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One-pot Synthesis of Oxoisoindoline-1,2,3-triazole Hybrid by a Ugi-click Reaction

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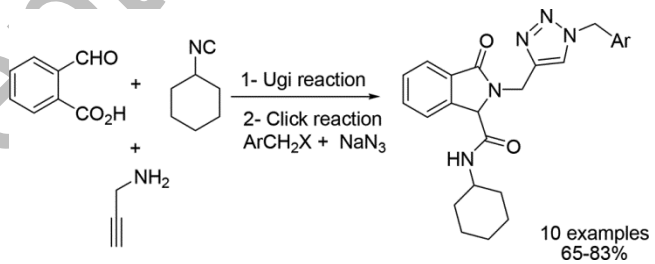
Abstract

1,2,3-Triazole-3-oxoisoindoline-1-carboxamide system was successfully synthesized by using a combination of Ugi and click reaction. This two-step, one-pot synthesis was started by the reaction of 2-formyl benzoic acid, propargyl amine and cyclohexyl isocyanide in ethanol. The resultant Ugi adduct underwent copper-catalyzed click reaction producing the desired products in good yields.

GRAPHICAL ABSTRACT



KEYWORDS: 1,2,3-Triazole, One-pot synthesis, Ugi-reaction, Multi-component reaction, Click reaction.

INTRODUCTION

Multi-component reaction (MCR) is a powerful strategy for the one-pot construction of diverse heterocyclic systems. Among them, isocyanide-based multi-component reactions (IMCR) [1] are one of the highly investigated reactions, which benefit from outstanding feature of isocyanides, meaning their ability to react with electrophiles and nucleophiles. Therefore, this reaction provides an ideal way for the synthesis of libraries of heterocycles. By employing Ugi reaction, a four-component, isocyanide-based process,[2] molecular diversity could be accessed under mild condition in which the resultant products are amenable for further transformations. Today, post Ugi transformations have become an exciting research area to create more complex scaffolds.[3] Performing these steps in a one-pot manner saves effort, time, and energy along with minimizing chemical waste and purification steps, provided an opportunity to reach the green chemistry principles.[4]

1,2,3-Triazole ring constitutes a significant functionality in diverse interesting compounds [5] with a wide range of applications including in pharmacologically active compounds,[6] dyes,[7] optically active materials,[8] agrochemicals [9] and synthesis of macromolecular architectures.[10] The 1,3-dipolar cycloaddition reaction between azide and alkyne [11] introduced by Sharpless [12] and Meldal [13] is a unique strategy for the preparation of 1,2,3-triazoles. Therefore, the presence of alkyne moiety is necessary which could be provided by commercially available triple-bond containing substrate. This led to the serious restriction in substrate variation. In this context, novel starting material should be designed to expand the collection of triazole-containing compounds.

Utilizing propargyl amine in three-component, four-center Ugi reaction resulted in alkyne substituted oxoisoindoline derivatives. Based on the biological importance of oxoisoindoline core,[14] it is highly desired to develop a simple and convenient method for the synthesis of novel molecules incorporating triazole and isoindolinones in one-pot, direct and atom economical manner.

RESULTS AND DISCUSSION

As our interest in developing novel heterocyclic compounds,[15] herein, we report the highly efficient synthesis of 1*H*-1,2,3-triazol-oxoisoindoline system in one-pot manner. As mentioned earlier, Ugi reaction has attracted special attention for combinatorial library construction. In this regard, the protocol of our reaction was started by the Ugi reaction between 2-formyl benzoic acid **1**, propargyl amine **2** and cyclohexyl isocyanide **3** in ethanol. After 24 h, benzyl azides **6**, prepared in situ from the reaction between appropriate benzyl bromide or benzyl chloride with sodium azide (NaN_3) in *t*-BuOH:H_2O (1:1) solvent system and in the presence of Et_3N, along with 10 mol% CuI was added to the crude Ugi adduct and the reaction was continued at room temperature for 24 h. The overall transformation was carried out under mild condition and gave the pure products after crystallization.

As shown in Table I, this reaction was successful in synthesizing ten new compounds with various substituents at different positions. The structures of all the synthesized compounds were established on the basis of ^{1}H NMR, ^{13}C NMR, IR, and elemental analyses. In the ^{1}H NMR spectrum of compound **7a**, two singlets appear at 2.27 ppm

(methyl group) and 5.49 (methylene group). The most deshielded proton is related to NH at 8.50 ppm, appeared as a doublet signal. The singlet at 8.06 ppm is assigned to triazole proton. The signals of NCH and CH units were found as multiplets at 3.51-3.53 and 5.10-5.13 ppm, respectively. In addition, the ^{13}C NMR spectrum exhibited signals related to carbonyl group at 165.3, 167.6 ppm.

CONCLUSION

In summary, we have discovered an efficient one-pot procedure comprising four-component Ugi reaction and click reaction to prepare *N*-cyclohexyl-(2-substituted-1*H*-1,2,3-triazol-4-yl)methyl)-3-oxoisoindoline-1-carboxamides. The desired products were obtained in good yields at room temperature and separated without the need to tedious work up step.

EXPERIMENTAL

Melting points were taken on a Kofler hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker FT-500, using tetramethylsilane (TMS) as an internal standard. The infrared (IR) spectra were obtained on a Nicolet Magna FT-IR 550 spectrophotometer (KBr disks). Mass spectra were recorded on an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus.

General Procedure For The Synthesis Of Compounds 7a-J

A solution 2-formyl benzoic acid (1 mmol), propargyl amine (1 mmol), cyclohexyl isocyanide (1 mmol) in ethyl alcohol (10 mL) was stirred for 24 h at room temperature and then concentrated under reduced pressure. A solution of an arylmethyl chloride or bromide (1.1 mmol), sodium azide (0.9 mmol), and triethylamine (1.3 mmol) in water (5 mL) and *tert*-butyl alcohol (5 mL) was stirred at room temperature for 1 h. This solution was added to the crude Ugi adduct along with 10 mol% CuI and the reaction was continued for another 24 h. Upon completion, the reaction was poured into ice-water and the resultant solid was purified by recrystallization from ethyl acetate/petroleum ether.

***N*-Cyclohexyl-2-((1-(4-Methylbenzyl)-1*H*-1,2,3-Triazol-4-Yl)Methyl)-3-Oxoisoindoline-1-Carboxamide (7a)**

Yield: 0.36 g (83 %); off-white powder; mp 180-182 ^{o}C. IR (KBr): 3288, 3051, 2930, 2880, 1691, 1351, 1178, 841 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.13-1.27 (m, 5H), 1.54-1.56 (m, 2H), 1.67-1.75 (m, 3H), 2.27 (s, 3H), 3.51-3.53 (m, 1H), 4.15 (d, *J* = 15.5 Hz, 1H), 5.10-5.13 (m, 2H), 5.49 (s, 2H), 7.16 (d, *J* = 7.5 Hz, 2H), 7.21 (d, *J* = 7.5 Hz, 2H), 7.50-7.52 (m, 2H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 8.06 (s, 1H), 8.50 (d, *J* = 7.5 Hz, 1H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.6, 24.3, 25.1, 32.2, 36.2, 48.0, 52.6, 62.5, 122.9, 123.3, 123.4, 128.0, 128.6, 129.2, 131.3, 132.8, 137.4, 141.7, 142.1, 142.7, 165.3, 167.6. MS: *m/z* (%) = 444 ([M]$^{+}$, 34), 428 (62), 338 (100), 296 (15), 91 (12), 77 (21). Anal. calcd. for $C_{26}H_{29}N_5O_2$: C, 70.41; H, 6.59; N, 15.79. Found: C, 70.36; H, 6.64; N, 15.85.

SUPPORTING INFORMATION

Full experimental details and ^{1}H and ^{13}C NMR spectra are available. This material can be found via the supplementary content section of this article's web page.

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REFERENCES

[1] (a) Domling, A. *Chem. Rev*. **2006**, *106*, 17-89 and references cited therein; (b) Sadjadi, S.; Heravi, M. M.; Nazari, N. *RSC Adv*. **2016**, *6*, 53203-53272; (c) Heravi, M. M.; Moghimi, S. *J. Iran. Chem. Soc*. **2011**, *8*, 306-373.

[2] Ugi, I. *Angew. Chem., Int. Ed. Engl*., **1962**, *1*, 8–20; (b) Ugi I.; Steinbruckner, C. *Chem. Ber*. **1961**, *94*, 734-742.

[3] (a) Zhu J.; Bienayme´, H. *Multicomponent Reactions*, Wiley-VCH, Weinheim, **2005**; (b) Banfi, L.; Basso, A.; Riva, R. *Top. Heterocycl. Chem*., **2010**, *23*, 1-39; (c) Hulme, C.; Dietrich, J. *Mol. Divers*. **2009**, *13*, 195-207; (c) Koopmanschap, G.; Ruijter, E.; Orru, R. V. A. *Beilstein J. Org. Chem*. **2014**, *10*, 544-598; (d) Upendra, K.; Sharma, N. Sharma, D. D.; Vachhani; Van der Eycken, E. V. *Chem. Soc. Rev*. **2015**, *44*, 1836-1860.

[4] (a) Yujiro, H. *Chem. Sci*. **2016**, *7*, 866-880; (b) Sydnes, M. O. *Curr. Green Chem.* **2016**, *1*, 216-226.

[5] Dehne, H. *Methoden der Organischen Chemie (Houben-Weyl)*, Thieme, Stuttgart, **1994**, 305-405.

[6] Hein, C. D.; Liu, X. M.; Wang, D. *Pharm. Res*. **2008**, *25*, 2216-2230.

[7] 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.

[8] Whiting, M.; Muldoon, J.; Lin, Y. C.; Silverman, S. M.; Lindstrom,W.; Olson, A. J.; Kolb, H. C.; Fine, M. J.; Sharpless, K. B.; Elder, J. H.; Fokin, V. V. *Angew. Chem. Int. Ed*. **2006**, *45*, 1435-1439.

[9] Bock, V. D.; Hiemstra, H.; Maarseveen, J. H. V. *Eur. J. Org. Chem*. **2006**, 51-68.

[10] Ke, Z.; Chow, H. F.; Chan, M. C.; Liu, Z.; Sze, K. H. *Org. Lett*. **2012**, *14*, 394-397.

[11] Huisgen, R. *1,3-Dipolar Cycloaddition Chemistry*; Wiley: New York, **1984**; 1-176.

[12] Rostovtsev, V. V.; Green, L. G.; Fokin,V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed*. **2002**, *41*, 2596-2599.

[13] Tornoe, C.; Christensen, C.; Meldal, M. *J. Org. Chem*. **2002**, *67*, 3057-3064.

[14] (a) Cappelli, A.; Nannicini, C.; Valenti, S.; Giuliani, G.; Anzini, M.; Mennuni, L.; Giordani, A.; Caselli, G.; Stasi, L. P.; Makovec, F.; Giorgi, G.; Vomero, S. *Chem. Med. Chem.* **2010**, *5*, 739-748; (b) Gandhi, V. B.; Luo, Y.; Liu, X.; Shi, Y.; Klinghofer, V.; Johnson, E. F.; Park, C.; Giranda, V. L.; Penning, T. D.; Zhu, G. D. *Bioorg. Med. Chem. Lett*. **2010**, *20*, 1023-1026; (c) Zhao, X. Z.; Maddali, K.; Smith, S. J.; Me´tifiot, M.; Johnson, B. C.; Marchand, C.; Hughes, S. H.; Pommier, Y.; Burke, T. R. Jr. *Bioorg. Med. Chem. Lett*. **2012**, *22*, 7309-7313; (d) De Cesco, S.; Deslandes, S.; Therrien, E.; Levan, D.; Cueto, M.; Cueto, R.; Cantin, L. D.; Mittermaier, A.; Juillerat-Jeanneret, L.; Moitessier, N. *J. Med. Chem*. **2012**, *55*, 6306-6315; (e) Macsari, I.; Besidski, Y.; Csjernyik, G.; Nilsson, L. I.; Sandberg, L.; Yngve, U.; A ° hlin, K.; Bueters, T.; Eriksson, A. B.; Lund, P. E.; Venyike, E.; Oerther, S.; Blakeman, K. H.; Luo, L.; Arvidsson, P. I. *J.*

Med. Chem. **2012**, *55*, 6866-6880; (f) Jindal, D. P.; Singh, B.; Coumar, M. S.; Bruni, G.; Massarelli, P. *Bioorg. Chem*. **2005**, *33*, 310-324.

[15] (a) Pilali, H.; Kamazani, S. F.; Moradi, S.; Moghimi, S.; Mahdavi, M. Firoozpour, L.; Shafiee, A.; Foroumadi, A. *Synth. Commun*. **2016**, *46*, 563-567; (b) Mahdavi, M.; Najafi, R.; Saeedi, M.; Alipour, E.; Shafiee, A.; Foroumadi, A. *Helv. Chim. Acta*. **2013**, *96*, 419-423. (c) Rahmani-Nezhad, S.; Khosravani, L.; Saeedi, M.; Divsalar, K.; Firoozpour, L.; Pourshojaei, Y.; Sarrafi, Y.; Nadri, H.; Moradi, A.; Mahdavi, M.; Shafiee, A.; Foroumadi, A. *Synth. Commun*. **2015**, *45*, 741-749; (d) Saeedi, M.; Mahdavi, M.; Foroumadi, A.; Shafiee, A. *Tetrahedron* **2013**, *69*, 3506-3510; (e) Rasouli, M. A.; Mahdavi, M.; Ranjbar, P. R.; Saeedi, M.; Shafiee, A.; Foroumadi, A. *Tetrahedron Lett*. **2012**, *53*, 7088-7092; (f) Farjadmand, F.; Arshadi, H.; Moghimi, S.; Nadri, H.; Moradi, A.; Eghtedari, M.; Jafarpour, F.; Mahdavi, M.; Shafiee, A.; Foroumadi, A. *J. Chem. Res*. **2016**, *40*, 188-191; (g) Asadi, M.; Ebrahimi, M.; Mahdavi, M.; Saeedi, M.; Ranjbar, P. R.; Yazdani, F.; Shafiee, A.; Foroumadi, A. *Synth. Commun*. **2013**, *43*, 2385-2392; (h) Ebrahimi, S. M.; Mahdavi, M.; Emami, S.; Saeedi, M.; Asadi, M.; Firoozpour, L.; Khoobi, M.; Divsalar, K.; Shafiee, A.; Foroumadi, A. *Synth*. *Commun.* **2014**, *44*, 665-673; (i) Rayatzadeh, A.; Saeedi, M.; Mahdavi, M.; Rezaee, Z.; Sabourian, R.; Mosslemin, M. H.; Akbarzadeh, T.; Foroumadi, A.; Shafiee, A. *Monatsh Chem*. **2015**, *146*, 637-643.

Table I. Synthesized products **7a-j**.

Product	**Ar**	**Isolated yield (%)**
7a	4-MeC_6H_4	83
7b	2-FC_6H_4	65
7c	3-FC_6H_4	68
7d	4-FC_6H_4	71
7e	2-ClC_6H_4	73
7f	3-ClC_6H_4	75
7g	4-ClC_6H_4	76
7h	2,3-*di*$Cl_2C_6H_3$	74
7i	2,4-*di*$Cl_2C_6H_3$	72
7j	4-BrC_6H_4	76

Scheme 1. Tandem synthesis of 1,2,3-triazole derivatives of 3-oxoisoindoline-1-carboxamide