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Ugi/Robinson–Gabriel reactions directed toward the synthesis of 2,4,5-trisubstituted oxazoles

Arthur Y. Shaw^a, Zhigang Xu^a, and Christopher Hulme^{a,b,*}

^aDepartment of Pharmacology and Toxicology, College of Pharmacy, BIO5 Oro Valley, The University of Arizona, 1580 E. Hanley Blvd., Oro Valley, AZ 85737, USA

^bDepartment of Chemistry and Biochemistry, The University of Arizona, Tucson, AZ 85721, USA

Abstract

This Letter discloses a novel concise synthesis of a series of 2,4,5-trisubstituted oxazoles via a tandem Ugi/Robinson–Gabriel sequence. Herein, 2,4-dimethoxybenzylamine **1** was used as an ammonia equivalent in combination with arylglyoxal **3** and supporting Ugi reagents, an isonitrile and carboxylic acid. As such the product of the acid treated Ugi intermediate is ideally configured to undergo a Robinson–Gabriel cyclodehydration reaction to yield the desired oxazole scaffold **5**.

Keywords

Multicomponent reactions; Ugi reaction; Robinson–Gabriel reaction; 2,4,5-Trisubstituted oxazoles; Vilsmeier–Haack reaction

Multicomponent reactions (MCRs) are powerful transformations in which three or more starting materials are incorporated in a one-pot manner to produce highly decorated products. Isocyanide-based multicomponent reactions (IMCRs) are of particular interest owing to the large number of starting materials available and a wide range of readily accessible pharmacologically relevant scaffolds.¹ The most well-known IMCR, the Ugi reaction, is carried out through the reaction of an amine, carbonyl compound, carboxylic acid, and isocyanide, which undergoes a condensation step to afford the corresponding functionalized α -acylamino amide.² The usefulness of this process as a powerful diversity generating step is demonstrated by tremendous applications in the synthesis of potential drug-like libraries of small molecules.^{1c,3} Indeed, an increasing number of elaborate, operationally friendly post-condensation modifications have been developed that employ the Ugi MCR to install structural diversity with strategically positioned internal amine nucleophiles promoting a series of ring-closing events.⁴ This methodology has been utilized for the design of pharmacologically relevant molecular scaffolds, some of which have ultimately led to clinical evaluation.⁵

Oxazoles are a class of five-membered heterocycles with plentiful applications in the pharmaceutical industry and natural products chemistry.⁶ Thanks to the merits of their useful properties and widespread distribution in nature, methodologies to develop the oxazole core structure have attracted a great deal of attention over the years.^{7–9} Among the developed methodologies is the well-known Robinson–Gabriel oxazole synthesis which involves intramolecular cyclization of an amide carbonyl onto a ketone group embedded in an *N*-acyl α -

aminoketone **6** with ensuing the elimination of water.^{10,11} To continue our research theme of developing robust methodologies with high user uptake in the pharmaceutical sector, it was envisioned that the application of 2,4-dimethoxybenzylamine **1** in the Ugi reaction, previously exploited by Sheehan et al,¹² in combination with arylglyoxal **3** and supporting reagents would enable oxazole synthesis in one single second step through acid mediated deprotection of the 2,4-dimethoxybenzyl protecting group followed by concomitant cyclodehydration (i.e., the Robinson–Gabriel reaction), Scheme 1.

Herein, we report the successful optimization of this methodology and production of a series of congeners submitted to the Molecular Libraries Small Molecule Repository (MLSMR). Thus, the Ugi product **5a** was prepared via an Ugi reaction (MeOH, rt, 36 h, 57%) that utilized 2,4-dimethoxybenzylamine **1**, 4-trifluorobenzoic acid **2a**, phenylglyoxal **3a**, and *n*-butylisocyanide **4a**, Scheme 2.

The 2,4-dimethoxybenzyl moiety in the Ugi product **5a** can be easily removed upon acid treatment to generate the *N*-acyl α -aminoketone **6**, Scheme 2. Cyclodehydration conditions for the conversion of the *N*-acyl α -aminoketone **6** to the oxazole **7** were subsequently examined. Interestingly, exposure of **5a** to 1.2 equiv of phosphorus oxychloride (POCl₃) (DMF, 80 °C, 2 h) resulted in debenzylation and desired cyclodehydration. However, significant formylation of the aryl ring derived from phenylglyoxal was also observed as the result of an additional Vilsmeier–Haack reaction exemplified in oxazole **8**, Figure 1.¹³

In further studies, upon treatment of **5** in 10% TFA (trifluoroacetic acid)/DCE at reflux for 20 h, only *N*-acyl α -aminoketone **6** was observed. Moreover, use of 10% TFAA (trifluoroacetic anhydride) in DCM (rt, 16 h) as the possible dehydrating reagent afforded only trace amounts of the desired product. Consequently, Robinson–Gabriel reaction conditions were employed in which **5** was treated with concentrated sulfuric acid (H₂SO₄) at 60 °C for 2 h to successfully afford oxazole **7** in a highly acceptable 72% isolated yield, Scheme 2.¹⁴ Encouraged by the robustness of this protocol, a series of the oxazole products were thus synthesized in good isolated yields, Figure 2. Several isocyanides such as cyclopentyl-**9**, cyclohexyl-**10**, *n*-pentyl-**11**, benzyl-**12**, and *n*-butyl-**13** were utilized and all performed well in both steps of the methodology. Little effect on the yield of the two-step reaction sequence was observed when either 4-chlorophenylglyoxal (**13–15**) or 4-trifluoromethoxyphenylglyoxal (**16–19**) was employed.

As noted earlier, an additional Vilsmeier–Haack reaction was observed when utilizing POCl₃ in DMF at 80 °C for 2 h. As shown in Figure 2, the Ugi product with a *N*-Cbz protecting group was subjected to the Robinson–Gabriel/Vilsmeier–Haack conditions to generate the oxazole **20** which bears a formyl group at the 4-position of the aryl ring derived from the phenylglyoxal, leaving the Cbz protecting group intact. Conversely, the Ugi product treated with concentrated H₂SO₄ at 60 °C for 4 h resulted in the Robinson–Gabriel cyclodehydration reaction and also removed the Cbz protecting group in the same pot to yield the corresponding oxazole **21** with a free 2° amine. As a result, both oxazole analogs **20** and **21** can be utilized for further diversification of the oxazole scaffold.

In summary, we have successfully employed an Ugi/Robinson–Gabriel sequence in which an ammonia equivalent and an arylglyoxal were incorporated into the initial Ugi reaction and subsequent acid treatment with H₂SO₄ enabled amidic deprotection and Robinson–Gabriel cyclization to afford the corresponding trisubstituted oxazole-carboxamide analogs **5**.

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References and notes

- For relevant reviews see: Zhu J, Bienayme H. Multicomponent Reactions. 2005 Wiley-VCH Weinheim. Hulme C, Gore V. Curr. Med. Chem. 2003; 10:51. [PubMed: 12570721] Dömling A. Chem. Rev. 2006; 106:17. [PubMed: 16402771] Hulme C, Lee Y-S. Mol. Div. 2008; 12:1. Bienaymé H, Hulme C, Oddon G, Schmitt P. Eur. J. Chem. 2000; 6:3321. Hulme C, Nixey T. Curr. Opin. Drug Discovery Dev. 2003; 6:921. Akritopoulou-Zanze I, Djuric SW. Heterocycles. 2007; 73:125.
- (a) Ugi I. Angew. Chem. 1962; 74:9. (b) Ugi I, Steinbrucker C. Chem. Ber. 1961; 94:734. (c) Ugi I. Angew. Chem. Int. Ed. Engl. 1962; 1:8. (d) Ugi I, Domling A, Horl W. Endeavor. 1994; 18:115.
- Akritopoulou-Zanze I. Curr. Opin. Chem. Biol. 2008; 12:324. [PubMed: 18312861]
- (a) Nixey T, Tempest P, Hulme C. Tetrahedron Lett. 2002; 43:1637. (b) Hulme C, Ma L, Romano J, Cherrier MP, Salvino J, Labaudiniere R. Tetrahedron Lett. 1889; 2000:41. (c) Hulme C, Chappeta S, Griffith C, Lee YS, Dietrich J. Tetrahedron Lett. 1939; 2009:50. (d) Xu Z, Shaw AY, Dietrich J, Cappelli AP, Nichol G, Hulme C. Mol. Div. 2012 in press.
- (a) Hulme C, Peng J, Tang SY, Burns CJ, Morize I, Labaudiniere R. J. Org. Chem. 1998; 63:8021. (b) Nixey T, Hulme C. Tetrahedron Lett. 2002; 43:6833. (c) Habashita H, Kokubo M, Hamano SI, Hamanaka N, Toda M, Shibayama S, Tada H, Sagawa K, Fukushima D, Maeda K, Mitsuya H. J. Med. Chem. 2006; 49:4140. [PubMed: 16821774] (d) Nishizawa R, Nishiyama T, Hiseichi K, Matsunaga N, Minamoto C, Habashita H, Takaoka Y, Toda M, Shibayama S, Tada H, Sagawa K, Fukushima D, Maeda K, Mitsuya H. Bioorg. Med. Chem. Lett. 2007; 17:727. [PubMed: 17118654] (e) Huang Y, Dömling A. Chem. Biol. Drug Des. 2010; 76:130. [PubMed: 20545946]
- (a) Ignatius JT, Michael JS. Chem. Rev. 1975:75. (b) Yeh VSC. Tetrahedron. 2004; 60:11995. (c) Jin Z. Nat. Prod. Rep. 2009; 26:382. [PubMed: 19240947]
- For a review see: Grant TG, Meyers AI. Tetrahedron. 1994; 50:2297. Graham TH. Org. Lett. 2010; 12:3614. [PubMed: 20704403] Murai K, Takahara Y, Matsushita T, Komatsu H, Fujioka H. Org. Lett. 2010; 12:3456. [PubMed: 20608663] Sakakura A, Kondo R, Ishihara K. Org. Lett. 1971; 2005:7. Davies JR, Kane PD, Moody CJ. Tetrahedron. 2004; 60:3967. Kreisberg JD, Magnus P, Shinde S. Tetrahedron Lett. 2002; 43:7393. Brain CT, Paul JM. Synlett. 1999:1642. Meyers AI, Tavares FX. J. Org. Chem. 1996; 61:8207. [PubMed: 11667808] Shapiro R. J. Org. Chem. 1993; 58:5759.
- (a) Wan C, Zhang J, Wang S, Fan J, Wang Z. Org. Lett. 2010; 12:2338. [PubMed: 20394433] (b) Shi B, Blake AJ, Lewis W, Campbell IB, Judkins BD, Moody CJ. J. Org. Chem. 2010; 75:152. [PubMed: 19954177] (c) Dos Santos A, El Kaïm L, Grimaud L, Ronsseray C. Chem. Commun. 2009:3907. (d) Bonne D, Dekhane M, Zhu J. Angew. Chem. Int. Ed. 2007; 46:2485. (e) Kumar MP, Liu R-S. J. Org. Chem. 2006; 71:4951. [PubMed: 16776526] (f) Merkul E, Müller TJ. J. Chem. Commun. 2006; 1:4817. (g) Barrett AGM, Cramp SM, Hennessy AJ, Procopiou PA, Roberts RS. Org. Lett. 2001; 3:271. [PubMed: 11430052]
- (a) Lechel T, Lentz D, Reissig H-U. Chem. Eur. J. 2009; 15:5432. [PubMed: 19388043] (b) Kison C, Opatz T. Chem. Eur. J. 2009; 15:843. [PubMed: 19072798] (c) Araki H, Katoh T, Inoue M. Tetrahedron Lett. 2007; 48:3713. (d) Keni M, Tepe JJ. J. Org. Chem. 2005; 70:4211. [PubMed: 15876123] (e) Wipf P, Aoyama Y, Benedum TE. Org. Lett. 2004; 6:3593. [PubMed: 15387556] (f) Coqueron P-Y, Didier C, Ciufolini MA. Angew. Chem. Int. Ed. 2003; 42:1411. (g) Wipf P, Methot J-L. Org. Lett. 2001; 3:1261. [PubMed: 11348209] (h) Eastwood FW, Perlmutter P, Yang Q. J. Chem. Soc. Perkin Trans. 1. 1997:35. (i) Ang KH, Prager RH, Smith JA, Weber B, Williams CM. Tetrahedron Lett. 1996; 37:675. (j) Yoo S-K. Tetrahedron Lett. 1992; 33:2159. (k) Jiang H, Huang H, Cao H, Qi C. Org. Lett. 2010; 12:5561. [PubMed: 21058706] (l) Lai P-S, Taylor MS. Synthesis. 2010; 9:1449. (m) El Kaïm L, Grimaud L, Schiltz A. Tetrahedron Lett. 2009; 50:5235. (n) dos Santos A, El Kaïm L, Grimaud L, Ronsseray C. Chem. Commun. 2009:3907. (o) Sun X, Janvier P, Zhao G, Bienaymé H, Zhu J. Org. Lett. 2001; 3:877. [PubMed: 11263905] (p) Chupp JP, Leschinsky KL. J. Heterocycl. Chem. 1980; 17:705.

10. Robinson R. J. Chem. Soc. Trans. 1909; 95:2167.
11. Gabriel S. Ber. 1910; 43:134.
12. Sheehan SM, Masters JJ, Wiley MR, Young SC, Liebeschuetz JW, Jones SD, Murray CW, Franciskovich JB, Engel DB, Weber WW, Marimuthu J, Kyle JA, Smallwood JK, Farnen MW, Smith GF. Bioorg. Med. Chem. Lett. 2003; 13:2255. [PubMed: 12824013]
13. Vilsmeier A, Haack A. Ber. 1927; 60:119.
14. *For the preparation of Ugi product 5 and general library protocol:* To a solution of 2,4-dimethoxybenzenylamine **1** (334.2 mg, 2.0 mmol), 4-trifluorobenzoic acid **2a** (380 mg, 2.0 mmol), phenylglyoxal monohydrate **3a** (304 mg, 2.0 mmol), and *n*-butylisocyanide **4a** (166 mg, 2.0 mmol) in methanol (3 mL), the resulting mixture was stirred at room temperature for 36 h. The reaction solution was concentrated in vacuo and the residue was purified by column chromatography (hexane/ethyl acetate, 1/9 to 1/3) to obtain the Ugi product **5** (633 mg, 57%). *For the preparation of oxazole product 7 and general library protocol:* To a solution of Ugi product **5** (600 mg, 1.07 mmol) in concentrated sulfuric acid (10 mL) the reaction mixture was stirred at 60 °C for 2 h and cooled in an ice bath. Ethyl acetate (30 mL) was added to the solution, followed by the addition of 1 N NaOH (30 mL) to neutralize. The organic layer was washed with brine, dried over MgSO₄, evaporated in vacuo to give the crude product **7**. The crude product was further purified by silica gel column chromatography (hexanes/ethyl acetate, 1/9 to 1/4) to afford oxazole **7** (299 mg, 72%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.40 (ddd, *J* = 16.9, 14.1, 8.9 Hz, 3H), 8.27 (d, *J* = 7.7 Hz, 1H), 7.74 (t, *J* = 7.7 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.59–7.35 (m, 4H), 3.69–3.39 (m, 2H), 1.73–1.61 (m, 2H), 1.55–1.40 (m, 2H), 1.06–0.95 (m, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 161.02, 156.89, 152.72, 130.78, 130.09, 129.56, 128.44, 128.37, 127.34, 127.30, 127.04, 123.42, 123.38, 39.18, 31.84, 20.29, 13.83 ppm. ESI 389 [MH]⁺.

Figure 1.
Formylated oxazole **8** derived from sequential Robinson–Gabriel/Vilsmeier–Haack reactions.

Figure 2. Synthesis of 2,4,5-trisubstituted oxazoles **9–21** (Ugi % isolated yield, deprotection/cyclodehydration % isolated yield).

Scheme 1.

Concise synthesis of 2,4,5-trisubstituted oxazole **5** via a tandem Ugi/Robinson–Gabriel sequence.

Scheme 2.
Synthesis of oxazole **7**.