Tetrahedron Letters 51 (2010) 3691–3695

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A convenient and efficient synthesis of *C*-carbamoyl-1,2,3-triazoles from alkyl bromide by a one-pot sequential addition: conversion of ester to amide using $Zr(Ot\text{-}Bu)_4$

Dongsik Yang, Mihyun Kwon, Yujin Jang, Heung Bae Jeon *

Department of Chemistry, Kwangwoon University, Seoul 139-701, Republic of Korea

ARTICLE INFO

Article history:
Received 16 March 2010
Revised 11 May 2010
Accepted 12 May 2010
Available online 15 May 2010

Keywords:
One-pot sequence
C-Carbamoyl-1,2,3-triazole
Zirconium *tert*-butoxide
Microwave irradiation

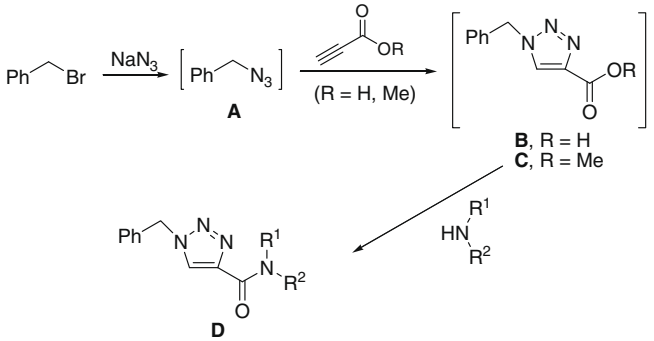
ABSTRACT

A convenient and efficient one-pot sequence has been developed for the synthesis of *C*-carbamoyl-1,2,3-triazoles from alkyl bromide using (i) sodium azide, (ii) methyl propiolate and copper iodide, and (iii) amines, zirconium *tert*-butoxide, and 1-hydroxybenzotriazole, under microwave irradiation. The sequential reactions in one-pot provided the desired *C*-carbamoyl-1,2,3-triazoles in excellent yields.

The formation of 1,2,3-triazoles using the copper(I)-catalyzed 1,3-dipolar cycloaddition of organic azides and alkynes[1] has become an increasingly attractive area because it is a highly efficient method in bond formations among diverse building blocks for chemical synthesis,[2] bioconjugation,[3] materials and surface science,[4] combinatorial chemistry,[5] and medicinal chemistry.[6] In particular, a number of compounds containing *C*-carbamoyl-1,2,3-triazoles have shown a broad spectrum of biological activities in recent days.[7] Even simple *C*-carbamoyl-1,2,3-triazole compounds also showed antiaggregating and antithrombotic activities.[8]

C-Carbamoyl-1,2,3-triazoles have been synthesized by 1,3-dipolar cycloaddition with alkyl azides and acetylenic amides, or by amide formation in last step after preparing 1,2,3-triazole esters using alkyl azides and acetylenic esters. The former method, however, has remained a problem for preparing acetylenic amides because they were synthesized in low yields,[9] and the latter method needed routine and tedious processes because of the long reaction time and the purification of the intermediates such as alkyl azide and 1,2,3-triazole ester. Therefore, it is still of interest to develop more efficient process for preparing *C*-carbamoyl-1,2,3-triazoles. Herein we report the convenient and efficient procedure for synthesizing *C*-carbamoyl-1,2,3-triazoles from the corresponding alkyl bromide by sequential addition of reagents and other reactants in one-pot without any purification of the intermediates generated in each stage.

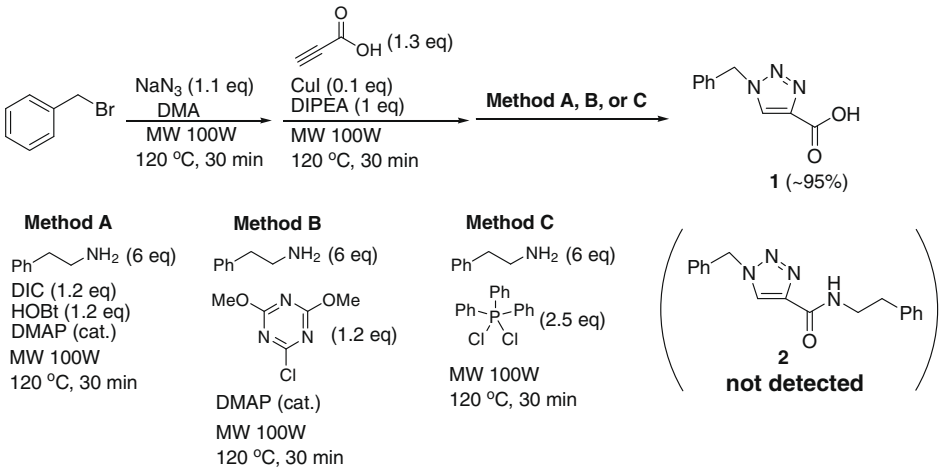
We envisioned that treatment of benzyl bromide with sodium azide would induce benzyl azide **A**, then addition of propiolic acid or methyl propiolate would provide 1,2,3-triazole acid **B** or ester **C** (Scheme 1). Without any purification of intermediates **A**, **B**, and **C**, subsequent reaction of **B** or **C** with amine would afford the desired *C*-carbamoyl-1,2,3-triazole **D**. Thus, initially we tried to prepare a *C*-carbamoyl-1,2,3-triazole **2** from benzyl bromide by following sequences in one-pot under microwave irradiation as shown in Scheme 2: (i) substitution of benzyl bromide by sodium azide in dimethylacetamide (DMA), (ii) copper(I)-catalyzed 1,3-dipolar cycloaddition with propionic acid in the presence of a catalytic amount of copper iodide to give 1,2,3-triazole-4-carboxylic acid



Scheme 1.

* Corresponding author. Tel.: +82 2 940 5583; fax: +82 2 911 8584.
E-mail address: hbj@kw.ac.kr (H.B. Jeon).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.05.046

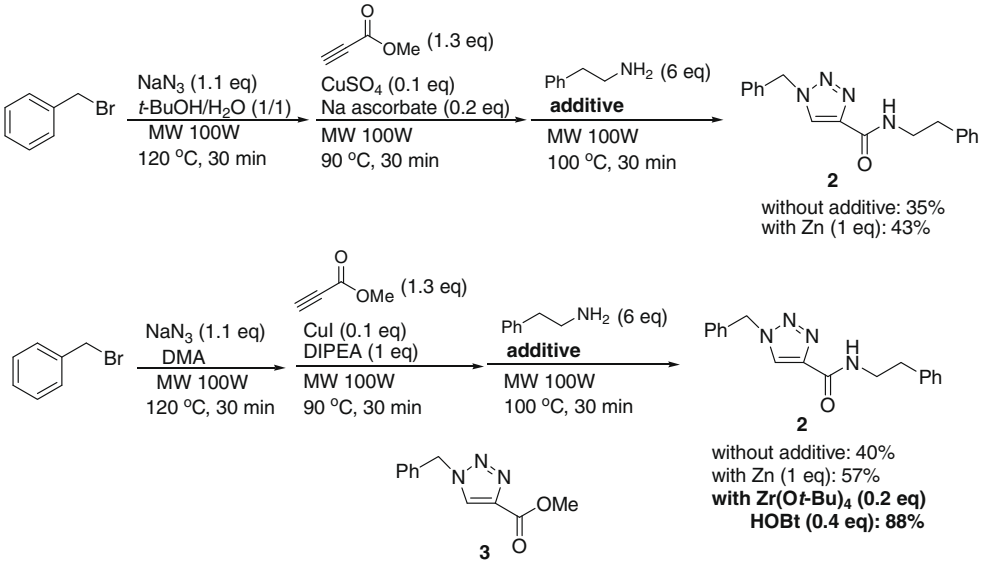


Scheme 2.

1, and (iii) coupling with phenethylamine in the presence of diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOBt). The first attempt afforded only 1,2,3-triazole-4-carboxylic acid **1** in good yield. Thus, we decided to employ other coupling reagents such as 2-chloro-4,6-dimethoxy-1,3,5-triazine[10] and dichlorotriphenylphosphorane[11] for coupling reaction with the acid **1** and phenethylamine in the last step. All attempts, however, failed to give the desired *C*-carbamoyl-1,2,3-triazole **2**, and only the acid **1** was produced in good yield (Scheme 2).

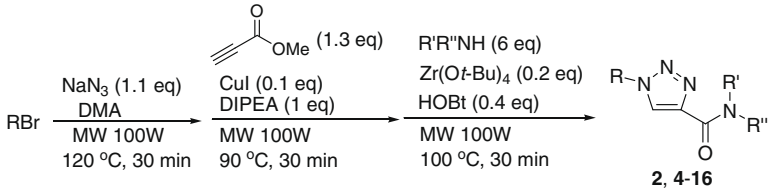
Next, we performed to prepare *C*-carbamoyl-1,2,3-triazole **2** by way of 1,2,3-triazole-4-ester **3** according to the following sequences in one-pot under microwave irradiation as shown in Scheme 3: (i) substitution of benzyl bromide by sodium azide in dimethylacetamide (DMA), (ii) copper(I)-catalyzed 1,3-dipolar cycloaddition with methyl propiolate in the presence of a catalytic amount of copper sulfate and sodium ascorbate to give 1,2,3-triazole-4-ester **3**, and (iii) coupling with phenethylamine in the presence of zinc[12] or without zinc. In this performance the desired *C*-carbamoyl-1,2,3-triazole **2** was produced in 43% yield with zinc and in 35% yield with no additive. Based on this interesting result, we changed copper sulfate and sodium ascorbate into copper iodide and diisopropylethylamine as reagents for copper(I)-catalyzed 1,3-dipolar cycloaddition in second stage. Thus, the desired product **2** was provided in 57% yield with zinc and in 40% yield with no additive. On the other hand, when a catalytic amount of zirconium(IV) *tert*-butoxide and HOBt[13] was employed as additive in the last stage, surprisingly, the sequential reaction afforded the desired product **2** in 88% yield[14] (Scheme 3 and entry 1 in Table 1).

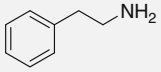
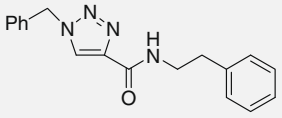
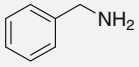
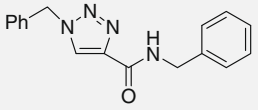
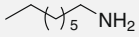
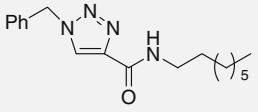
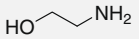
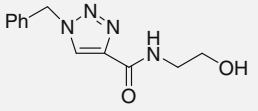
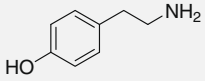
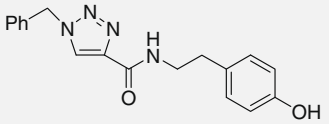
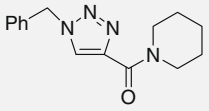
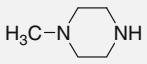
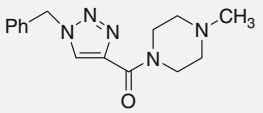
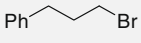
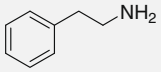
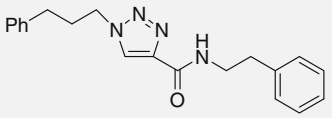
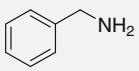
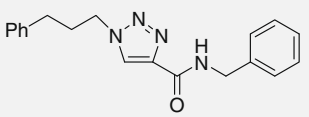
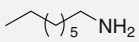
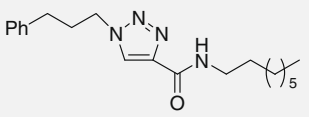
Therefore, the generality of this sequential addition process using sodium azide, methyl propiolate, copper iodide, zirconium(IV) *tert*-butoxide, and HOBt from alkyl bromide for preparing *C*-carbamoyl-1,2,3-triazoles was investigated with a variety of amines under microwave irradiation. The reactions were carried out by following sequential addition of reagents and reactants to alkyl bromide: (i) sodium azide in dimethylacetamide (DMA), (ii) methyl propiolate in the presence of a catalytic amount of copper iodide, and (iii) amines in the presence of a catalytic amount of zirconium(IV) *tert*-butoxide and HOBt. All reactions performed gave the *C*-carbamoyl-1,2,3-triazoles in excellent yields (Table 1). To benzyl bromide, the above-mentioned sequential addition, (i) and (ii), was performed. Then, primary amines such as benzylamine and octylamine in the last step were reacted to afford the desired *C*-carbamoyl-1,2,3-triazole **4** and **5** in 72% and 85% yields, respectively (entries 2 and 3). In case of benzylamine, a little low yield



Scheme 3.

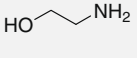
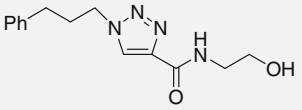
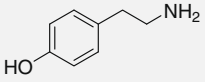
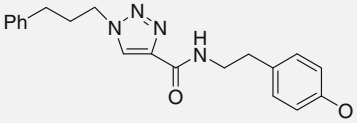
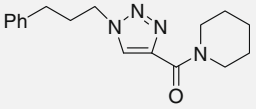
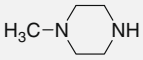
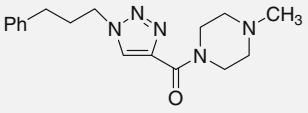
Table 1
Synthesis of *C*-carbamoyl-1,2,3-triazoles from alkyl bromide using a one-pot sequential reaction



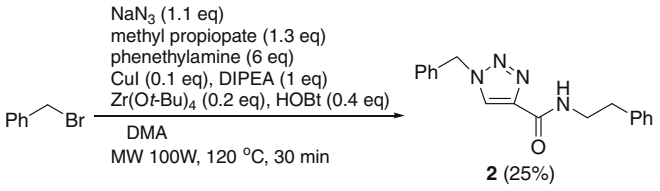
Entry	Alkyl bromide	Amine	Product	Yield[a] (%)
1			 **2**	88
2			 **4**	72
3			 **5**	85
4			 **6**	89
5			 **7**	91
6			 **8**	89[b]
7			 **9**	85[b]
8			 **10**	81
9			 **11**	81
10			 **12**	83

(*continued on next page*)

Table 1 (*continued*)

Entry	Alkyl bromide	Amine	Product	Yield[a] (%)
11			 **13**	93
12			 **14**	93
13			 **15**	84[b]
14			 **16**	82[b]

[a] Isolated yields.
[b] MW 100 W, 120 °C in the third step.



Scheme 4.

of the desired product **4** results from the poor solubility in a mixture of hexane and ethyl acetate which is the eluting solvent in column chromatography. The reaction of primary amines, such as 2-hydroxyethylamine and 4-(2-aminoethyl)phenol, with hydroxyl group also provided the corresponding *C*-carbamoyl-1,2,3-triazoles **6** and **7** in excellent yields (entries 4 and 5). However, the reaction of cyclic secondary amines such as piperidine and *N*-methylpiperazine did not give the desired products **8** and **9** at same temperature (100 °C) with primary amines. When the reaction temperature was elevated to 120 °C, the reactions afforded the products **8** and **9** in 89% and 85% yields, respectively (entries 6 and 7). To 3-phenylpropyl bromide, the same sequential reactions were performed with various amines. All amines investigated provided the desired *C*-carbamoyl-1,2,3-triazoles **10–16** in excellent yields (entries 8–14). The aliphatic secondary amines such as dibenzylamine and dihexylamine, however, were not reacted with 1,2,3-triazole-4-ester **3** even at 150 °C because of the steric hindrance. After performing the complete sequential reaction, the only product was 1,2,3-triazole-4-ester **3**.

On the other hand, when all reagents and reactants such as sodium azide, methyl propiolate, copper iodide, DIPEA, phenethylamine, zirconium(IV) *tert*-butoxide, and HOBt to benzyl bromide in DMA were added at once and were reacted as multi-component one-pot reaction at 120 °C for 30 min under microwave irradiation, the reaction was very complicated and the desired product **2** was provided only in 25% yield (Scheme 4).

In conclusion, we have found that the one-pot sequential reactions by addition of (i) sodium azide in dimethylacetamide (DMA), (ii) methyl propiolate in the presence of a catalytic amount of copper iodide, and (iii) amines in the presence of a catalytic amount of zirconium(IV) *tert*-butoxide and HOBt one by one to alkyl bromide under microwave irradiation provided the desired *C*-carbamoyl-1,2,3-triazoles in excellent yields. We also found that zirconium(IV) *tert*-butoxide and HOBt are important reagents to convert 1,2,3-triazole-4-esters into *C*-carbamoyl-1,2,3-triazoles in one-pot sequential reaction. Moreover, this process is very convenient and efficient method because it significantly reduced reaction times and tedious procedures such as work-up and purification at each step.

Acknowledgments

We thank for the support of Korea Research Foundation (KRF) grant funded by the Korean Government (MOEHRD) (No. 2007-331-C00156) and research grant of Kwangwoon University in 2008 for this work.

References and notes

1. (a) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057; (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.
2. (a) Billing, J. F.; Nilsson, U. J. *J. Org. Chem.* **2005**, *70*, 4847; (b) van Maarseveen, J. H.; Horne, W. S.; Ghadiri, M. R. *Org. Lett.* **2005**, *7*, 4503; (c) Bodine, K. D.; Gin, D. Y.; Gin, M. S. *Org. Lett.* **2005**, *7*, 4479; (d) Zhou, Z.; Fahrni, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 8862; (e) Jin, T.; Kamijo, S.; Yamamoto, Y. *Eur. J. Org. Chem.* **2004**, 3789; (f) Bodine, K. D.; Gin, D. Y.; Gin, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 1638; (g) Seo, T. S.; Li, Z.; Ruparel, H.; Ju, J. *J. Org. Chem.* **2003**, *68*, 609; (h) Fazio, F.; Bryan, M. C.; Blixt, O.; Paulson, J. C.; Wong, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 14397.
3. (a) Speers, A. E.; Cravatt, B. F. *Chem. Biol.* **2004**, *11*, 535; (b) Deiters, A.; Cropp, T. A.; Mukherji, M.; Chin, J. W.; Anderson, J. C.; Schultz, P. G. *J. Am. Chem. Soc.* **2003**, *125*, 11782; (c) Link, A. J.; Tirrell, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 11164; (d) Lee, L. V.; Mitchell, M. L.; Huang, S.-J.; Fokin, V. V.; Sharpless, K. B.; Wong, C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 9588; (e) Speers, A. E.; Adam, G. C.; Cravatt, B. F. *J. Am. Chem. Soc.* **2003**, *125*, 4686; (f) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192; (g) Breinbauer, R.; Kohn, M. *ChemBioChem* **2003**, *4*, 1147.
4. (a) Diaz, D. D.; Punna, S.; Holzer, P.; McPherson, A. K.; Sharpless, K. B.; Fokin, V.; Finn, M. G. *J. Polym. Sci., Part A* **2004**, *42*, 4392; (b) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Fréchet, J. M. J.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2004**, *43*, 3928; (c) Lee, J. K.; Chi, Y. S.; Choi, I. S. *Langmuir* **2004**, *20*, 3844; (d) Collman, J. P.; Devaraj, N. K.; Chidsey, C. E. D. *Langmuir* **2004**, *20*, 1051.

5. Lober, S.; Rodriguez-Loaiza, P.; Gmeiner, P. *Org. Lett.* **2003**, *5*, 1753.
6. (a) Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. D.; Stper, D.; Yagi, B. H. *J. Med. Chem.* **2000**, *43*, 953; (b) Alvarez, R.; Velazquez, S.; San-Felix, A.; Aquaro, S.; De Clercq, E.; Perno, C.-F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4194; (c) Buckle, D. R.; Rockell, C. J. M.; Smith, H.; Spicer, B. A. *J. Med. Chem.* **1986**, *29*, 2262; (d) Wamhoff, H. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; pp 669–732.
7. (a) Ouberai, M.; Dumy, P.; Chierici, S.; Garcia, J. *Bioconjugate Chem.* **2009**, *20*, 2123; (b) Mathew, T.; Billich, A.; Cavallari, M.; Bornancin, F.; Nussbaumer, P.; De Libero, G.; Vasella, A. *Chem. Biodivers.* **2009**, *6*, 705; (c) Li, L.; Lin, B.; Yang, Z.; Zhang, L.; Zhang, L. *Tetrahedron Lett.* **2008**, *49*, 4491; (d) Kapoerchan, V.; Wiesner, M.; Overhand, M.; Van der Marel, G.; Koning, F.; Overkleeft, H. *Bioorg. Med. Chem.* **2008**, *16*, 2053; (e) Ng, S. L.; Yang, P. U.; Chen, K. Y. T.; Srinivasan, R.; Yao, S. Q. *Org. Biomol. Chem.* **2008**, *6*, 844.
8. Cwiklicki, A.; Rehse, K. *Arch. Pharm. Pharm. Med. Chem.* **2004**, *337*, 156.
9. (a) Lee, B. Y.; Park, S. R.; Jeon, H. B.; Kim, K. S. *Tetrahedron Lett.* **2006**, *47*, 5105; (b) Katritzky, A. R.; Singh, S. K. *J. Org. Chem.* **2002**, *67*, 9077; (c) Jinag, H.; Ma, S.; Zhu, G.; Lu, X. *Tetrahedron* **1996**, *52*, 10945.
10. Kaminski, Z. J. *Tetrahedron Lett.* **1985**, *26*, 2901.
11. Azumaya, I.; Okamoto, T.; Imabeppu, F.; Takayanagi, H. *Tetrahedron* **2003**, *59*, 2325.
12. Arora, R.; Paul, S.; Gupta, R. *Can. J. Chem.* **2005**, *83*, 1137.
13. Han, J.; Lee, J. P.; Lobkovsky, E.; Porco, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 10039.
14. *Typical procedure for* **2**: A solution of benzyl bromide (100 mg, 0.59 mmol), sodium azide (42 mg, 0.64 mmol), and DMA (1.0 mL) in a 10-mL pressurized vial was stirred for 30 min at 120 °C in microwave reactor. After cooling to room temperature, methyl propiolate (71 mg, 0.76 mmol), copper iodide (11 mg, 0.058 mmol), and DIPEA (0.1 mL, 0.58 mmol) were added. The resulting solution was stirred for 30 min at 90 °C in microwave reactor. After cooling to room temperature, zirconium(IV) *tert*-butoxide (45 mg, 0.12 mmol), HOBt (30 mg, 0.23 mmol), and phenethylamine (0.44 mL, 3.50 mmol) were added. The resulting solution was stirred for 30 min at 100 °C in microwave reactor. After cooling to room temperature, the reaction mixture was concentrated to remove DMA. The residue was diluted with CH_2Cl_2 (30 mL) and washed with saturated $NaHCO_3$ solution (20 mL × 3). The organic layer was separated, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 5:2) to give the desired *C*-carbamoyl-1,2,3-triazole **2** (159 mg, 88%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.41–7.21 (m, 11H), 5.53 (s, 2H), 3.70 (q, J = 6.8 Hz, 2H), 2.91 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 143.6, 138.6, 133.7, 129.2, 129.0, 128.7, 128.6, 128.2, 126.5, 125.2, 54.5, 40.3, 35.8. HRMS (M+Na) calcd 329.1378, found 329.1395. Anal. Calcd for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.63; H, 5.70; N, 18.57.