One-pot synthesis of oxoisoindoline-1,2,3-triazole hybrid by a Ugi–click reaction

Sara Akrami, Loghman Firoozpour, Fereshteh Goli-Garmroodi, Setareh Moghimi, Mohammad Mahdavi, Afsaneh Zonouzi & Alireza Foroumadi

To cite this article: Sara Akrami, Loghman Firoozpour, Fereshteh Goli-Garmroodi, Setareh Moghimi, Mohammad Mahdavi, Afsaneh Zonouzi & Alireza Foroumadi (2016) One-pot synthesis of oxoisoindoline-1,2,3-triazole hybrid by a Ugi–click reaction, Synthetic Communications, 46:20, 1708-1712, DOI: 10.1080/00397911.2016.1223313

To link to this article: http://dx.doi.org/10.1080/00397911.2016.1223313
One-pot synthesis of oxoisindoline-1,2,3-triazole hybrid by a Ugi–click reaction

Sara Akramia, Loghman Firoozpurb, Fereshteh Goli-Garmroodi, Setareh Moghimi, Mohammad Mahdavib, Afsaneh Zonouzia, and Alireza Foroumadi

School of Chemistry, College of Science, University of Tehran, Tehran, Iran; bDrug Design and Development Research Center, Tehran University of Medical Sciences, Tehran, Iran; cDepartment of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran; dDepartment of Medicinal Chemistry, Faculty of Pharmacy and Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran

ABSTRACT
1,2,3-Triazole-3-oxoisindoline-1-carboxamide system was successfully synthesized by using a combination of Ugi and click reactions. 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 a copper-catalyzed click reaction, producing the desired products in good yields.

INTRODUCTION
Multicomponent reactions (MCR) are powerful strategies for the one-pot construction of diverse heterocyclic systems. Among them, isocyanide-based multicomponent reactions (IMCR) are some of the highly investigated reactions, which benefit from one of the outstanding features of isocyanides, their ability to react with electrophiles and nucleophiles. Therefore, this reaction provides an ideal way for the synthesis of libraries of heterocycles. By employing the Ugi reaction, a four-component, isocyanide-based process, molecular diversity could be accessed under mild conditions 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. Performing these steps in a...
one-pot manner saves effort, time, and energy along with minimizing chemical waste and purification steps, providing an opportunity to embody green chemistry principles.\textsuperscript{[4]}

The 1,2,3-triazole ring has significant functionality in diverse interesting compounds\textsuperscript{[5]} with a wide range of applications in pharmacologically active compounds,\textsuperscript{[6]} dyes,\textsuperscript{[7]} optically active materials,\textsuperscript{[8]} agrochemicals,\textsuperscript{[9]} and synthesis of macromolecular architectures.\textsuperscript{[10]} The 1,3-dipolar cycloaddition reaction between azide and alkyne\textsuperscript{[11]} introduced by Sharpless\textsuperscript{[12]} and Meldal\textsuperscript{[13]} is a unique strategy for the preparation of 1,2,3-triazoles. Therefore, the presence of an alkyne moiety is necessary, which could be provided by a commercially available triple-bond-containing substrate. This led to serious restriction in substrate variation. In this context, a novel starting material should be designed to expand the collection of triazole-containing compounds. Utilizing propargyl amine in a three-component, four-center Ugi reaction resulted in alkyne substituted oxoisoindoline derivatives. Based on the biological importance of the oxoisoindoline core,\textsuperscript{[14]} it is highly desired to develop a simple and convenient method for the synthesis of novel molecules incorporating triazole and isoindolinones in a one-pot, direct, and atom-economical manner.

**Results and discussion**

As our interest in developing novel heterocyclic compounds,\textsuperscript{[15]} herein we report the highly efficient synthesis of 1H-1,2,3-triazol-oxoisoindoline system in a one-pot manner. As mentioned earlier, the 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\textsubscript{3}) in t-BuOH/H\textsubscript{2}O (1:1) solvent
system and in the presence of Et₃N, 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 conditions and gave the pure products after crystallization.

As shown in Table 1, this reaction was successful in synthesizing ten new compounds with various substituents at different positions. The structures of all the synthesized compounds were characterized on the basis of ¹H NMR, ¹³C NMR, infrared (IR), and elemental analyses. In the ¹H 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 and appeared as a doublet signal. The singlet at 8.06 ppm is assigned to a 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 ¹³C NMR spectrum exhibited signals related to carbonyl groups at 165.3 and 167.6 ppm.

**Conclusion**

In summary, we have discovered an efficient one-pot procedure comprising a four-component Ugi reaction and click reaction to prepare N-cyclohexyl-(2-substituted-1H-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 for a tedious workup step.

**Experimental**

Melting points were taken on a Kofler hot-stage apparatus and are uncorrected. ¹H and ¹³C 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 of 2-formyl benzoic acid (1 mmol), propargyl amine (1 mmol), and 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)-1H-1,2,3-triazol-4-yl)methyl)-3-oxoisoindoline-1-carboxamide (7a)**

Yield: 0.36 g (83%); off-white powder; mp 180–182 °C. IR (KBr): 3288, 3051, 2930, 2880, 1691, 1351, 1178, 841 cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆): 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. ¹³C NMR (125 MHz, DMSO-d₆): 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 C₂₆H₂₉N₅O₂: C, 70.41; H, 6.59; N, 15.79. Found: C, 70.36; H, 6.64; N, 15.85.

**Acknowledgments**

This work was supported and funded by Research Council of Tehran University of Medical Sciences (TUMS); Grant no. 94-03-92-30366, and Iran National Science Foundation (INSF).

**References**


