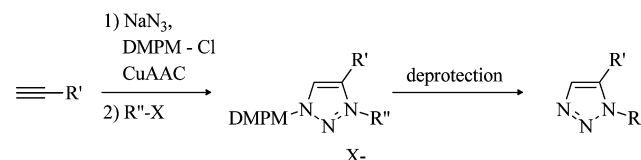
**ABSTRACT:** A simplified ionic liquid-phase synthesis of 1,5-disubstituted 1,2,3-triazole was developed. Nineteen 1,5-disubstituted 1,2,3-triazoles were successfully obtained by merely washing the ionic liquid phase with ether, thus avoiding the need for intermediate purification.

**KEYWORDS:** heterocyclic compound, triazole, ionic liquid

Triazole is a high-grade, useful material that is widely employed in a variety of industries. For example, various types of triazoles are used in physiologically active substances and in organic materials.<sup>1</sup> Developed by Sharpless et al., the most versatile method for 1,4-disubstituted 1,2,3-triazole synthesis involves the use of acetylene and azide with a copper catalyst (copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC)).<sup>2</sup> This method allows reactions to be performed in organic solvents or water with an inexpensive copper catalyst that enables the highly selective synthesis of 1,4-disubstituted 1,2,3-triazole.

In contrast, relatively few reports describe the selective synthesis of 1,5-disubstituted triazoles. In addition to the 1,5-disubstituted 1,2,3-triazole method based on the reaction of an azide and alkyne, other methods are available that use a ruthenium catalyst,<sup>3</sup> magnesium or lithium acetylide,<sup>4</sup> or hydroxide ions.<sup>5</sup> Furthermore, click reactions using a silyl acetylene derivative for the synthesis of 1,5-disubstituted products have been reported.<sup>6</sup> This year, Ying-Chun and co-workers reported the Ce(OTf)<sub>3</sub> catalyzed synthesis of 1,5-disubstituted 1,2,3-triazole from azides.<sup>7</sup> However, these synthetic methods have several disadvantages, including the need for expensive transition metals, limited bases that can be used for displacement, and the requirement for anhydrous conditions. Considering these drawbacks, we recently reported a selective method for the synthesis of new 1,5-disubstituted 1,2,3-triazoles from a triazolium salt. (Scheme 1)<sup>8</sup>

This synthetic method was highly successful for the selective synthesis of 1,5-disubstituted 1,2,3-triazole using a deprotection reaction after obtaining the 1-protected-3,4-disubstituted 1,2,3-triazolium salts. These salts resulted from the copper(I)-catalyzed azide–alkyne cycloaddition between the organic azides and

Scheme 1. Synthesis of 1,5-Disubstituted 1,2,3-Triazoles via Triazolium Salt Intermediates<sup>7</sup>

terminal alkynes, which yielded 1,4-disubstituted 1,2,3-triazoles and allowed for further reaction with alkyl halides.

However, this synthetic method is not free of disadvantages. In this case, the compounds must be isolated and purified after the individual stages of the reaction. To overcome these problems, a study was conducted regarding the ionic liquid phase synthesis of the new 1,5-disubstituted 1,2,3-triazole in ionic liquid-supported benzyl chloride

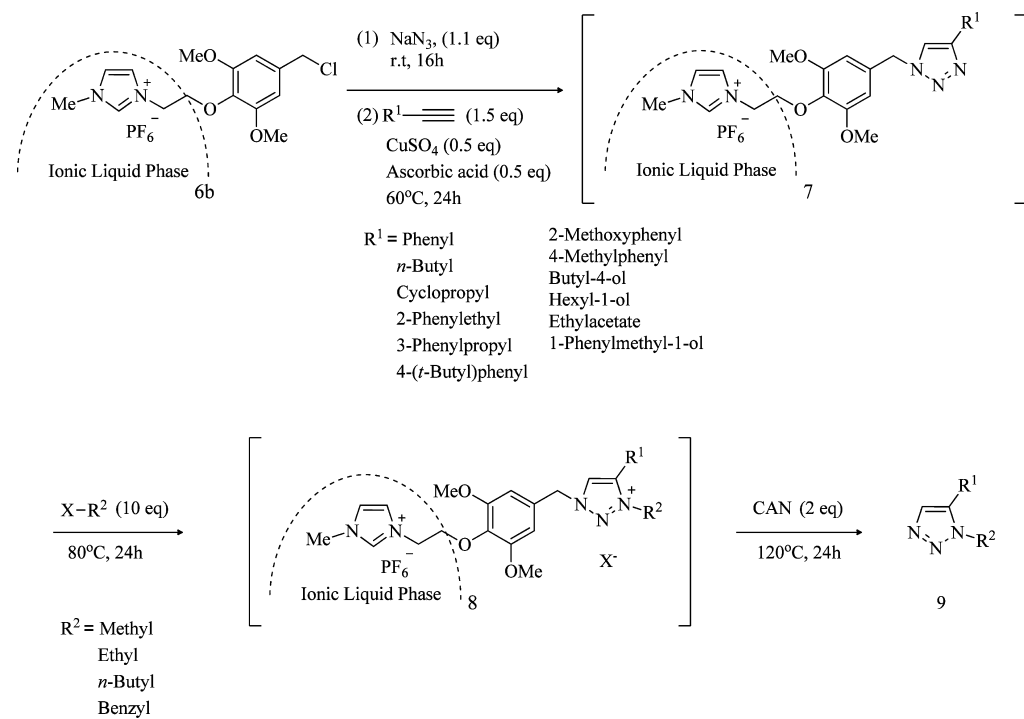
An ionic liquid is a liquid salt at room temperature and is not readily volatile or flammable. In addition, ionic liquids are environmentally benign.<sup>9</sup> Furthermore, because an ionic liquid is highly polar and exhibits low volatility, it is possible to refine an ionic liquid by washing it with a solvent with low polarity. Consequently, it is feasible to perform the reaction by using the ionic liquid as a stationary phase. In addition to these favorable properties, impurities may be removed easily from ionic liquids after the reaction with low polarity solvents.

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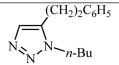
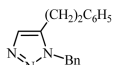
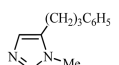
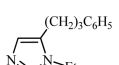
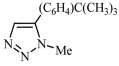
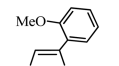
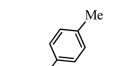
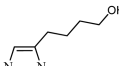
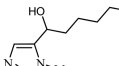
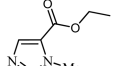
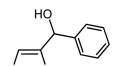
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Table 1. Ionic Liquid Phase Synthesis of 1,5-Disubstituted 1,2,3-Triazoles



	$\text{R}^1$	$\text{R}^2$	X	1,5-Triazole	Yield (%)
1	Phenyl	Methyl	I		72%
2	$n$ -Butyl	Methyl	I		78%
3	Cyclopropyl	Methyl	I		81%
4	Cyclopropyl	Ethyl	I		71%
5	Cyclopropyl	$n$ -Butyl	I		66%
6	Cyclopropyl	Benzyl	Br		70%
7	2-Phenylethyl	Methyl	I		88%
8	2-Phenylethyl	Ethyl	I		78%

Table 1. continued

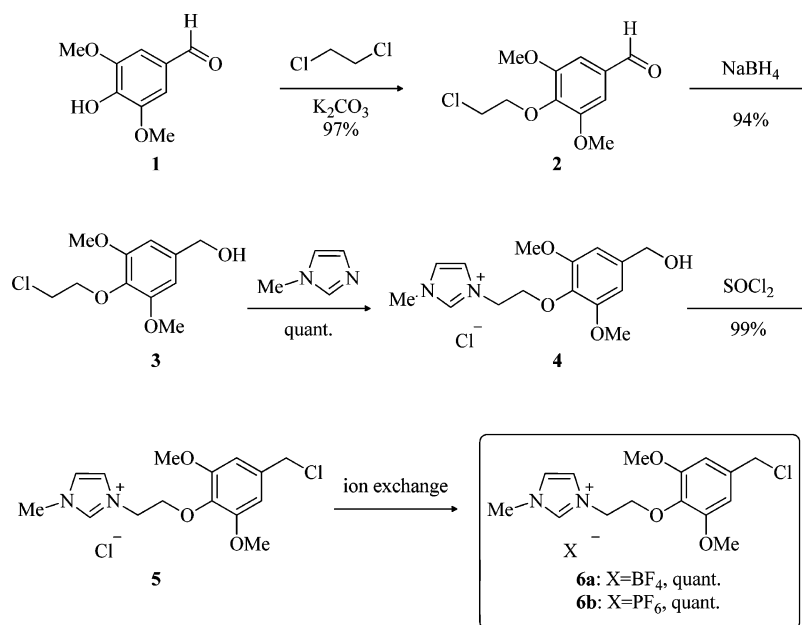
	R <sup>1</sup>	R <sup>2</sup>	X	1,5-Triazole	Yield (%)
9	2-Phenylethyl	<i>n</i> -Butyl	I		71%
10	2-Phenylethyl	Benzyl	Br		54%
11	3-Phenylpropyl	Methyl	I		83%
12	3-Phenylpropyl	Ethyl	I		70%
13	4-( <i>t</i> -Butyl)phenyl	Methyl	I		56%
14	2-Methoxyphenyl	Methyl	I		77%
15	4-Methylphenyl	Methyl	I		35%
16	Butyl-4-ol	Methyl	I		39%
17	Hexyl-1-ol	Methyl	I		80%
18	Ethylacetate	Methyl	I		20%
19	1-Phenylmethyl-1-ol	Methyl	I		23%

First, the synthesis was conducted with ionic liquid-supported dimethoxy benzyl chloride as the stationary phase (Scheme 2). (Previously, we studied the 1,5-disubstituted 1,2,3-triazoles via triazolium salt with various protecting group (for example, benzyl, monomethoxy benzyl and dimethoxy benzyl, etc.) We discovered dimethoxy benzyl was a very good protecting group for this synthetic methodology. Therefore, we chose liquid-supported dimethoxybenzyl chloride for the stationary phase.) After an alkyl base linker was combined with the raw aldehyde starting material by syringe addition (1), the methyl imidazole was allowed to react to form an imidazolium skeleton (4). Ionic liquid 5 was obtained in the

last stage. Furthermore, by performing ion exchange with ionic liquid 5, ionic liquids 6a and 6b, (with the BF<sub>4</sub> or PF<sub>6</sub> anions, respectively) were synthesized. The above-mentioned 3 types of ionic liquid-supported benzyl chlorides (5, 6a, and 6b) exhibited different stabilities. Ionic liquids 5 and 6a decomposed over several days. However, ionic liquid 6b remained unchanged for more than one month, even at room temperature. Accordingly, the ionic liquid phase synthesis of 1,5-disubstituted triazole with a highly stable ionic liquid (6b) with the PF<sub>6</sub> anion was performed. (Table 1)

After the introduction of an azide into the ionic liquid-supported benzyl chloride (6b), the 1,4-disubstituted (7) product

Scheme 2. Synthesis of an Ionic Liquid-Supported Benzyl Chloride



was synthesized by employing the copper-catalyzed regioselective Huisgen cycloaddition of azides and terminal alkynes (known as the click reaction). Next, we prepared ionic liquid-supported triazolium salts (**8**) from the ionic liquid-supported 1,4-disubstituted-1,2,3-triazole (**7**) by reacting with alkyl halide under heat. Finally, the 1,5-disubstituted 1,2,3-triazole was synthesized by deprotection. However, this reaction with ionic liquid-supported 3,4-dimethoxybenzyl triazolium salts (**8**) was difficult. We examined the deprotection of the ionic liquid-supported triazolium salts (**8**) using palladium on carbon (Pd/C) in the presence of hydrogen gas or trifluoroacetic acid. However, neither method was successful. Thus, we developed methods for the deprotection of triazolium salts (**8**). Ceric ammonium nitrate (CAN) was an efficient reagent for the cleavage of the ionic liquid-supported 3,4-dimethoxybenzyl group. Thus, salts **8** were treated with CAN (2 equiv) at 120 °C to afford 1,5-disubstituted 1,2,3-triazole in excellent yields.

To investigate the substrate generality of this synthetic method, the synthesis of 19 1,5-triazoles was performed using alkyl halides and acetylenes. The reaction occurred favorably in all instances. However, the syntheses with ethyl 1-methyl-1*H*-1,2,3-triazole-5-carboxylate (entry 18) and (1-methyl-1*H*-1,2,3-triazole-5-yl)(phenyl)methanol (entry 19), only achieved yields of approximately 20%.

In summary, we successfully prepared an ionic liquid-supported benzyl chloride with exceptional stability. This benzyl chloride was applied to a simplified 1,5-disubstituted triazole synthesis. This synthetic method was effective in generating different 1,5-disubstituted triazoles. Overall, 19 1,5-disubstituted triazoles were obtained by washing the ionic liquid phase with ether, thus avoiding rigorous purification of the intermediates.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, <sup>1</sup>H NMR, <sup>13</sup>C NMR, and HRMS spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org/>.

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### Notes

The authors declare no competing financial interest.

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