CuBr-CATALYZED SYNTHESIS OF 1,4,5-TRISUBSTITUTED 1,2,3-TRIAZOLES THROUGH CYCLOADDITION OF AZIDES TO ALKENES

Bo Yang,1 Mian-Chen Zou,2 Feng Chen,2 and Kai-Jie Fan1
1Department of Thoracic Surgery, PLA General Hospital, Beijing, China
2State Key Laboratory of Natural and Biomimetic Drugs, Peking University, Beijing, China

GRAPHICAL ABSTRACT

Abstract We developed a CuBr-catalyzed synthesis of 1,4,5-trisubstituted 1,2,3-triazoles with moderate to good yields via azide–alkene cycloaddition and oxidative aromatization using air as oxidant. The reaction is simple and easily handled with inexpensive and readily available copper catalysis.

Keywords Copper(I) bromide; cycloaddition; 1,2,3-triazole

INTRODUCTION

1,2,3-Triazoles are attractive molecules and widely used in organic synthesis, materials sciences, drug development, and bioconjugation chemistry (Fig 1). The traditional preparation methods of 1,2,3-triazoles by 1,3-dipolar cycloaddition of azides and alkynes under thermal conditions. Great developments have been realized as click chemistry, copper-catalyzed azide–alkyne cycloaddition (CuAAC), which provides a simple method to join together organic molecules efficiently under mild conditions, has been explored in depth. The copper- and ruthenium-catalyzed azide–alkyne cycloaddition reactions are powerful strategies for the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles and 1,5-disubstituted 1,2,3-triazoles.

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Address correspondence to Bo Yang, Department of Thoracic Surgery, PLA General Hospital, Fuxing Rd. 28, Haidian District, Beijing 100853, China. E-mail: 301yangbo@gmail.com
However, internal alkynes are rarely developed[^4] and 1,4,5-trisubstituted 1,2,3-triazoles are difficult to synthesize through this strategy.

Moreover, 1,2,3-triazoles could also be prepared using alkenes instead of alkynes via 1,3-dipolar cycloaddition with leaving groups.[^5] 1,2,3-Triazoles also could be obtained from quinones and azides.[^6] Recently, Tripathi and coworkers reported a regioselective [3 + 2] cycloaddition of chalcones with a sugar azide.[^7] Yao and coworkers developed an regioselective synthesis of 1,4-disubstituted/1,4,5-trisubstituted 1,2,3-triazoles catalyzed by CuI through azide–alkene cycloaddition using N,N-diisopropylethyl-amine (DIPEA) as base under an oxygen atmosphere.[^8] The processes of 1,3-dipolar cycloaddition followed by oxidative aromatization are proposed for this transformation. Although this method provides new route for the synthesis of

| Entry | 2a (eq.) | Catalyst (mol%) | T (°C) | Yield (%) |
|-------|----------|----------------|--------|-----------|
| 1     | 2.0      | CuBr (1)       | 80     | 40        |
| 2     | 1.0      | CuBr (1)       | 110    | 61        |
| 3     | 1.0      | CuI (1)        | 110    | 64        |
| 4     | 1.0      | Cu(OAc)₂ (1)   | 110    | 58        |
| 5     | 1.0      | FeCl₂ (1)      | 110    | 56        |
| 6     | 1.5      | CuBr (1)       | 110    | 66        |
| 7     | 1.5      | CuBr (5)       | 110    | 81        |
| 8     | 1.5      | —              | 110    | 38        |

[^4]: Isolated yield.
1,2,3-triazoles with moderate to excellent yields, high catalyst loading and usage of base are drawbacks that could restrict the application of this methodology. Herein, we reported an alternative method for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles with low catalyst loading in the absence of base.

Scheme 1. The scope of this transformation.
RESULTS AND DISCUSSION

(E)-Chalcone and (azidomethyl)cyclohexane were chosen as the substrates for this reaction. (1-(Cyclohexylmethyl)-5-phenyl-1H-1,2,3-triazol-4-yl)(phenyl)methanone (3aa) could be obtained in 40% yield in the presence of 1 mol% CuBr catalyst in 80 °C (Table 1, entry 1). When the temperature was raised to 110 °C, the yield could be improved to 61% (Table 1, entry 2). Some other copper and iron catalysts gave poor yields for this transformation (Table 1, entries 3–5). Finally, the optimized result was realized when 5 mol% CuBr was used and the yield could be achieved in 81% (Table 1, entries 6 and 7). Only 38% yield was obtained when no catalyst was used and 50% (E)-chalcone (1a) was recovered (Table 1, entry 8). Also little by-product could be detected by thin-layer chromatographic (TLC) monitoring. Unfortunately, it could not be isolated and identified successfully. The result shows that the copper catalyst is necessary for this transformation. We assume that a triazoline intermediate, which could be generated via 1,3-dipolar cycloaddition, undergoes oxidation under copper and air conditions.\[^8\]

With the optimized reaction conditions in hand, the scope of this 1,2,3-triazole synthesis was investigated (Scheme 1). To our delight, various substituted internal olefins could react with (azidomethyl)cyclohexane to give corresponding 1,2,3-triazol successfully with moderate to good yields. When 1-azidononane was used instead of (azidomethyl)cyclohexane, the desired products also could be obtained with moderate to good yields. The results indicate that the present reaction system has wide substrate scope.

CONCLUSION

In summary, we developed a CuBr-catalyzed synthesis of 1,4,5-trisubstituted 1,2,3-triazoles via azide–alkene cycloaddition and oxidative aromatization using air as oxidant. The present method is simple and convenient for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles with moderate to good yields. The catalyst amount is low and additive is unnecessary for this transformation. Further exploration of the mechanism and synthetic application is ongoing in our group.

EXPERIMENTAL

All manipulations were conducted under an air atmosphere. \(^1\)H NMR spectra were recorded on a Bruker Avance III-400 spectrometer. Chemical shifts (in ppm) were referenced to tetramethylsilane (δ = 0 ppm) in CDCl₃ as an internal standard. \(^13\)C NMR spectra were obtained by using the same NMR spectrometers and were calibrated with CDCl₃ (δ = 77.00 ppm). High-resolution mass spectra were recorded using a Fourier transform ion cyclotron resonance mass spectrometer (APEX IV, Bruker).

**General Procedure for Synthesis of 1,2,3-Triazol**

The mixture of 1 (0.6 mmol), 2 (0.9 mmol, 125.3 mg), copper bromide (0.003 mmol, 4.0 mg), and DMF (2.0 mL) was stirred at 110 °C under air. After 36 h, water (5 mL) was added to the mixture and extracted with ethyl acetate.
The product was dried with anhydrous magnesium sulfate, concentrated, and purified by flash chromatography on silicon gel to afford 3.

\((5\text{-}(4\text{-}\text{Chlorophenyl})\text{-}1\text{-}(\text{cyclohexylmethyl})\text{-}1H\text{-}1,2,3\text{-}\text{triazol-4-yl})\text{(phenyl) Methanone (3ba)\) }

\(^{1}\text{H NMR (CDCl}_3, 400 MHz): \delta = 8.29 (d, J = 7.2 Hz, 2H), 7.59–7.53 \text{ (m, 1H), 7.51–7.43 (m, 4H), 7.34 (d, J = 8.4 Hz, 2H), 4.08 (d, J = 7.2 Hz, 2H), 1.95–1.83 (m, 1H), 1.68–1.60 (m, 3H), 1.51 (d, J = 11.6 Hz, 2H), 1.23–0.88 (m, 3H), 0.86–0.79 (m, 2H);} \(^{13}\text{C NMR (CDCl}_3, 100 MHz): \delta = 186.1, 143.4, 140.7, 136.9, 136.0, 132.9, 131.1, 130.5, 128.9, 128.1, 125.1, 54.0, 38.2, 30.2, 25.8, 25.2. IR (KBr): 3433, 2919, 2849, 1656, 1547, 1487, 1452 cm\(^{-1}\). HRMS: (ESI) calcd. for C\(_{22}\)H\(_{22}\)ClN\(_{3}\)O \([\text{M + H}]^+\) 380.1529, found 380.1525. Mp 108 °C.

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**SUPPORTING INFORMATION**

Full experimental details and \(^{1}\text{H} and \(^{13}\text{C} NMR spectra can be accessed on the publisher’s website.**

**REFERENCES**

1. (a) Nair, D. P.; Podgórski, M.; Chatani, S.; Gong, T.; Xi, W.; Fenoli, C. R.; Bowman, C. N. *Chem. Mater.* 2014, 26, 724; (b) Yim, C.-B.; Dijkstra, I.; Merkx, R.; Versluis, C.; Eek, A.; Mulder, G. E.; Rijpers, D. T. S.; Boerman, O. C.; Liskamp, R. M. J. *J. Med. Chem.* 2010, 53, 3944; (c) Tripathi, R. P.; Yadav, A. K.; Ajay, A.; Bisht, S. S.; Chaturvedi, V.; Sinha, S. K. *Eur. J. Med. Chem.* 2010, 45, 142; (d) Meldal, M.; Tornoe, C. W. *Chem. Rev.* 2008, 108, 2952; (e) Chen, H.; Taylor, J. L.; Abrams, S. R. *Bioorg. Med. Chem. Lett.* 2007, 17, 1979; (f) Bock, V. D.; Speijer, D.; Hiemstra, H.; Van Maarseveen, J. H. *Org. Biomol. Chem.* 2007, 5, 971; (g) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* 2007, 36, 1249; (h) Wang, J.; Sui, G.; Mocharla, V. P.; Lin, R. J.; Phelps, M. E.; Kolb, H. C.; Tseng, H.-R. *Angew. Chem. Int. Ed.* 2006, 45, 5276; (i) Manetsch, R.; Krasinski, A.; Rauschel, J.; Taylor, P.; Sharpless, K. B.; Kolb, H. C. *J. Am. Chem. Soc.* 2004, 126, 12809; (j) Agard, N. J.; Prescher, J. A.; Bertozzi, C. R. *J. Am. Chem. Soc.* 2004, 126, 15046; (k) Kolb, H. C.; Sharpless, K. B. *Drug Disc. Today* 2003, 8, 1128; (l) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* 2002, 41, 2596 (m) Maliakal, A.; Lem, G.; Turro, N. J.; Ravichandran, R.; Suhadolnik, J. C.; DeBellis, A. D.; Wood, M. G.; Lau, J. J. *Phys. Chem. A* 2002, 106, 7680.

2. (a) Huisgen, R. *Proc. Chem. Soc.* 1961, 357; (b) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* 1963, 2, 565; (b) Huisgen, R. *Angew. Chem. Int. Ed. Engl.* 1963, 2, 633; (c) Yang, C.-H.; Sherf, H.-J.; Wang, R.-H.; Wang, J.-C. *J. Chin. Chem. Soc.* 2002, 49, 95; (d) Shriteha, T.; Kodlaa, A.; Abu-Orabib, S. T.; Madwaras, R.; Atfeh, A. *Jordan J. Chem.* 2011, 6, 81.

3. (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* 2001, 40, 2004; (b) Rostovtsev, V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* 2002, 41, 2596; (c) Worrell, B. T.; Malik, J. A.; Fokin, V. V. *Science* 2013, 340, 457. For
reviews, see (d) Hein, J. E.; Fokin, V. V. Chem. Soc. Rev. 2010, 39, 1302; (e) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Angew. Chem. Int. Ed. 2001, 40, 2004.

4. Candelon, N.; Lastécouères, D.; Diallo, A. K.; Aranzaes, J. R.; Astruc, D.; Vincent, J.-M. Chem. Commun. 2008, 741.

5. (a) Hansen, S. G.; Jensen, H. H. Synlett 2009, 3275; (b) Sengupta, S.; Duan, H.; Lu, W.; Petersen, J. L.; Shi, X. Org. Lett. 2008, 10, 1493; (c) Roque, D. R.; Neill, J. L.; Antoon, J. W.; Stevens, E. P. Synthesis 2005, 2497; (e) Peng, W.; Zhu, S. Tetrahedron 2003, 59, 4395; (d) Peng, W.; Zhu, S. Synlett 2003, 187.

6. Chan, K. Y.; Zhang, J.; Chang, C.-W. T. Bioorg. Med. Chem. Lett. 2011, 21, 6353.

7. (a) Singh, N.; Pandey, S. K.; Tripathi, R. P. Carbohydr. Res. 2010, 345, 1641; (b) Ajay, A.; Sharma, S.; Gupt, M. P.; Bajpai, V.; Hamidullah, Kumar, B.; Kaushik, M. P.; Konwar, R.; Ampapathi, R. S.; Tripathi, R. P. Org. Lett. 2012, 14, 4306.

8. Janreddy, D.; Kavala, V.; Kuo, C.-W.; Chen, W.-C.; Ramesh, C.; Kotipalli, T.; Kuo, T.-S.; Chen, M.-L.; He, C.-H.; Yao, C.-F. Adv. Synth. Catal. 2013, 355, 2918.