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Synthesis of novel fused isoxazoles and isoxazolines by sequential Ugi/INOC reactions

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Abstract—We report the synthesis of novel fused isoxazoles and isoxazolines by employing an unprecedented Ugi/INOC synthetic sequence. The coupling of the Ugi multicomponent reaction with the intramolecular *N*-oxide cyclization provides access to unique heterocyclic ring systems in two steps from easily available starting materials in moderate to good overall yields.

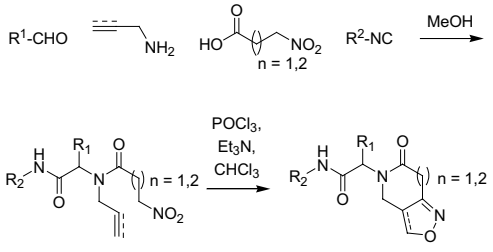
Multicomponent reactions (MCRs) have found numerous applications in organic and diversity-oriented synthesis by accessing highly functionalized molecules in straightforward one step transformations.[1] In recent years there has been growing interest in combinations of multicomponent reactions with secondary transformations to produce heterocyclic molecules.[2]

As a part of our ongoing effort to discover novel heterocyclic chemotypes that are readily prepared from commercially available starting materials we became interested in the Ugi reaction as a powerful tool to assemble molecules suitable for further transformations.[3] Recently, we described a facile route to complex heterocyclic scaffolds by the sequential Ugi/Heck cyclization.[4]

Herein, we report on our efforts to generate novel fused isoxazole and isoxazoline containing heterocycles by combining the Ugi reaction with the intramolecular nitrile oxide cycloaddition (INOC) reaction.[5] We were attracted to this combination by the fact that the functional groups required for INOC, namely a double or triple bond and a nitro group are compatible with the Ugi transformation. Furthermore, the Ugi adducts provide unique starting scaffolds for subsequent [2 + 3] cycloadditions leading ultimately to novel fused heterocycles.

Reactions of carboxylic acids bearing a nitro group (Scheme 1) with an allyl or propargyl amine and various isocyanides and aldehydes provided substrates suitable for the [2 + 3] cycloadditions (Table 1).

Initially, we employed Mukaiyama conditions[6] for the in situ generation of the nitrile oxide from the nitro group (Table 1, entry 1). The reaction was sluggish and even after extended heating produced only small amounts of the desired product along with the corresponding byproduct urea from the isocyanate. We were able to improve the reaction time and yields by employing $POCl_3$ in the presence of excess Et_3N in $CHCl_3$. The reaction proceeded to about 50% conversion from starting material to product within the first 30 min when 1 equiv of $POCl_3$ and 3 equiv of Et_3N were employed. We were unable to get the reaction to go to completion by prolonging the reaction times and/or heating. Addition of one more portion of reagents



Scheme 1. General synthetic route.

Keywords: Ugi; INOC; Sequential multicomponent reactions; Isoxazoles; Isoxazolines; Fused rings.
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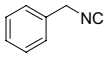
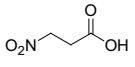
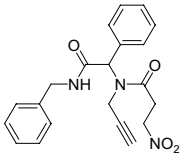
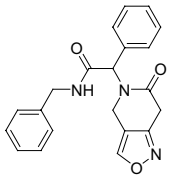
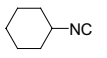
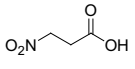
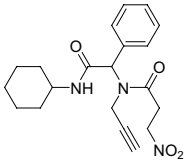
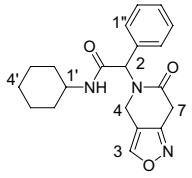
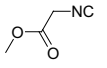
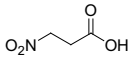
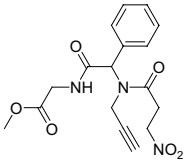
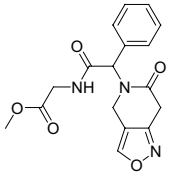
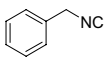
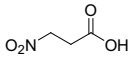
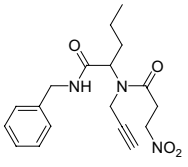
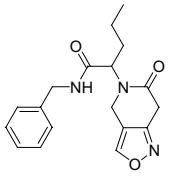
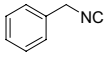
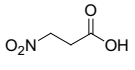
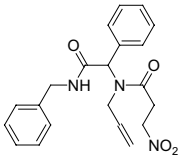
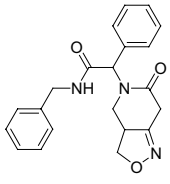
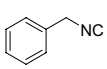
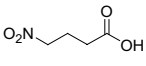
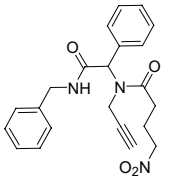
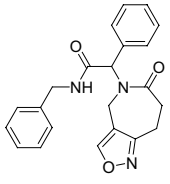
Table 1. Results of six- and seven-membered ring closure

	Aldehyde	Amine	Isocyanide	Acid	Ugi product[a]	Ugi yield (%)	INOC Product	INOC yield (conditions)[b]
1						51		17% (A) 53% (B)
2						79		63% (B)
3						50		56% (B)
4						66		64% (B)
5						59		47% (B)[c]
6						50		27% (B)

[a] Ugi multicomponent reactions were carried out in MeOH at rt with reaction times ranging from 24–28 h. All products were isolated via flash chromatography or recrystallization.

[b] (A) PhNCO, cat. Et_3N, toluene, 80 °C, 48 h. (B) $POCl_3$, Et_3N, $CHCl_3$, rt, 2–3 h.

[c] A 1:1 mixture of diastereomers as determined by NMR integration.

resulted in complete conversion, however reaction with excess $POCl_3$ and Et_3N resulted in significant decomposition and lower yields. Our optimized protocol[7] involved the initial reaction of the Ugi adduct with 1.5 equiv of $POCl_3$ and 4 equiv of Et_3N for half an hour, followed by an additional 0.5 equiv of $POCl_3$ and 2 equiv of Et_3N for 2 h. The reaction proceeded cleanly from starting material to product to provide the fused six-membered lactams to isoxazoles and isoxazolines. Seven-membered lactams could also be obtained (entry 6), albeit, in somewhat lower yields. To the best of our knowledge, all of the fused systems in Table 1 have never been reported before.

Conclusions

We have demonstrated that the Ugi multicomponent reaction followed by the intramolecular nitrile oxide cyclization provides access to unique fused isoxazole and isoxazoline ring systems. The present methodology

can be used for the synthesis of diverse libraries and for further manipulations that will be reported in due course.

Acknowledgements

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References and notes

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3. Examples of post-Ugi transformations include the following: Diels–Alder reactions (a) Paulvannan, K. *Tetrahedron Lett.* **1999**, *40*, 1851–1854; (b) Wright, D. L.; Robotham, C. V.; Aboud, K. *Tetrahedron Lett.* **2002**, *43*, 943–946; Aminocyclizations (c) Tempest, P.; Ma, V.; Thomas, S.; Hua, Z.; Kelly, M. G.; Hulme, C. *Tetrahedron Lett.* **2001**, *42*, 4959–4962; (d) Hulme, C.; Ma, L.; Kumar, N. V.; Krolikowski, P. H.; Allen, A. C.; Labaudiniere, R. *Tetrahedron Lett.* **2000**, *41*, 1509–1514; (e) Hulme, C.; Peng, J.; Morton, G.; Salvino, J. M.; Herpin, T.; Labaudiniere, R. *Tetrahedron Lett.* **1998**, *39*, 7227–7230; (f) Strocker, A. M.; Keating, T. A.; Tempest, P. A.; Armstrong, R. W. *Tetrahedron Lett.* **1996**, *37*, 1149–1152; (g) Short, K. M.; Ching, B. W.; Mjalli, A. M. M. *Tetrahedron Lett.* **1996**, *37*, 7489–7492; Nucleophilic aromatic substitutions (h) Cristau, P.; Vors, J.-P.; Zhu, J. *Tetrahedron Lett.* **2003**, *44*, 5575–5578; (i) Tempest, P.; Ma, V.; Kelly, M. G.; Jones, W.; Hulme, C. *Tetrahedron Lett.* **2001**, *42*, 4963–4968; Lactonizations Park, S. J.; Keum, G.; Kang, S. B.; Koh, H. Y.; Kim, Y. *Tetrahedron Lett.* **1998**, *39*, 7109–7112; (j) Ring-closing metathesis Hebach, C.; Kazmaier, U. *Chem. Commun.* **2003**, 596–597; (k) Beck, B.; Larbig, G.; Mejat, B.; Magnin-Lachaux, M.; Picard, A.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2003**, *5*, 1047–1050; (l) Banfi, L.; Basso, A.; Guanti, G.; Riva, R. *Tetrahedron Lett.* **2003**, *44*, 7655–7658; Wittig reaction Beck, B.; Picard, A.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2004**, *6*, 39–42.
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7. A representative procedure is demonstrated by the preparation of *N*-cyclohexyl-2-(6-oxo-6,7-dihydro-4H-isoxazolo[4,3-*c*]pyridin-5-yl)-2-phenyl-acetamide (INOC product, Table 1, entry 2). A solution of $POCl_3$ (0.014 mL, 0.15 mmol) in $CHCl_3$ (0.5 mL) was added dropwise to a mixture of the Ugi adduct (Table 1, entry 2) (0.037 g, 0.1 mmol) and Et_3N (0.056 mL, 0.4 mmol) in $CHCl_3$ (0.5 mL). After 0.5 h Et_3N (0.028 mL, 0.2 mmol) and $POCl_3$ (0.007 mL, 0.075 mmol) in $CHCl_3$ (0.25 mL) were added and the reaction mixture was stirred for 1 h at which point water was added. The crude product was extracted with CH_2Cl_2 and purified by preparative reverse phase HPLC using a 0.1% aqueous TFA/acetonitrile gradient. ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 8.68 (s, 1H, H3), 8.23 (d, $J = 7.80$ Hz, 1H, NH), 7.42–7.34 (m, 3H, H2″, H3″), 7.25–7.23 (m, 2H, H1″), 6.32 (s, 1H, H2), 4.67 (d, $J = 14.97$ Hz, 1H, H4), 3.84 (d, $J = 15$ Hz, 1H, H4), 3.82 (s, 2H, H7), 3.65–3.59 (m, 1H, H1′), 1.80–1.63 (m, 4H, H2′, H3′), 1.56–1.53 (m, 1H, H4′), 1.27–1.06 (m, 5H, H2′, H3′, H4′). MS (ESI, M + H) 354. NOEs were observed between H3/H4, H4/H1″, H4/H2, H2/NH and H2/H1″.