DOI 10.5012/bkcs.2011.32.7.2453

An Efficient Solid-Phase Synthesis of α-1,2,3-Triazoloamide Derivatives *via* Click Chemistry

Young-Dae Gong,[†] Kyung Hoon Min,[‡,*] and Taeho Lee[*]

Research Institute of Pharmaceutical Sciences, College of Pharmacy, Kyungpook National University, Daegu 702-701, Korea. [*]E-mail: tlee@knu.ac.kr
[†]Department of Chemistry, Dongguk University, Seoul 100-715, Korea
[‡]College of Pharmacy, Chung-Ang University, Seoul 156-756, Korea. [*]E-mail:khmin@cau.ac.kr
Received April 26, 2011, Accepted May 9, 2011

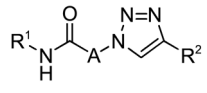
Key Words : Combinatorial chemistry, Solid-phase synthesis, Click chemistry, α-1,2,3-Triazoloamides

Combinatorial chemistry has become an extremely powerful technique for the rapid generation of small, drug-like organic molecule libraries for medicinal chemistry programs within the pharmaceutical industry.[1,2] In the past, various methods were developed for the synthesis of 1,2,3-triazoles. One very useful organic transformation is the 1,3-dipolar cycloaddition reaction of azides with alkynes which has been extensively studied by Huisgen *et al*.[3] Recently, Sharpless and co-workers have reported remarkable high-yielding syntheses of 1,2,3-triazoles with excellent regioselectivity using a Cu(I)-catalyzed [3+2] cycloaddition reaction.[4] This reaction has become a powerful method for generating combinatorial libraries and has found increasing applications in lead discovery and lead optimization.[5] Among a variety of bioisosteres of the amide moiety, 1,2,3-triazoles have gained increasing attention in drug discovery.[6] 1,2,3-Triazoles can mimic the topological and electronic features of an amide bond and can actively participate in hydrogen bonding and dipole-dipole interactions.

Many α-1,2,3-triazoloamides **1** (Figure 1) or α-1,2,3-triazoloketones exhibit a wide range of biological properties.[7,8] For example, α-1,2,3-triazoloamides have demonstrated activities as lymphoid tyrosine phosphatase (Lyp, PTPN22) inhibitors,[7a] as fatty acid synthase (FAS) inhibitors for antitumor agents,[7b] as human neuraminidase 3 (NEU3) inhibitor,[7c] as promoters of *E. coli* biofilm formation,[7d] and as protein tyrosine phosphatase (PTP) inhibitors.[7e] α-1,2,3-Triazoloketones compounds also have been used as Src kinase inhibitors[8a] and as cytotoxic agents against several cancer cell lines.[8b]

Herein, we describe recent progress on the first solid-phase synthetic protocol for the preparation of α-1,2,3-triazoloamides **1** (Figure 1), which is applicable to high throughput construction of drug-like compound libraries.

For the divergent synthesis of the α-1,2,3-triazoloamides, we employed the known AMEBA (Acid sensitive Methoxy Benzaldehyde)[9] resin **2** (from Merrifield resin) as the starting material in this synthesis (Scheme 1).

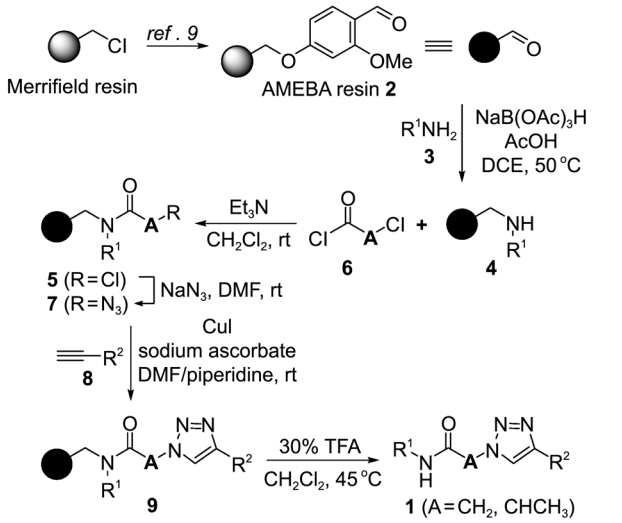


1 (A = CH_2, $CHCH_3$)

Figure 1. Structure of the α-1,2,3-triazoloamides.

The reductive amination reaction of the aliphatic or aromatic amines **3** (the first diversity element) and resin **2** with sodium triacetoxyborohydride gave polymer bounded secondary amines **4**. The progress of this reaction (R^1 = Ph) was monitored by using ATR-FTIR (Attenuated Total Reflection Fourier Transform Infrared) which showed that the weak NH stretching band at 3424 cm^{-1} appeared and the disappearance of stretching band of aldehyde at 1678 cm^{-1} (Figure 2).

Solid supported chloroamides **5** with the second potential diversity element **A** can be easily prepared by the reaction of amine resin **4** with chloro acid chloride **6** and triethylamine in CH_2Cl_2 at room temperature. The progression of this process (R^1 = Ph, **A** = CH_2) was monitored by using ATR-FTIR which displayed the disappearance of the characteristic NH band at 3424 cm^{-1} and appearance of the amide carbonyl stretching band at 1666 cm^{-1}. In the reaction of amine resin **4** with 3-chloropropionyl chloride, the desired β-chloroamide resin of **5** (R^1 = Ph, R = Cl, **A** = CH_2CH_2)



Scheme 1. Solid-phase synthesis of α-1,2,3-triazoloamide derivatives **1**.

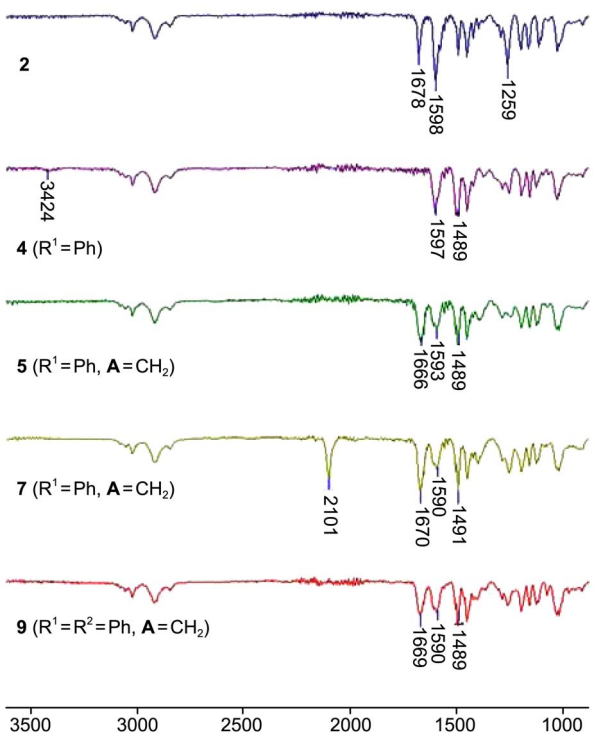


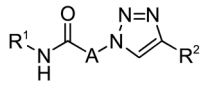
Figure 2. ATR-FTIR spectra of resins **2**, **4**, **5**, **7** and **9** ($R^1 = R^2 =$ Ph, **A** = CH_2).

was not formed because of an elimination of β-chloroamide.[10] Treatment of α-chloroamides resin of **5** (R = Cl, **A** = CH_2 or $CHCH_3$) with sodium azide in DMF at room temperature, provides the resin-bound α-azidoamide **7** (R = N_3). This reaction (R^1 = Ph, **A** = CH_2) also monitored by the characteristic appearance of the azide at 2101 cm^{-1}.

The various [3+2] Huisgen cycloaddition conditions were examined for the reaction of α-azidoamide resin **7** and terminal acetylene **8**. First, general methods[11] for Cu-catalyzed 1,3-dipolar cycloaddition ($CuSO_4$/sodium ascorbate or CuI/diisopropylethylamine) under various solvents (H_2O/*t*-BuOH, EtOH, or THF) were unsuccessful. In contrast, the desired α-1,2,3-triazoloamide resin **9** was obtained by employing a condition using excess reagents (3 equiv. CuI, 3 equiv. sodium ascorbate, DMF/piperidine (4:1), room temperature). Under these conditions, the completion of the reaction ($R^1 = R^2$ = Ph, **A** = CH_2) was confirmed by using ATR-FTIR (specifically, the disappearance of the azide stretching band at 2101 cm^{-1}). Finally, the resulting resin-bound product **9** was cleaved from the solid support under acidic conditions (30% TFA in CH_2Cl_2) to provide the α-1,2,3-triazoloamide **1** (for **1a**; 93% over six steps from Merrifield resin).[11c,12]

By using the new solid-phase synthetic route, we were able to prepare a number of α-1,2,3-triazoloamide derivatives **1** displayed in Table 1 starting from Merrifield resin and appropriate primary amines (R^1NH_2), α-chloroacetyl chloride (Cl-**A**-COCl), and terminal acetylenes ($R^2C{\equiv}CH$). In most cases, α-1,2,3-triazoloamide derivatives **1** were obtained with high purities, > 95% as judged from LC-MS traces (integration of diode array 200-400 nm traces).

Table 1. The prepared α-1,2,3-triazoloamide derivatives **1** using a solid-phase synthetic route[a]



1

Entry	Products	R^1	A	R^2	Yield (%)[b]
1	**1a**	Ph	CH_2	Ph	93
2	**1b**	Ph	CH_2	4-MeO-Ph	91
3	**1c**	Ph	CH_2	4-CN-Ph	83
4	**1d**	Ph	CH_2	3-thiophenyl	82
5	**1e**	Ph	CH_2	2-pyridyl	85
6	**1f**	Ph	CH_2	*n*-Bu	92
7	**1g**	4-MeO-Ph	CH_2	Ph	92
8	**1h**	4-MeO-Ph	CH_2	4-MeO-Ph	94
9	**1i**	4-MeO-Ph	CH_2	4-CN-Ph	89
10	**1j**	4-MeO-Ph	CH_2	3-thiophenyl	85
11	**1k**	4-MeO-Ph	CH_2	2,4-di-F-Ph	87
12	**1l**	4-MeO-Ph	CH_2	Bn	85
13	**1m**	4-MeO-Ph	CH_2	4-NMe_2-Ph	79
14	**1n**	4-MeO-Ph	CH_2	4-PhO-Ph	92
15	**1o**	4-MeO-Ph	CH_2	3-Me-Ph	89
16	**1p**	*n*-Bu	CH_2	Ph	81
17	**1q**	*n*-Bu	CH_2	4-MeO-Ph	88
18	**1r**	*n*-Bu	CH_2	4-CN-Ph	83
19	**1s**	*n*-Bu	CH_2	3-thiophenyl	80
20	**1t**	*n*-Bu	CH_2	2-pyridyl	89
21	**1u**	*n*-Bu	CH_2	*n*-Bu	89
22	**1v**	*i*-Pr	CH_2	Ph	79
23	**1w**	*i*-Pr	CH_2	4-MeO-Ph	87
24	**1x**	*i*-Pr	CH_2	3-thiophenyl	77
25	**1y**	*i*-Pr	CH_2	2-pyridyl	84
26	**1z**	*i*-Pr	CH_2	*n*-Bu	83
27	**1aa**	2-MeO-Ph	$CHCH_3$	Ph	88
28	**1ab**	2-MeO-Ph	$CHCH_3$	4-MeO-Ph	91
29	**1ac**	2-MeO-Ph	$CHCH_3$	4-CN-Ph	87
30	**1ad**	2-MeO-Ph	$CHCH_3$	3-thiophenyl	80
31	**1ae**	2-MeO-Ph	$CHCH_3$	2-pyridyl	83
32	**1af**	*n*-Bu	$CHCH_3$	Ph	83
33	**1ag**	*n*-Bu	$CHCH_3$	4-MeO-Ph	81
34	**1ah**	*n*-Bu	$CHCH_3$	4-CN-Ph	79
35	**1ai**	*n*-Bu	$CHCH_3$	3-thiophenyl	78
36	**1aj**	*n*-Bu	$CHCH_3$	2-pyridyl	84
37	**1ak**	*n*-Bu	$CHCH_3$	*n*-Bu	81
38	**1al**	*i*-Pr	$CHCH_3$	Ph	88
39	**1am**	*i*-Pr	$CHCH_3$	4-MeO-Ph	83
40	**1an**	*i*-Pr	$CHCH_3$	2-pyridyl	81

[a]All reactions were performed on 150-200 mg scale of resin **9** and the purities of compounds **1** were over 95% as judged from LC-MS traces (integration of diode array 200-400 nm traces) [b]Six-step overall yield from Merrifield resin (loading capacity = 0.94 mmol/g).

In summary, the yields for α-1,2,3-triazoloamides produced by using this solid-phase approach ranged from 78 to 94% for six linear steps starting with Merrifield resin, indicating that the average yield for each step of > 95%. In addition, the α-1,2,3-triazoloamides were obtained in high

purities (> 95%) as judged from LC-MS and ^{1}H NMR analyses. This investigation, has led to the development of the first solid-phase route for the synthesis of α-1,2,3-triazoloamides derivatives that contain three diversity positions. The strategy allows for a ready access to a large library and is potentially applicable to the preparation of other 1,2,3-triazole derivatives. Further studies in this area are underway, and the results of these studies will be reported in due course.

Experimental

Procedure for AMEBA Resin 2. Merrifield resin (53.2 g, 50.0 mmol, 0.94 mmol/g) was treated with 4-formyl-3-methoxyphenol (22.8 g, 150.0 mmol), potassium iodide (83.0 mg, 0.5 mmol), and potassium carbonate (20.7 g, 150.0 mmol) in DMF (300 mL). The mixture was shaken at room temperature for 10 h, and then filtered, washed several times with H_2O, DMF, MeOH, and CH_2Cl_2, and dried in a vacuo to give AMEBA resin **2** (59.0 g): On-bead ATR-FTIR (neat) ν_{max} 1678, 1598, 1259 (cm^{-1}).

General Procedure for Preparation of for α-1,2,3-Triazoloamides 1 on Solid-phase: A typical procedure for the desired α-1,2,3-triazoloamide **1**, as exemplified for **1a** ($R^1 = R^2 = Ph$, $A = CH_2$).

Preparation of Resin 4: A mixture of AMEBA resin **2** (10 g, theoretically 8.5 mmol), aniline (**3a**, 2.3 mL, 25.5 mmol), sodium triacetoxyborohydride (5.4 g, 25.5 mmol), and acetic acid (0.49 mL, 8.5 mmol) in DCE was heated at 50 °C for 12 h. The reaction mixture was cooled to room temperature, and then filtered, washed several times with H_2O, DMF, MeOH, and CH_2Cl_2, and dried in a vacuum oven to give amine resin **4a** (10.6 g): On-bead ATR-FTIR (neat) ν_{max} 3424, 1597, 1489 (cm^{-1}).

Preparation of Resin 5: The amine resin **4a** (3.0 g, theoretically 2.4 mmol) was treated with 2-chloroacetyl chloride (**6a**, 0.57 mL, 7.2 mmol) and triethylamine (1.0 mL, 7.2 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was shaken at room temperature for 5 h, and then filtered, washed several times with H_2O, DMF, MeOH, and CH_2Cl_2, and dried in a vacuum oven to give amide resin **5a** (3.16 g): On-bead ATR-FTIR (neat) ν_{max} 1666, 1593, 1489 (cm^{-1}).

Preparation of Resin 7: The α-chloroamide resin **5a** (2.8 g, theoretically 2.1 mmol) was treated with sodium azide (0.47 g, 7.2 mmol) in DMF. The reaction mixture was shaken at room temperature for 12 h, and then filtered, washed several times with H_2O, DMF, MeOH, and CH_2Cl_2, and dried in a vacuum oven to give α-azidoamide resin **7a** (2.8 g): On-bead ATR-FTIR (neat) ν_{max} 2101, 1670, 1590, 1491 (cm^{-1}).

Preparation of Resin 9: To a mixture of α-azidoamide resin **7a** (570 mg, theoretically 0.42 mmol) and phenylacetylene (**8a**, 0.07 mL, 0.6 mmol) in DMF/piperidine (4:1) was added copper(I) iodide (229 mg, 1.27 mmol) and sodium ascorbate (57 mg, 1.27 mmol) at room temperature. The reaction mixture was shaken at room temperature for 12 h, and then filtered, washed several times with H_2O, DMF, MeOH, and CH_2Cl_2, and dried in a vacuum oven to give α-1,2,3-triazoloamide resin **9a** (606 mg): On-bead ATR-FTIR (neat) ν_{max} 1669, 1590, 1489 (cm^{-1}).

Preparation of α-1,2,3-triazoloamide 1: The α-1,2,3-triazoloamide resin **9a** (157 mg, theoretically 0.10 mmol) was added 30% TFA in CH_2Cl_2 (3 mL). The reaction mixture was stirred at 45 °C for 1day and the mixture was filtered and washed with CH_2Cl_2 and MeOH. The filtrate was evaporated in vacuo and the residue was dissolved in CH_2Cl_2 and extracted with saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 twice and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the target *N*-phenyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetamide (**1a**) was obtained as a light yellow solid (23 mg, 93% from Merrifield resin). ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.39 (s, 2H), 7.09 (m, 1H), 7.33-7.36 (m, 3H), 7.46 (m, 2H), 7.60 (m, 2H), 7.88 (m, 2H), 8.60 (s, 1H), 10.51 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 52.4, 119.3, 123.1, 123.8, 125.1, 127.9, 128.9, 130.7, 138.4, 146.2, 164.2; LC-MS (ESI) *m/z* 279 ($[M+1]^+$).

Acknowledgments. This study was supported by a grant of the Korea Healthcare technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea (A090325), and in part by a grant (KIAT201010) from the Ministry of Knowledge Economy, Republic of Korea.

References and Notes

1. (a) Dolle, R. E.; Le Bourdonnec, B.; Worm, K.; Morales, G. A.; Thomas, C. J.; Zhang, W. *J. Comb. Chem.* **2010**, *12*, 765-806. (b) Gong, Y.-D.; Lee, T. *J. Comb. Chem.* **2010**, *12*, 393-409. (c) Dolle, R. E.; Le Bourdonnec, B.; Goodman, A. J.; Morales, G. A.; Thomas, C. J.; Zhang, W. *J. Comb. Chem.* **2009**, *11*, 739-790. (d) Dolle, R. E.; Le Bourdonnec, B.; Goodman, A. J.; Morales, G. A.; Thomas, C. J.; Zhang, W. *J. Comb. Chem.* **2008**, *10*, 753-800. (e) Kennedy, J. P.; Williams, L.; Bridges, T. M.; Daniels, R. N.; Weaver, D.; Lindsley, C. W. *J. Comb. Chem.* **2008**, *10*, 345-354.
2. Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; In *Combinatorial Chemistry: Drugs, Catalysts, Materials*; Wiley-VCH: Weinheim, Germany, 2002.
3. (a) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; p 1-176. (b) Smithe, C. D.; Baxendale, I. R.; Lanners, S.; Hayward, J. J.; Smith, S. C.; Ley, S. V. *Org. Biomol. Chem.* **2007**, *5*, 1559.-1561.
4. For recent reviews, see: (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004-2021. (b) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51-68.
5. (a) Manetsch, R.; Krasinski, A.; Radic, Z.; Raushel, J.; Taylor, P.; Sharpless, K. B.; Kolb, H. C. *J. Am. Chem. Soc.* **2004**, *126*, 12809-12818; Lee, L. V.; Mitchell, M. L.; Huang, S. J.; Fokin, V. V.; Sharpless, K. B.; Wong, C. H. *J. Am. Chem. Soc.* **2003**, *125*, 9588-9589. (b) Kolb, H. C.; Sharpless, K. B. *Drug Discov. Today* **2003**, *8*, 1128-1137. (c) Lewis, W. G.; Green, L. G.; Grynszpan, F.; Radic, Z.; Carlier, P. R.; Taylor, P.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 1053-1055.
6. (a) Kim, S.; Cho, M.; Lee, T.; Lee, S.; Min, H.-Y.; Lee, S. K. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4584-4587. (b) Lee, T.; Cho, M.; Ko, S.-Y.; Youn, H.-J.; Baek, D. J.; Cho, W.-J.; Kang, C.-Y.; Kim, S. *J. Med. Chem.* **2007**, *50*, 585-589. (c) (b) Wang, Q.;

Chittaboina, S.; Barnhill, H. N. *Lett. Org. Chem.* **2005**, *2*, 293-301.
7. For biological activities of α-1,2,3-triazoloamides, see: (a) Vang, T.; Xie, Y.; Liu, W. H.; Vidovi, D.; Liu, Y.; Wu, S.; Smith, D. H.; Rinderspacher, A.; Chung, C.; Gong, G.; Mustelin, T.; Landry, D. W.; Rickert, R. C.; Schürer, S. C.; Deng, S.-X.; Tautz, L. *J. Med. Chem.* **2011**, *54*, 562-571. (b) Ngai, M. H.; Yang, P.-Y.; Liu, K.; Shen, Y.; Wenk, M. R.; Yao, S. Q.; Lear, M. J. *Chem. Commun.* **2010**, *46*, 8335-8337. (c) Zou, Y.; Albohy, A.; Sandbhor, M.; Cairo, C. W. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7529-7533. (d) Reed, C. S.; Huigens, R. W., III.; Rogers, S. A.; Melander, C. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6310-6312. (e) Xie, J.; Seto, C. T. *Bioorg. Med. Chem.* **2007**, *15*, 458-473.
8. For biological activities of α-1,2,3-triazoloketones, see: (a) Kumar, D.; Reddy, V. B.; Kumar, A.; Mandal, D.; Tiwari, R.; Parnag, K. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 449-452. (b) Vantikommu, J.; Palle, S.; Reddy, P. S.; Ramanatham, V.; Khagga, M.; Rallapothula, V. R. *Eur. J. Med. Chem.* **2010**, *45*, 5044-5050.
9. Fivush, A. M.; Wilson, T. M. *Tetrahedron Lett.* **1997**, *38*, 7151-7154.
10. The cleavage of the resin **5** (R^1 = Ph, R = Cl, **A** = CH_2CH_2) under 30% TFA in CH_2Cl_2 at room temperature provided a *N*-phenylacrylamide as a major product.
11. (a) Duval, R.; Kolb, S.; Braud, E.; Genest, D.; Garbay, C. *J. Comb. Chem.* **2009**, *11*, 947-950. (b) Bonnet, D.; Riché, S.; Loison, S.; Dagher, R.; Frantz, M.-C.; Boudier, L.; Rahmeh, R.; Mouillac, B.; Haiech, J.; Hibert, M. *Chem. Eur. J.* **2008**, *14*, 6247-6254. (c) Donnelly, P. S.; Zanatta, S. D.; Zammit, S. C.; White, J. M.; Williams, S. J. *Chem. Commun.* **2008**, 2459-2461. (d) Lv, G.; Mai, W.; Jin, R.; Gao, L. *Synlett* **2008**, 1418-1422. (e) Cao, J.; Huang, X. *J. Comb. Chem.* **2008**, *10*, 526-533.
12. Ananthanarayanan, C.; Ramakrishnan, V. T. *Indian J. Chem. B* **1989**, *28B*, 228-230.