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A versatile synthesis of fused triazolo derivatives by sequential Ugi/alkyne–azide cycloaddition reactions

Irini Akritopoulou-Zanze,* Vijaya Gracias and Stevan W. Djuric

Scaffold-Oriented Synthesis, Abbott Laboratories, R4CP, AP10, 100 Abbott Park Road, Abbott Park, IL 60064-6099, USA

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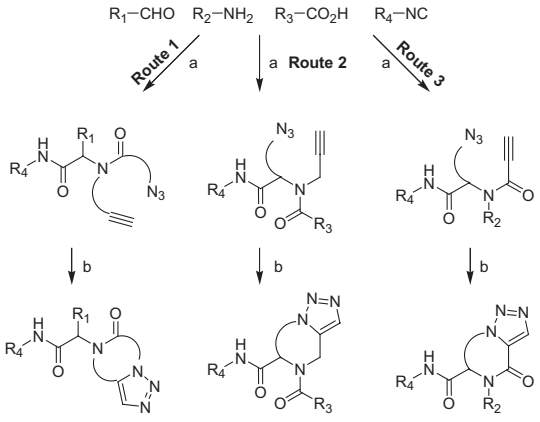
Abstract—We report a facile synthesis of fused dihydrotriazolo[1,5-*a*]pyrazinones and triazolobenzodiazepines by an Ugi/alkyne–azide cycloaddition synthetic sequence. The coupling of the Ugi multi-component reaction with the intramolecular alkyne–azide cycloaddition provides access to highly functionalized heterocyclic ring systems in two steps from easily available starting materials in excellent overall yields.

The combination of isocyanide-based multi-component reactions[1] with secondary transformations is a powerful approach to access numerous highly functionalized heterocyclic molecules in few steps from commercially available starting materials.[2] As part of our own group's efforts to develop short and versatile routes to a variety of novel heterocyclic structures we have explored the synthesis of fused five-, six-, and seven-membered ring bicyclic structures by employing Ugi/Heck[3] and Ugi/INOC[4] sequences.

We now report the facile construction of fused triazolo derivatives by the sequential Ugi/intramolecular alkyne–azide cycloaddition (IAAC). The required azide functionality is compatible with Passerini[5] and Ugi[6] reaction conditions and the intramolecular alkyne–azide cycloaddition has been applied in simple systems.[7]

The synthetic sequences are described in Scheme 1. A variety of six- and seven-membered ring systems fused to triazoles have been synthesized as we have successfully used coupling partners containing azide functionality on the carboxylic acid (Route 1) or aldehyde inputs (Routes 2 and 3) and acetylenic functionality on the amine (Routes 1 and 2) or carboxylic acid (Route 3) input.



Scheme 1. General synthetic routes. Reagents and conditions: (a) MeOH, 24–48 h, rt; (b) benzene, reflux, 4–18 h.

Azides were purchased from commercial vendors or prepared according to known procedures as illustrated in Scheme 2.[8] The Ugi reactions proceeded smoothly to provide the desired intermediates in moderate to high yields (Table 1). Heating of the Ugi adducts in benzene afforded the cyclized products in excellent yields.[9] The intramolecular azide–alkyne cycloaddition was also attempted using room temperature copper catalyzed conditions[10] (entry 3, IAAC product, 80% yield).

Thus, by manipulation of the components of the Ugi reaction we could readily access fused dihydrotriazolo[1,5-*a*]pyrazinones (Table 1, entries 1 and 2) and

Keywords: Multi-component reactions; Ugi; Intramolecular azide–alkyne cycloaddition; Fused triazolo derivatives; Dihydrotriazolo [1,5-*a*]pyrazinones; Triazolobenzodiazepines; Sequential Ugi/IAAC; Fused heterocycles.
* Corresponding author. Tel.: +1 847 937 5006; fax: +1 847 935 0310; e-mail: irini.zanze@abbott.com

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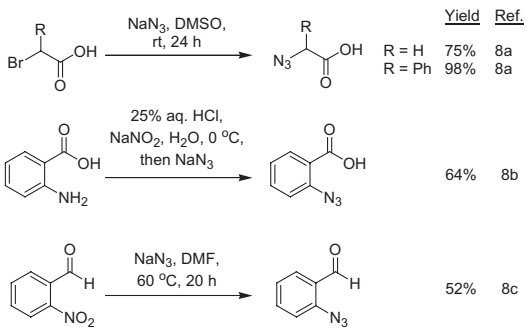


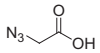
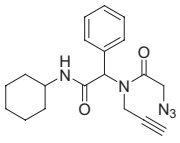
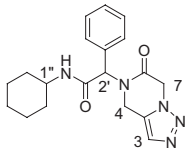
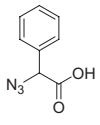
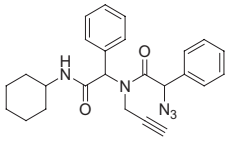
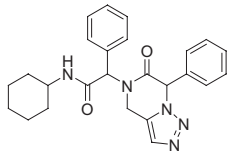
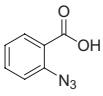
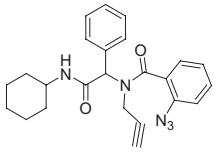
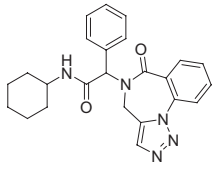
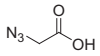
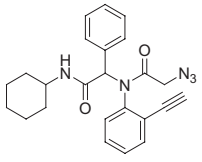
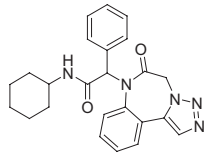
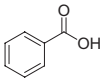
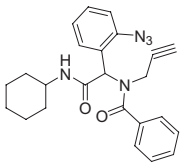
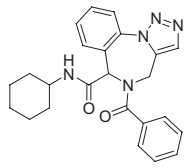
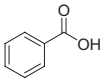
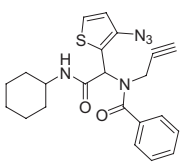
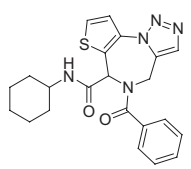
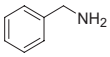
Scheme 2. General synthetic routes for the preparation of azides.

triazolobenzodiazepines (entries 3–7). These molecules represent scaffolds that remain relatively under-explored in the chemical literature.[7,11]

Conclusions

We have demonstrated that the combination of the Ugi multi-component reaction with the intramolecular azide–alkyne cyclization provides access to unique fused triazole ring systems. The present methodology can be used for the synthesis of diverse scaffolds and libraries thereof.

Table 1. Results of six- and seven-membered ring closure

	Aldehyde	Amine	Isocyanide	Acid	Ugi product	Ugi yield[a] (%)	IAAC product	IAAC yield[a] (%)
1						65		86
2						65		98
3						81		96
4						71		97
5						51		96
6						33		97
7						50		86

[a] Isolated yield after filtration or purification by column chromatography.

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9. A representative procedure is demonstrated by the preparation of *N*-cyclohexyl-2-(6-oxo-6,7-dihydro-4*H*-[1,2,3]triazolo[1,5-*a*]pyrazin-5-yl)-2-phenyl-acetamide (IAAC product, Table 1, entry 1). A suspension of 2-[(2-azido-acetyl)-prop-2-ynyl-amino]-*N*-cyclohexyl-2-phenyl-acetamide (Ugi adduct, Table 1, entry 1) (35 mg, 0.1 mmol) in benzene (2 mL) was heated at reflux and the reaction was followed by TLC. After 4 h TLC indicated complete consumption of the starting material and formation of product. The reaction mixture was cooled and the resulting solid was filtered to provide 30 mg of a white solid (86% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.32 (d, J = 7.67 Hz, 1H, NH), 7.59 (s, 1H, H3) 7.47–7.34 (m, 3H, aromatic), 7.29–7.27 (m, 2H, aromatic), 6.32 (s, 1H, H2′), 5.29–5.14 (m, 2H, H7), 4.94 (d, J = 16.26 Hz, 1H, H4a), 4.05 (d, J = 15.96 Hz, 1H, H4b), 3.71–3.55 (m, 1H, H1″), 1.87–1.47 (m, 5H, cyclohexyl), 1.01–1.35 (m, 5H, cyclohexyl). ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm 167.4 (C1′), 163.2 (C6), 134.7 (aromatic), 128.9 (C3), 128.8 (aromatic), 128.3 (aromatic), 58.7 (C2′), 48.7 (C7), 47.8 (C1″), 39.2 (C4), 32.2 (cyclohexyl), 32.1 (cyclohexyl), 25.1 (cyclohexyl), 24.5 (cyclohexyl), 24.4 (cyclohexyl). MS ESI (M+H) 354. NOEs were observed between H3/H4, NH/H2′, H2′H3, H2′/aromatics.
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