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SHORT COMMUNICATION

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One-Pot, Three-Component Synthesis of 1,4,5-Trisubstituted 1,2,3-Triazoles Starting from Primary Alcohols

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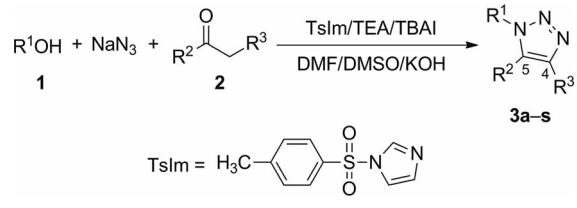
A novel, one-pot, three-component approach for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles through the cycloaddition of a wide range of primary alcohols with sodium azide and active methylene ketones in the presence of *N*-(*p*-toluenesulfonyl)imidazole, tetrabutylammonium iodide, and triethylamine in DMF/DMSO has been developed.

Introduction

1,2,3-Triazoles are an important class of heterocyclic compounds that have attracted a great deal of attention from synthetic and medicinal chemists due to their potential biological activities.[1] However, most of the research has been focused on the synthesis and bioassay of 1,4- or 1,5-disubstituted 1,2,3-triazoles.[2] In recent years, 1,4,5-trisubstituted 1,2,3-triazoles have found important applications in various areas, especially as medicine against many diseases[3] including influenza A virus,[4] herpes simplex viruses type-1 (HSV-1),[5] and human platelet aggregation.[6] However, up to now, only a few methods for the synthesis of fully substituted 1,2,3-triazoles have been described.[7] In 2009, Fokin and co-workers developed a general and highly efficient copper(I)-catalyzed method for the chemo- and regioselective synthesis of 1,4,5-trisubstituted 5-iodo-1,2,3-triazoles from organic azides and iodoalkynes.[8] These 5-iodo-1,2,3-triazoles are useful and versatile synthetic intermediates that can be easily modified to allow further functionalization at the C-5 position.[9] One of the most attractive approaches to the synthesis of fully decorated 1,2,3-triazoles is the direct Pd- or Cu-catalyzed arylation of 1,4-disubstituted triazoles with aryl halides.[10] Some other known methods for the synthesis of fully substituted 1,2,3-triazoles include cycloadditions of azides with bromomagnesium acetylides, followed by reaction with an electrophile;[11] reactions of azides with active methylene compounds;[3b,12] Ru-catalyzed cycloadditions of azides and internal alkynes;[13] the one-pot, three-component reactions of arylazides, amines, and diketene.[14] More recently, Wang et al. developed the first regiospecific synthesis of 1,4,5-trisubstituted 1,2,3-triazoles by treatment of aryl azides with β-keto esters, 1,3-diketones, or 3-keto-3-phenylpropionitrile by using diethylamine (5 mol-%) as an organocatalyst.[15] Although these methods exhibited high specificity and selectivity for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles, they are associated with several shortcomings that include the use of unstable and dangerous organic azides,[16] the use of expensive metal catalysts, limited variation of the azides (most substrates are aryl azides), a lack of versatility, and multistep procedures. In view of these limitations, there is still a need for a mild and widely applicable approach for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles from simple and easily available starting materials. In this communication, we report a direct, one-pot, three-component protocol for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles from readily available primary alcohols, sodium azide, and active methylene ketones in the presence of tetrabutylammonium iodide (TBAI), triethylamine (TEA), and *N*-(*p*-toluenesulfonyl)imidazole (TsIm) in a mixed DMF/DMSO solvent system (Scheme 1).



Scheme 1. Synthesis of 1,4,5-trisubstituted 1,2,3-triazoles through the one-pot, three-component reaction of primary alcohols, sodium azide, and active methylene ketones.

Results and Discussion

In our preceding paper, we reported a novel and efficient protocol for the synthesis of 1,4-disubstituted 1,2,3-triazoles by the Cu^{I}-catalyzed, one-pot, three-component re-

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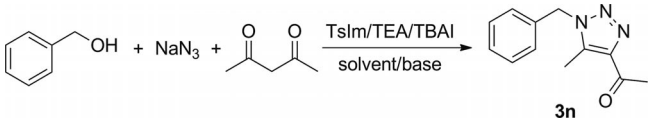
action of primary alcohols, sodium azide, and terminal alkynes.[17] To extend our previous work, we tried to prepare 1,4,5-trisubstituted 1,2,3-triazoles from primary alcohols, sodium azide, and active methylene ketones. In 2007, Rad et al. synthesized a variety of azides from alcohols by using a TsIm/TEA/TBAI/DMF system.[18] Encouraged by their results, in our initial studies, benzyl alcohol, sodium azide, and acetylacetone were selected as representative substrates to investigate the possibility of the formation of trisubstituted triazoles in one pot in the presence of TsIm, TEA, and TBAI (Scheme 2). It was found that **3n** could be obtained efficiently in our preliminary experiment (the ^{1}H NMR and ^{13}C NMR spectra of compound **3n** were identical to those in the literature[7g]).



Scheme 2. Model reaction for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles.

Generally, base plays an important role in the formation of fully substituted 1,2,3-triazoles. For example, Wang used diethylamine as a catalyst[15] and Cottrell used K_2CO_3[12] as a base to improve the efficiency of the cyclization of azides and active methylene ketones, respectively. Thus, our first effort focused on the search of a suitable base. As indicated in Table 1, among the various bases tested, KOH promoted the reaction effectively and 1.2 equiv. of KOH gave an excellent yield of the cyclization product (Table 1, entry 7), whereas only low yield of **3n** was obtained when diethylamine was used as the base (Table 1, entry 2).

Table 1. Effect of base on the yield of **3n** at 80 °C.[a]

Entry	Base	Yield [%][b]
1	none	31
2	diethylamine (1.2 equiv.)	30
3	K_2CO_3 (1.2 equiv.)	68
4	pyridine (1.2 equiv.)	25
5	KOH (0.4 equiv.)	40
6	KOH (0.8 equiv.)	52
7	KOH (1.2 equiv.)	91

[a] Reaction conditions: benzyl alcohol (2.5 mmol), DMF (5 mL), TsIm (5 mmol), sodium azide (5 mmol), TBAI (0.08 mmol), TEA (5 mmol), 80 °C, 10 h. Then, acetylacetone (3 mmol), base, and DMSO (5 mL) were added to the reaction solution. Reaction was continued for 12 h at 80 °C. [b] Yield obtained by GC analysis.

The yields were also significantly affected by the solvent. The best result was obtained when the reaction was conducted in a mixture of DMF/DMSO (Table 2, entry 5). It should be noted that all solvents were purchased commercially and used without further drying. There is almost no difference in yield between dry and "wet" DMF/DMSO. Finally, the influence of reaction temperature on the yield was also examined. The reaction proceeded smoothly at 80 °C for 22 h in DMF/DMSO, affording the expected product in 91% yield.

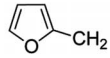
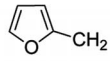
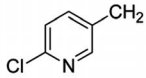
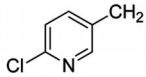
Table 2. Effect of the solvent on the yield of **3n** at 80 °C.[a]

Entry	Solvent (10 mL)	Yield [%][b]
1	THF	0
2	1,4-dioxane	0
3	DMSO	10
4	DMF	61
5	DMSO + DMF (5 mL + 5 mL)	91

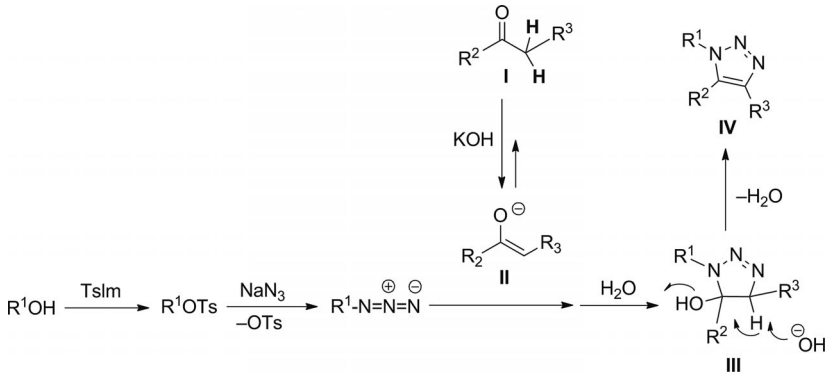
[a] Reaction conditions: benzyl alcohol (2.5 mmol), solvent (5 mL), TsIm (5 mmol), sodium azide (5 mmol), TBAI (0.08 mmol), TEA (5 mmol), 80 °C, 10 h. Then, acetylacetone (3 mmol), potassium hydroxide (3 mmol), and solvent (5 mL) were added to the reaction solution. Reaction was continued for 12 h at 80 °C. [b] Yield obtained by GC analysis.

With the optimized reaction conditions in hand, we set out to survey the generality and scope of this novel, one-

Table 3. One-pot, three-component synthesis of 1,4,5-trisubstituted 1,2,3-triazoles.[a]

Entry	R^1	R^2	R^3	Product	Yield [%][b]
1	CH_3	Ph	CN	**3a**	81
2	CH_3CH_2	Ph	CN	**3b**	80
3	CH_3CH_2	CH_3	$COCH_3$	**3c**	78
4	$CH_3(CH_2)_2$	Ph	CN	**3d**	82
5	$CH_3(CH_2)_2$	CH_3	$COCH_3$	**3e**	80
6	$CH_3(CH_2)_3$	Ph	CN	**3f**	83
7	$CH_3(CH_2)_3$	CH_3	$COCH_3$	**3g**	80
8	$CH_3(CH_2)_4$	Ph	CN	**3h**	84
9	$CH_3(CH_2)_4$	CH_3	$COCH_3$	**3i**	81
10	$PhSCF_2CH_2$	Ph	CN	**3j**	48
11	$PhSCF_2CH_2$	CH_3	$COCH_3$	**3k**	60
12	$PhSCF_2CH_2$	CH_3	$CO_2C_2H_5$	**3l**	52
13	$PhCH_2$	Ph	CN	**3m**	85
14	$PhCH_2$	CH_3	$COCH_3$	**3n**	86
15	$PhCH_2$	CH_3	$CO_2C_2H_5$	**3o**	74
16		Ph	CN	**3p**	83
17		CH_3	$COCH_3$	**3q**	82
18		Ph	CN	**3r**	86
19		CH_3	$COCH_3$	**3s**	84
20	$PhCH_2$	Ph	$COCH_3$	mixture	–
21	$PhCH_2$	CF_3	$CO_2C_2H_5$	–	–
22	$PhCH_2$	CHF_2	$CO_2C_2H_5$	–	–

[a] Reaction conditions: alcohol **1** (2.5 mmol), DMF (5 mL), TsIm (5 mmol), sodium azide (5 mmol), TBAI (0.08 mmol), TEA (5 mmol), 80 °C, 10 h. Then, active methylene ketone **2** (3 mmol), potassium hydroxide (3 mmol), and DMSO (5 mL) were added to the reaction solution. Reaction was continued for 12 h at 80 °C. [b] Isolated yield.



Scheme 3. Proposed reaction mechanism.

pot, three-component reaction; a variety of primary alcohols and several active methylene ketones were examined under the optimized conditions (Table 3). In most cases, this three-component reaction proceeded efficiently to give the corresponding 1,4,5-trisubstituted 1,2,3-triazoles, and no regioisomers were observed. Aliphatic alcohols, even methanol and ethanol, reacted efficiently to give the corresponding fully substituted 1,2,3-triazoles in high yields (Table 3, entries 1–9). The synthesis of **3a**–**i** is particularly useful. Small alkyl organic azides such as methyl azide, ethyl azide, and *n*-propyl azide are generally not only toxic and expensive but also explosive when heated or shaken. This new approach avoids the isolation of organic azides and can be expanded to prepare 1-alkyl-4,5-trisubstituted 1,2,3-triazoles when small alkyl azides are unstable or unavailable. However, when secondary alcohols were used as substrates, very few cyclization products were obtained. Furan-2-ylmethanol and (6-chloropyridin-3-yl)-methanol also worked well with this protocol (Table 3, entries 16–19). When 2,2-difluoro-2-phenylsulfanylethanol (Table 3, entries 10–12) was used, the desired products were obtained only in moderate yield. Additionally, the results also indicated that acetylacetone and 3-oxo-3-phenylpropanenitrile could afford higher yields of the 1,2,3-triazoles than ethyl acetoacetate. When the reaction of aliphatic primary alcohols and sodium azide with ethyl acetoacetate was conducted under the same reaction conditions, almost no cycloaddition product was detected. The reaction of an unsymmetrical diketone such as 1-phenylbutane-1,3-dione with benzyl alcohol and sodium azide gave a mixture of regioisomeric 1,4,5-trisubstituted 1,2,3-triazole products (Table 3, entry 20), and the ratio of regioisomers was nearly 1:1. Unfortunately, the reaction did not proceed well with ethyl 4,4-difluoroacetoacetate or ethyl 4,4,4-trifluoroacetoacetate as substrates, as the desired products were not isolated (Table 3, entries 21–22). Because of the low pK_a values of fluorinated substrates (ethyl trifluoroacetoacetate, pK_a = 7.63; ethyl acetoacetate, pK_a = 11), they might form more stable enolates, precluding further transformation.

On the basis of the above observations, a mechanism for the formation of **3a**–**s** is briefly outlined in Scheme 3. In the first step, the base-activated alcohol reacts with TsIm to give an alkyl tosylate (R^1OTs). Subsequently, the alkyl tosylate undergoes nucleophilic substitution with the azide ion to afford an alkyl azide (R^1N_3). Enolate **II** is generated by active methylene ketone **I** in the presence of KOH. Cycloaddition between enolate **II** and the alkyl azide can provide intermediate **III**, and the reaction is finalized by dehydration of the alcohol group by a strong base, resulting in the loss of water and the formation of triazole product **IV**.

Conclusions

In summary, we developed a novel method for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles by the one-pot, three-component cycloaddition of primary alcohols, sodium azide, and active methylene ketones at 80 °C in the presence of *N*-(*p*-toluenesulfonyl)imidazole, tetrabutylammonium iodide, and triethylamine in DMF/DMSO. The mild reaction conditions, high yields, and one-pot reaction without the necessity to isolate the unstable and hazardous azides (especially aliphatic azide) are main merits of this method. The most remarkable feature of this method is that it provides easy access to fully substituted 1,2,3-triazoles from commercially available primary alcohols.

Experimental Section

General Procedure for the Preparation of 3a–s: To a stirred solution of alcohol **1** (2.5 mmol) in DMF (5 mL) was successively added TsIm (1.11 g, 5 mmol),[18] sodium azide (0.33 g, 5 mmol), TBAI (0.04 g, 0.08 mmol), and TEA (0.50 g, 5 mmol). The mixture was stirred for 10 h at 80 °C. Then, the mixture was cooled to room temperature, active methylene ketone **2** (3 mmol), potassium hydroxide (0.17 g, 3 mmol), and DMSO (5 mL) were added to the solution. The reaction was continued for 12 h (TLC) at 80 °C and then quenched with H_2O (10 mL). The resulting suspension was filtered, and the filtrate was diluted with CH_2Cl_2, washed successively with H_2O and brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure to leave the crude product. The resultant crude residue was purified by chromatography on silica gel (petroleum ether/EtOAc = 10:1) to afford target compound **3**.

Supporting Information (see footnote on the first page of this article): Experimental procedures, full characterization data, and copies of the ^1H NMR and ^{13}C NMR spectra for all compounds.

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[1] a) J. E. Hein, V. V. Fokin, *Chem. Soc. Rev.* **2010**, *39*, 1302–1315; b) V. Calderone, F. L. Fiamingo, G. Amato, I. Giorgi, O. Livi, A. Martelli, E. Martinotti, *Eur. J. Med. Chem.* **2008**, *43*, 2618–2626; c) K. A. Kalesh, K. Liu, S. Q. Yao, *Org. Biomol. Chem.* **2009**, *7*, 5129–5136; d) M. van Dijk, D. T. S. Rijkers, R. M. J. Liskamp, C. F. van Nostrum, W. E. Hennink, *Bioconjugate Chem.* **2009**, *20*, 2001–2016.

[2] a) A. Tam, U. Arnold, M. B. Soellner, R. T. Raines, *J. Am. Chem. Soc.* **2007**, *129*, 12670–12671; b) L. K. Rasmussen, B. C. Boren, V. V. Fokin, *Org. Lett.* **2007**, *9*, 5337–5339; c) R. Srinivasan, M. Uttamchandani, S. Q. Yao, *Org. Lett.* **2006**, *8*, 713–716; d) A. Dondoni, *Chem. Asian J.* **2007**, *2*, 700–708.

[3] a) S. G. Agalave, S. R. Maujan, V. S. Pore, *Chem. Asian J.* **2011**, *6*, 2696–2718; b) V. Calderone, F. L. Fiamingo, G. Amato, I. Giorgi, O. Livi, A. Martelli, E. Martinotti, *Eur. J. Med. Chem.* **2008**, *43*, 2618–2626; c) H. Shu, S. Izenwasser, D. Wade, E. D. Stevens, M. L. Trudell, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 891–893; d) S. M. Bromidge, R. Arban, B. Bertani, S. Bison, M. Borriello, P. Cavanni, G. D. Forno, R. Di-Fabio, D. Donati, S. Fontana, M. Gianotti, L. J. Gordon, E. Granci, C. P. Leslie, L. Moccia, A. Pasquarello, I. Sartori, A. Sava, J. M. Watson, A. Worby, L. Zonzini, V. Zucchelli, *J. Med. Chem.* **2010**, *53*, 5827–5843.

[4] H. Cheng, J. Wan, M. I. Lin, Y. Liu, X. Lu, J. Liu, Y. Xu, J. Chen, Z. Tu, Y. E. Cheng, K. Ding, *J. Med. Chem.* **2012**, *55*, 2144–2153.

[5] A. K. Jordão, V. F. Ferreira, T. M. L. Souza, G. G. de Souza Faria, V. Machado, J. L. Abrantes, M. C. B. V. de Souza, A. C. Cunha, *Bioorg. Med. Chem.* **2011**, *19*, 1860–1865.

[6] A. K. Jordão, V. F. Ferreira, E. S. Lima, M. C. B. V. de Souza, E. C. L. Carlos, H. C. Castro, R. B. Geraldo, C. R. Rodrigues, M. C. B. Almeida, A. C. Cunha, *Bioorg. Med. Chem.* **2009**, *17*, 3713–3719.

[7] a) L. Li, G. Zhang, A. Zhu, L. Zhang, *J. Org. Chem.* **2008**, *73*, 3630–3633; b) S. A. Lermontov, S. V. Shkavrov, A. N. Pushin, *J. Fluorine Chem.* **2000**, *105*, 141–147; c) Y. Liu, W. Yan, Y. Chen, J. L. Petersen, X. Shi, *Org. Lett.* **2008**, *10*, 5389–5392; d) G. A. Romeiro, L. O. R. Pereira, M. C. B. V. de Souza, V. F. Ferreira, A. C. Cunha, *Tetrahedron Lett.* **1997**, *38*, 5103–5106; e) R. H. Wiley, K. Hussung, J. Moffat, *J. Org. Chem.* **1956**, *21*, 190–192; f) C. R. Becer, R. Hoogenboom, U. S. Schubert, *Angew. Chem.* **2009**, *121*, 4998–5006; *Angew. Chem. Int. Ed.* **2009**, *48*, 4900–4908; g) V. R. Campos, P. A. Abreu, H. C. Castro, C. R. Rodrigues, A. K. Jordão, V. F. Ferreira, M. C. B. V. de Souza, F. da C. Santos, L. A. Moura, T. S. Domingos, C. Carvalho, E. F. Sanchez, A. L. Fuly, A. C. Cunha, *Bioorg. Med. Chem.* **2009**, *17*, 7429–7434.

[8] a) J. E. Hein, J. C. Tripp, L. B. Krasnova, K. B. Sharpless, V. V. Fokin, *Angew. Chem.* **2009**, *121*, 8162–8165; *Angew. Chem. Int. Ed.* **2009**, *48*, 8018–8021; b) C. Spiteri, J. E. Moses, *Angew. Chem.* **2010**, *122*, 33–36; *Angew. Chem. Int. Ed.* **2010**, *49*, 31–33.

[9] a) J. Deng, Y. M. Wu, Q. Y. Chen, *Synthesis* **2005**, *16*, 2730–2738; b) Y. M. Wu, J. Deng, Y. Li, Q. Y. Chen, *Synthesis* **2005**, *8*, 1314–1318; c) A. R. Bogdan, K. James, *Org. Lett.* **2011**, *13*, 4060–4063.

[10] a) L. Ackermann, R. Vicente, *Org. Lett.* **2009**, *11*, 4922–4925; b) S. Fukuzawa, H. Oki, M. Hosaka, J. Sugasawa, S. Kikuchi, *Org. Lett.* **2007**, *9*, 5557–5560; c) L. Ackermann, H. K. Potukuchi, D. Landsberg, R. Vicente, *Org. Lett.* **2008**, *10*, 3081–3084; d) S. Chuprakov, N. Chernyak, A. S. Dudnik, V. Gevorgyan, *Org. Lett.* **2007**, *9*, 2333–2336; e) T. He, M. Wang, P. Li, L. Wang, *Chin. J. Chem.* **2012**, *30*, 979–984; f) S. Fukuzawa, E. Shimizu, K. Ogata, *Heterocycles* **2009**, *78*, 645–655.

[11] A. Krasiński, V. V. Fokin, K. B. Sharpless, *Org. Lett.* **2004**, *6*, 1237–1240.

[12] I. F. Cottrell, D. Hands, P. G. Houghton, G. R. Humphrey, S. H. B. Wright, *J. Heterocycl. Chem.* **1991**, *28*, 301–304.

[13] a) L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, G. Jia, *J. Am. Chem. Soc.* **2005**, *127*, 15998–15999; b) B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia, V. V. Fokin, *J. Am. Chem. Soc.* **2008**, *130*, 8923–8930.

[14] a) T. F. Niu, L. Gu, W. B. Yi, Ch. Cai, *ACS Comb. Sci.* **2012**, *14*, 309–315; b) N. T. Pokhodylo, V. S. Matiychuk, M. D. Obushak, *J. Comb. Chem.* **2009**, *11*, 481–485.

[15] L. J. T. Danence, Y. Gao, M. Li, Y. Huang, J. Wang, *Chem. Eur. J.* **2011**, *17*, 3584–3587.

[16] a) E. F. V. Scriven, K. Turnbull, *Chem. Rev.* **1988**, *88*, 297–368; b) S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem.* **2005**, *117*, 5320–5374; *Angew. Chem. Int. Ed.* **2005**, *44*, 5188–5240.

[17] J. Zhang, J. J. Wu, L. Shen, G. Y. Jin, S. Cao, *Adv. Synth. Catal.* **2011**, *353*, 580–584.

[18] M. N. S. Rad, S. Behrouz, A. Khalafi-Nezhad, *Tetrahedron Lett.* **2007**, *48*, 3445–3449.

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