Tetrahedron Letters 53 (2012) 2592–2594

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Hydrazine-mediated cyclization of Ugi products to synthesize novel 3-hydroxypyrazoles

Arthur Y. Shaw [a], Jonathan A. McLaren [a], Gary S. Nichol [b], Christopher Hulme [a,b,*]

[a] Department of Pharmacology and Toxicology, College of Pharmacy, BIO5 Oro Valley, The University of Arizona, 1580 E. Hanley Blvd., Oro Valley, AZ 85737, USA
[b] Department of Chemistry and Biochemistry, The University of Arizona, Tucson, AZ 85721, USA

ARTICLE INFO

*Article history:*
Received 23 February 2012
Accepted 8 March 2012
Available online 24 March 2012

*Keywords:*
Multicomponent reaction
Ugi reaction
3-Hydroxypyrazole
Hydrazine-mediated cyclization

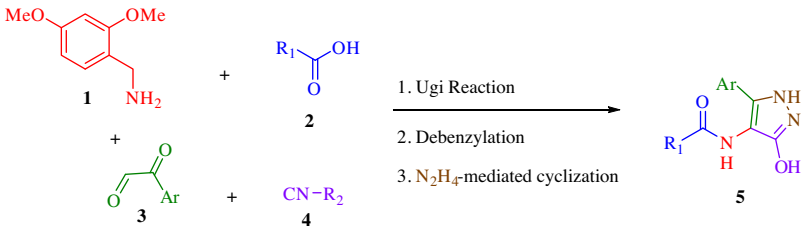
ABSTRACT

This report discloses a novel concise synthesis of a series of 3-hydroxypyrazoles **5** via a tandem Ugi/debenzylation /hydrazine-mediated cyclization sequence. Herein, *n*-butyl isocyanide **4b** was utilized as an alternative to classical convertible isocyanides enabling high yielding hydrazine-mediated cyclization. Taken together, a novel class of 3-hydroxypyrazoles **5a**–**5i** was synthesized with a potential to be of interest in future library enrichment strategies.



In spite of scarcity in nature,[1] the pyrazole scaffold has been significantly studied mainly due to the discovery of interesting properties exhibited by a great number of its derivatives. Pyrazole, a five-membered heterocycle containing two adjacent nitrogen atoms, is a motif found in a number of small molecules that possess a broad spectrum of pharmaceutical activities.[2] Particularly noteworthy is celecoxib, containing a 1-arylpyrazole motif which is a selective cyclooxygenase-2 (COX-2) inhibitor for the treatment of a plethora of indications that include osteoarthritis, rheumatoid arthritis, acute pain, and others.[3] As a consequence, a variety of methodologies to develop pyrazole derivatives have been intensively explored in the past decade.[4]

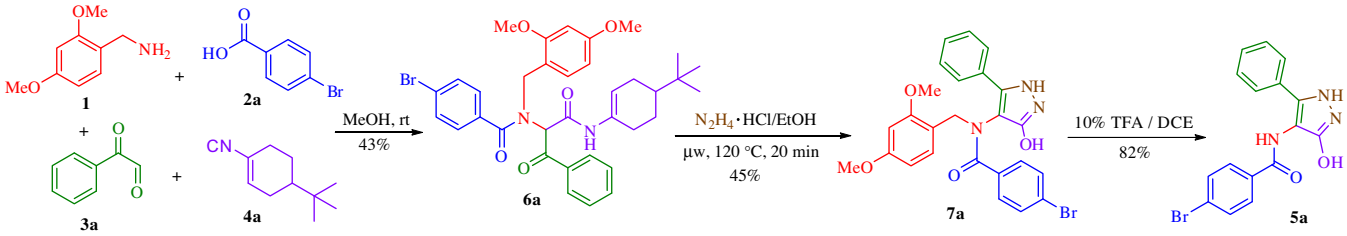
Multi-component reactions (MCRs) are powerful transformations in which three or more starting materials are incorporated in a one-pot fashion to produce highly functionalized products. Isocyanide-based multicomponent reactions (IMCRs) are of particular interest thanks in part to the large number of commercially available starting materials and a wide range of readily accessible pharmacologically relevant scaffolds.[5] The most well-known IMCR, the Ugi reaction, is carried out through the reaction of an amine, carbonyl compound, carboxylic acid, and isocyanide, which undergo a condensation step to afford the corresponding functionalized α-acylamino amide.[6] The usefulness of such a process as a powerful diversity generating step has been demonstrated by numerous




**Scheme 1.** Synthesis of 3-hydroxypyrazoles **5**.

* Corresponding author.
*E-mail address:* hulme@pharmacy.arizona.edu (C. Hulme).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.03.033




**Scheme 2.**

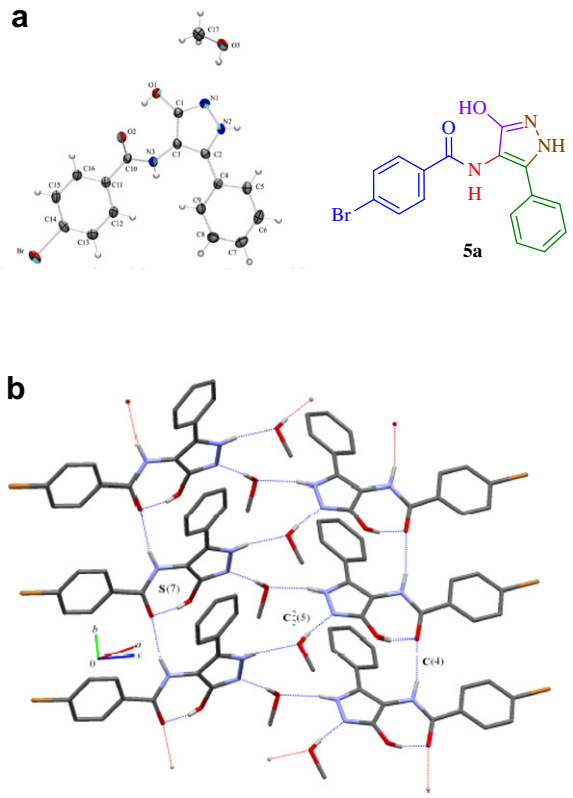



**Figure 1.** (a) Crystal structure of **5a**. (b) Depiction of intra-molecular H-bonds between the pyrazole 3-hydroxyl group and amide carbonyl. In addition intermolecular bonds are seen between methanol and both the hydroxyl pyrazole (–OH) and pyrazole nitrogen (N).

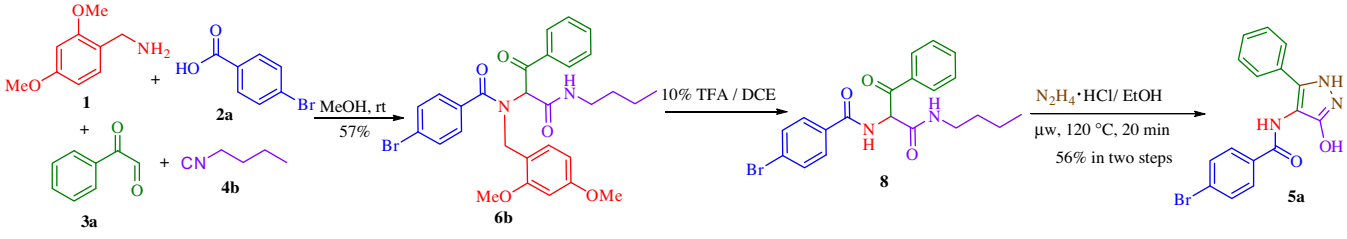
applications in the synthesis of potential drug-like libraries of small molecules.[5c,7] Indeed recently, we have successfully developed a concise synthesis of 2,4,5-trisubstituted oxazoles via a tandem Ugi/Robinson-Gabriel sequence.[8] Of particular relevance to this Letter are the extensive studies performed by Krasavin et al. who often employs hydrazines as the amine equivalent to subsequently generate new molecular diversity.[9] Herein we would like to report a novel hydrazine-mediated cyclization of the Ugi condensation product that affords unique 3-hydroxypyrazoles **5** via a tandem Ugi/debenzylation/hydrazine-mediated cyclization sequence, Scheme 1.

Initial optimization studies focused on 4-*tert*-butyl cyclohexen-1-yl isocyanide **4a**, employed as a convertible isocyanide to increase the acid catalyzed electrophilicity of the isocyanide derived amide carbonyl which in turn was expected to promote the key cyclization step.[10] Thus Ugi product **6a** was initially prepared (MeOH, rt, 36 h, 43%) utilizing 2,4-dimethoxybenzenylamine **1**,[11] 4-bromobenzoic acid **2a**, phenylglyoxal **3a,** and 4-*tert*-butyl cyclohexen-1-yl isocyanide **4a**, Scheme 2.

Subsequent treatment of **6a** with hydrazine mono-hydrochloride in ethanol (accelerated via microwave irradiation) successfully afforded the 3-hydroxypyrazole **7a** in 45% isolated yield. At this stage the unaccounted for mass balance seemed to be composed of several unidentified side products. Removal of the 2,4-dimethoxybenzyl moiety from **7a** was successfully carried out at 80 °C for 10 min under microwave irradiation in 10% TFA/DCE solution to afford the corresponding 3-hydroxypyrazole **5a** (82% isolated yield) which was characterized by X-ray crystallographic analysis, Figure 1a. Interestingly, an intra-molecular hydrogen bond was observed between the 3-hydroxyl group and the carboxamide carbonyl of **5a**, Figure 1b.

Not satisfied with the first two steps of the sequence (both <50%), attempts to further optimize yields were undertaken through replacement of **4a** with *n*-butyl isocyanide **4b**, and an alteration in the order of the reaction sequence Scheme 3.[12] Consequently, the Ugi product **6b** was prepared in improved yields (**6a**, 43%, **6b**, 57%) and debenzylation was conducted prior to pyrazole formation to afford the *N*-acyl-α-aminoketone **8**, Scheme 3. Without further purification, *N*-acyl-α-aminoketone **8** was subjected to hydrazine-mediated cyclization conditions to give the desired 3-hydroxypyrazole **5a** with improved conversion (56% isolated yield in two steps).[13]

With satisfactory conditions in place, a small array of 3-hydroxypyrazoles was thus synthesized with diversity being generated through the utilization of various carboxylic acids **2** and arylglyoxals **3** to establish the scope of the methodology. Indeed, the new tandem Ugi/debenzylation/hydrazine-mediated cyclization sequence furnished




**Scheme 3.**

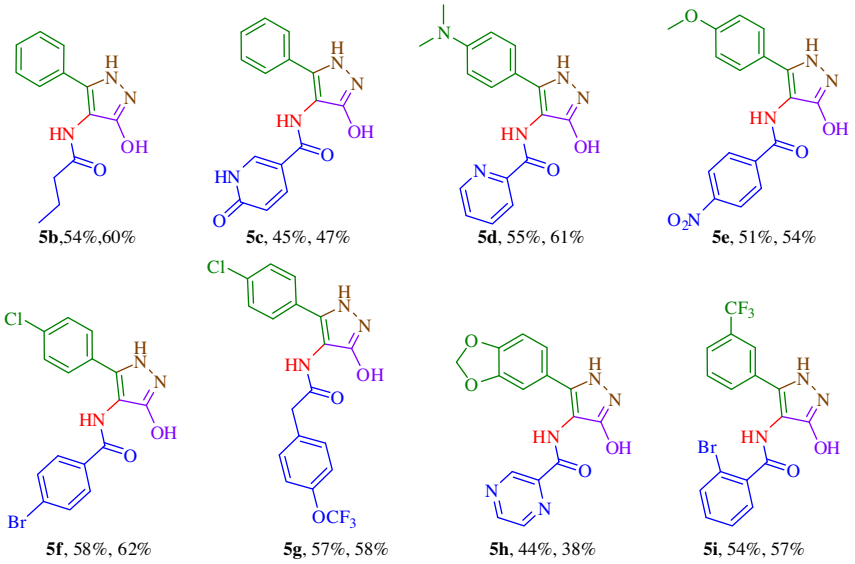



**Figure 2.** Structures of 3-hydroxypyrazoles **5b**–**5i** (Ugi% isolated yield, debenzylation/$N_2H_4$-mediated cyclization% isolated yield for two steps).

Ugi products and 3-hydroxypyrazoles with yields ranging from 44% to 58% and 38–62%, respectively, Figure 2.

In summary, a series of novel 3-hydroxypyrazoles **5a**–**5i** were synthesized in three steps employing a tandem Ugi/debenzylation/hydrazine-mediated cyclization sequence and *n*-butyl isocyanide **4b** was an effective replacement for 4-*tert*-butyl cyclohexen-1-yl isocyanide **4a** for the hydrazine-mediated cyclization step. The novel class of 3-hydroxypyrazoles is fully expected to be of high interest in medicinal chemistry groups, in particular those involved in kinase inhibitor design.

## Acknowledgments

We would like to thank the Office of the Director, NIH, and the National Institute of Mental Health for funding (1RC2MH090878-01). Particular thanks to N. Schechter (PSM) for copy editing.

## References and notes

1. Parameswaran, P. S.; Naik, C. G.; Hegde, V. R. *J. Nat. Prod.* **1997**, *60*, 802.
2. (a) Mowbray, C. E.; Burt, C.; Corbau, R.; Gayton, S.; Hawes, M.; Perros, M.; Tran, I.; Price, D. A.; Quinton, F. J.; Selby, M. D.; Stupple, P. A.; Webster, R.; Wood, A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5857; (b) Wyatt, P. G.; Woodhead, A. J.; Berdini, V.; Boulstridge, J. A.; Carr, M. G.; Cross, D. M.; Davis, D. J.; Devine, L. A.; Early, T. R.; Feltell, R. E.; Lewis, E. J.; MsMenamin, R. L.; Navarro, E. F.; O'Brien, M. A.; O'Reilly, M.; Reule, M.; Saxty, G.; Seavers, L. A.; Smith, D.-M.; Squires, M.; Trewartha, G.; Walker, M. T.; Woolford, A. J.-A. *J. Med. Chem.* **2008**, *51*, 4986; (c) Wickens, P.; Kluender, H.; Dixon, J.; Brennan, C.; Achebe, F.; Bacchiocchi, A.; Bankston, D.; Bierer, D.; Brands, M.; Braun, D.; Brown, M. S.; Chuang, C.-Y.; Dumas, J.; Enyedy, I.; Hofilena, G.; Hong, Z.; Housley, T.; Jones, B.; Khire, U.; Kreiman, C.; Kumarasinghe, E.; Lowinger, T.; Ott-Morgan, R.; Perkins, L.; Phillips, B.; Schoenleber, R.; Scott, W. J.; Sheeler, R.; Redman, A.; Sun, X.; Taylor, I.; Wang, L.; Wilhelm, S.; Zhang, X.; Zhang, M.; Sullivan, E.; Carter, C.; Miglarese, M.; Levy, J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4378; (d) de Paulis, T.; Hemstapat, K.; Chen, Y.; Zhang, Y.; Saleh, S.; Alagille, D.; Baldwin, R. M.; Tamagnan, G. D.; Conn, P. J. *J. Med. Chem.* **2006**, *49*, 3332; (e) Bekhit, A. A.; Abdel-Aziem, T. *Bioorg. Med. Chem.* **2004**, *12*, 1935; (f) Tanitame, A.; Oyamada, Y.; Ofuji, K.; Fujimoto, M.; Suzuki, K.; Ueda, T.; Terauchi, H.; Kawasaki, M.; Nagai, K.; Wachi, M.; Yamagishi, J.-I. *Bioorg. Med. Chem.* **2004**, *12*, 5515; (g) Zhou, H.-B.; Carlson, K. E.; Stossi, F.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 108; (h) Chimenti, F.; Fioravanti, R.; Bolasco, A.; Manna, F.; Chimenti, P.; Secci, D.; Befani, O.; Turini, P.; Ortuso, F.; Alcaro, S. *J. Med. Chem.* **2007**, *50*, 425.
3. Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347.
4. Fustero, S.; Sanchez-Rosello, M.; Barrio, P.; Simon-Fuentes, S. *Chem. Rev.* **2011**, *111*, 6984.
5. (a)For relevant reviews see: *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Weinheim, 2005; (b) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51; (c) Dömling, A. *Chem. Rev.* **2006**, *106*, 17; (d) Hulme, C.; Nixey, T. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 921; (e) El Kaim, L.; Grimaud, L. *Tetrahedron* **2009**, *65*, 2153; (f) Banfi, L.; Riva, R.; Basso, A. *Synlett* **2010**, 23.
6. (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.
7. Akritopoulou-Zanze, I. *Curr. Opin. Chem. Biol.* **2008**, *12*, 324.
8. Shaw, A. Y.; Xu, Z.; Hulme, C. *Tetrahedron Lett.* **2012**, *53*, 1998.
9. (a) Krasavin, M.; Bushkova, E.; Parchinsky, V.; Shumsky, A. *Synthesis* **2010**, *6*, 933; (b) Bushkova, E.; Parchinsky, V.; Krasavin, M. *Mol. Diversity* **2010**, *41*, 493.
10. Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574.
11. Sheehan, S. M.; Masters, J. J.; Wiley, M. R.; Young, S. C.; Liebeschuetz, J. W.; Jones, S. D.; Murray, C. W.; Franciskovich, J. B.; Engel, D. B.; Weber, W. W.; Marimuthu, J.; Kyle, J. A.; Smallwood, J. K.; Farmen, M. W.; Smith, G. F. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2255.
12. Hulme, C.; Chappeta, S.; Dietrich, J. *Tetrahedron Lett.* **2009**, *50*, 4054.
13. For the preparation of Ugi product **6b** and general library protocol: To a solution of 2,4-dimethoxybenzenylamine **1** (334.2 mg, 2.0 mmol), 4-bromobenzoic acid **2a** (398 mg, 2.0 mmol), phenylglyoxal monohydrate **3a** (304 mg, 2.0 mmol) and *n*-butyl isocyanide **4b** (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 (ethyl acetate/hexane, 1/9 to 1/3) to obtain the Ugi product **6b** (645 mg, 57%). For the preparation of 3-hydroxypyrazole **5a** and general library protocol: To a solution of Ugi product **6b** (566 mg, 1.0 mmol) in 10% TFA/DCE solution (3 mL), the resulting mixture was heated at 80 °C for 10 min under microwave irradiation to obtain ketoamide **10**. The reaction solution was evaporated in vacuo and the residue was dissolved in ethyl acetate (20 mL), washed with 1 N NaOH (20 mL) and brine (20 mL), dried over $MgSO_4$ and evaporated in vacuo to get *N*-acyl-α-aminoketone **8b**. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.11–8.01 (m, 2H), 7.78–7.70 (m, 2H), 7.61 (ddq, $J$ = 5.2, 2.6, 1.2 Hz, 3H), 7.54–7.46 (m, 2H), 6.81 (s, 1H), 6.06–6.00 (m, 1H), 3.33–3.14 (m, 2H), 1.52–1.39 (m, 2H), 1.35–1.20 (m, 3H), 0.93–0.81 (m, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 192.86, 166.54, 166.11, 134.50, 134.24, 132.06, 131.78, 128.86, 128.83, 127.18, 60.21, 39.65, 31.31, 19.88, 13.62 ppm. For the preparation of 3-hydroxypyrazole **5a** and general library protocol: Without further purification, a mixture of *N*-acyl-α-aminoketone **8b** and $NH_2NH_2$ HCl (343 mg, 5.0 mmol) in ethanol (3 mL) heated under microwave irradiation at 120 °C for 20 min. The reaction solution was evaporated in vacuo and the residue was purified by column chromatography (eluent, ethyl acetate/hexane, 1/4 to 9/1) to afford 3-hydroxypyrazole **5a** (214 mg, 56% in two steps). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.58 (s, 1H), 7.95–7.86 (m, 2H), 7.76–7.68 (m, 2H), 7.60 (dt, $J$ = 6.2, 4.0 Hz, 2H), 7.38 (dd, $J$ = 10.3, 4.7 Hz, 2H), 7.33–7.25 (m, 1H), 3.28 (s, 2H) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 166.16, 133.87, 131.81, 130.18, 129.09, 128.35, 126.15, 125.64 ppm.