Concise Synthesis of Isoquinoline via the Ugi and Heck Reactions

ARTICLE *in* ORGANIC LETTERS · OCTOBER 2004

Impact Factor: 6.36 · DOI: 10.1021/ol048791n · Source: PubMed

ORGANIC LETTERS

2004
Vol. 6, No. 18
3155−3158

Concise Synthesis of Isoquinoline via the Ugi and Heck Reactions

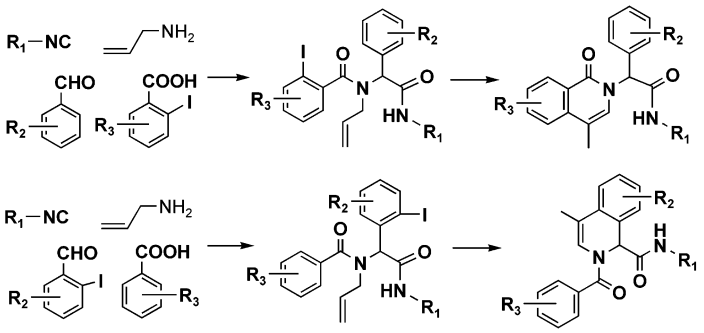
Zheng Xiang,[†] Tuoping Luo,[†] Kui Lu,[†] Jiayue Cui,[†] Xiaomeng Shi,[†] Reza Fathi,*[,‡] Jiahua Chen,*[,†] and Zhen Yang*[,†,‡]

Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Beijing, 100871, China, Laboratory of Chemical Genetics, Shenzhen Graduate School of Peking University, The University Town, Shenzhen, 518055, China, and VivoQuest, Inc., 711 Executive Blvd, Valley Cottage, New York 10989

zyang@chem.pku.edu.cn

Received June 24, 2004

ABSTRACT



Two types of isoquinoline scaffolds were successfully constructed in a combinatorial format via the Ugi four-component reaction and the Pd-catalyzed intramolecular Heck reaction, starting from readily available starting materials.

Isoquinoline is an important heterocyclic template that is presented in a variety of natural products and pharmaceuticals.[1] For example (Figure 1), narciclasine **1** is a powerful antitumor agent that inhibits eukaryotic protein synthesis at the ribosomal level.[2a] Compound **2** is a lead molecule for the development of inhibitors of topoisomerase I.[2b] Compound **3** was identified as an orally active inhibitor of Lck kinase.[2c]

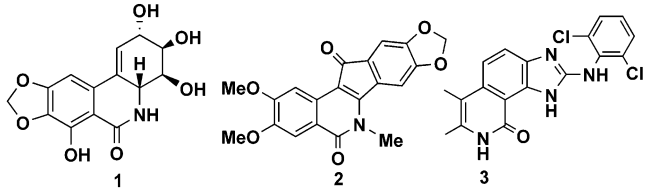


Figure 1. Biologically active isoquinolines.

As part of our ongoing discovery program, we are interested in the design, synthesis, and development of diverse small molecules[3] that can act against known protein targets, as well as the perturbation of protein function in a phenotypic assay to discover novel protein targets. Hence,

[†] College of Chemistry, Beijing, and Shenzhen Graduate School of Peking University.

[‡] VivoQuest, Inc.

(1) (a) Croisy-Delcey, M.; Croisy, A.; Carrez, D.; Huel, C.; Chiaroni, A.; Ducrot, P.; Bisagni, E.; Jin, L.; Leclercq, G. *Bioorg. Med. Chem.* **2000**, *8*, 2629. (b) Bentley, K. W. *The Isoquinoline Alkaloids*; Harwood Academic Publishers: Australia, 1998; Vol. 1.

(2) (a) For a review see: Polt, R. Amaryllidaceae Alkaloids with Antitumor Activity. In *Organic Synthesis, Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, 1996; Vol. 3, p 109. (b) Kohlhagen, G.; Paull, K.; Cusgman, M.; Nagafuji, P.; Pommier, Y. *Mol. Pharmacol.* **1998**, *54*, 50. (c) Snow, R. J.; Cardozo, M. G.; Morwick, T. M.; Busacca, C. A.; Dong, Y.; Echner, R. J.; Jakes, S.; Kapadia, S.; Lukas, S.; Moss, N.; Panzenbeck, M.; Peet, G. W.; Peterson, J. D.; Prokopowicz, A. P.; Sellati, R.; Tschantz, M. A. *J. Med. Chem.* **2002**, *45*, 3394.

(3) Liao, Y.; Hu, Y.; Wu, J.; Zhu, Q.; Donovan, M.; Fathi, R.; Yang, Z. *Curr. Med. Chem.* **2003**, *10*, 2285.

10.1021/ol048791n CCC: $27.50
Published on Web 08/04/2004

the synthesis of potent and selective small molecules by facile chemical routes may provide an avenue to explore biological systems, in addition to creating lead molecules for clinical drug development. Isoquinoline possesses diverse biological activities and encompasses an ideal pharmacophore for further combinatorial diversification.

Although many methods are available for the synthesis of isoquinoline,[6] alternative diversity-oriented approaches would be desirable. Herein we present a two-step approach for the construction of two types of isoquinoline scaffolds via Ugi four-component reaction (U-4CR)[4] and the Pd-catalyzed intramolecular Heck reaction.[5]

Multicomponent reactions such as Ugi reaction have generated much interest because of their synthetic potential, their importance in combinatorial chemistry, and their capacity to generate molecular diversity. In Ugi four-component reaction, an amine, an aldehyde, a carboxylic acid, and an isocyanide react in a one-pot process to provide the diverse α-acylamino amides **5** in generally good yields (Figure 2). This synthetic method has been used to assemble

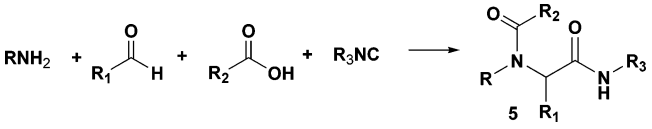
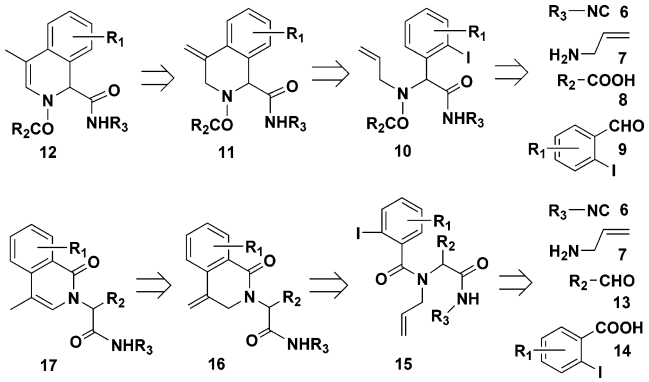


Figure 2. Ugi four-component reaction.

a broad range of complex molecular scaffolds in a short reaction sequence.[7]

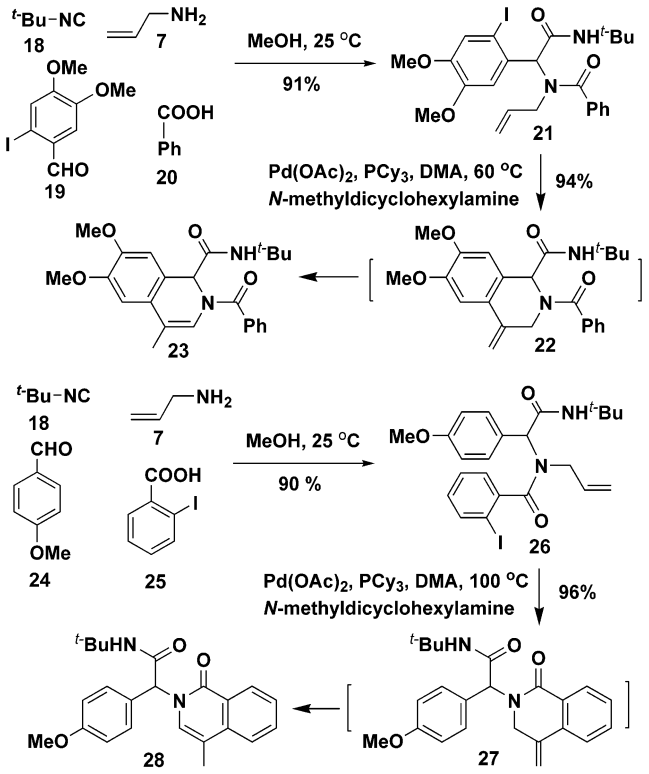
It is envisaged that substrates containing functionalities such as the Ugi products **10** and **15** (see Scheme 1) can

Scheme 1. Retrosynthetic Analysis



sequentially undergo the Pd-catalyzed intramolecular Heck and double-bond isomerization to generate isoquinoline

Scheme 2. Two-Step Syntheses of Isoquinolines **23** and **28**



scaffolds **12** and **17** via the intermediates **11** and **16**, respectively, in one pot. Therefore, multifunctional use of

(4) (a) Ugi, I.; Lohberger, S.; Karl, R. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 2, Part 2, Sect. 4.6, p 1083. (b) Ugi, I.; Demharter, A.; Horl, W.; Schmid, T. *Tetrahedron* **1996**, *52*, 11657. (c) Armstrong, R.; Combs, A.; Tempest, P.; Brown, D.; Keating, T. *Acc. Chem. Res*. **1996**, *29*, 123. (d) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (e) Bienayme, H.; Hulme, C.; Oddon, G.; Schmidt, P. *Chem. Eur. J.* **2000**, *6*, 3321.

(5) (a) Link, J. T.; Overman, L. In *Metal Catalyzed Cross Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; p 99. (b) Braese, S.; de Meijere, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., de Meijere, A., Eds.; John Wiley and Sons: Hoboken, NJ, 2002; p 1223. (c) Dounay, A. B.; Overman, L. E. *Chem. Rev*. **2003**, *103*, 2945.

(6) (a) *Organic Reactions*; John Wiley & Sons: London, 1951; Vol. VI, Chapters 2−4. (b) Maassarani, F.; Pfeffer, M.; Le Borgne, G. *J. Chem. Soc., Chem. Commun.* **1987**, 565. (c) Wu, G.; Geib, S. J.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1988**, *53*, 3288. (d) Girling, I. R.; Widdowson, D. A. *Tetrahedron Lett*. **1982**, *23*, 4281. (e) Roesch, K. R.; Larock, R. C. *J. Org. Chem*. **1998**, *63*, 5306. (f) Ramakrishna, T. V. V.; Sharp, P. R. *Org. Lett*. **2003**, *5*, 877. (g) Dai, G.; Larock, R. C. *J. Org. Chem*. **2003**, *68*, 920. (h) Huang, Q.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 980 and related references therein.

(7) (a) Ugi, I.; Demharter, A.; Horl, W.; Schmid, T. *Tetrahedron* **1996**, *52*, 11657. (b) Keating, T. A.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 8935. (c) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449. (d) Pitlik, J.; Townsend, C. A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3129. (e) Hanusch-Kompa, C.; Ugi, I. *Tetrahedron Lett.* **1998**, *39*, 2725. (f) Hulme, C.; Peng, J.; Tang, S.-Y.; Burns, C. J.; Morize, I.; Labaudiniere, R. *J. Org. Chem.* **1998**, *63*, 8021. (g) Ugi, I.; Hörl, W.; Hanusch-Kompa, C.; Schmid, T.; Herdtweck, E. *Heterocycles* **1998**, *47*, 965. (h) Park, S. J.; Keum, G.; Kang, S. B.; Koh, H. Y.; Lee, D. H.; Kim, Y. *Tetrahedron Lett*. **1998**, *39*, 71096. (i) Hulme, C.; Cherrier, M. P. *Tetrahedron Lett*. **1999**, *40*, 5295. (j) Nixey, T.; Kelly, M.; Hulme, K. *Tetrahedron Lett.* **2000**, *41*, 8729. (k) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (l) Lee, D.; Sello, J. K.; Schreiber, S. L. *Org. Lett.* **2000**, *2*, 709. (m) Hulme, C.; Ma, L.; Kumar, V.; Krolikowski, P. H.; Allen, A. C.; Labaduiniere, R. *Tetrahedron Lett.* **2000**, *41*, 1509. (n) Cristau, P.; Vors, J. P.; Zhu, J. *Org. Lett*. **2001**, *3*, 4079. (o) Kim, Y. B.; Choi, E. H.; Keum, G.; Kang, S. B.; Lee, D. H.; Koh, H. Y.; Kim, Y. *Org. Lett.* **2001**, *3*, 4149. (p) Gedey, S.; Van der Eycken, J.; Fulop, F. *Org. Lett*. **2002**, *4*, 1967. (q) Zhu, J. *Eur. J. Org. Chem*. **2003**, 1133.

Table 1. Two-Step Syntheses of Type I Isoquinolines

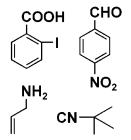
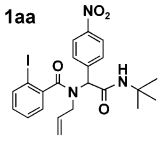
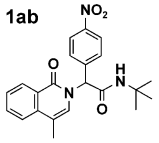
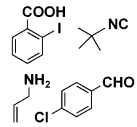
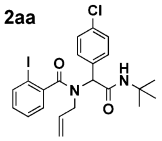
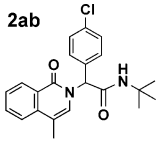
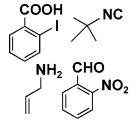
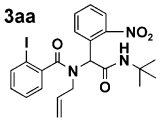
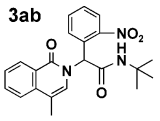
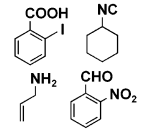
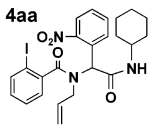
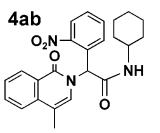
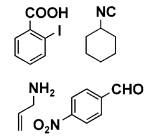
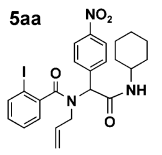
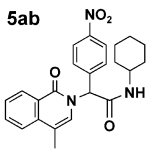
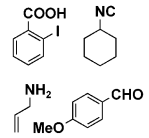
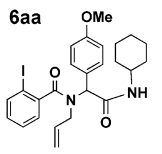
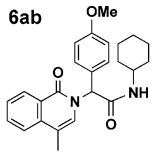
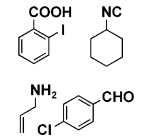
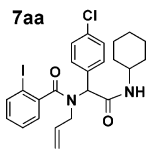
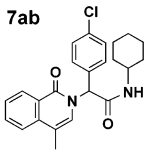
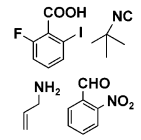
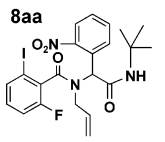
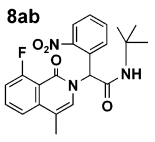
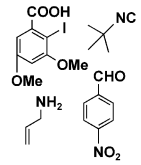
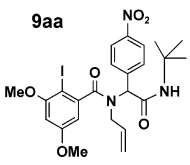
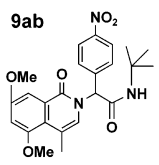
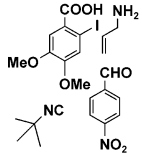
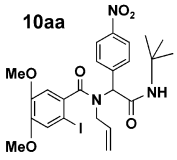
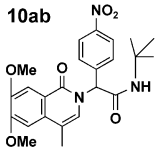
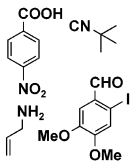
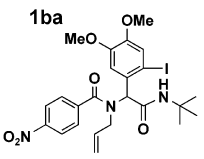
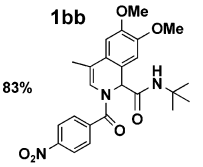
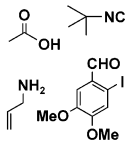
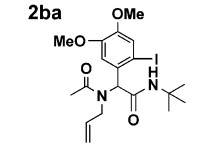
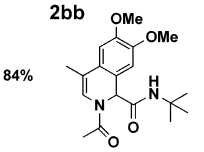
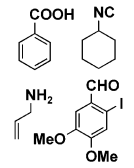
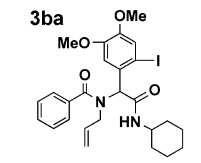
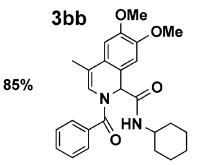
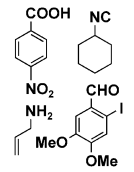
entry	starting material	Ugi product	yield	Heck product	yield
1			93%		92%
2			91%		95%
3			84%		94%
4			98%		93%
5			80%		92%
6			85%		92%
7			88%		96%
8			81%		81%
9			89%		75%
10			88%		93%

Table 2. Two-Step Syntheses of Type II Isoquinolines

entry	starting material	Ugi product	yield	Heck product	yield
1			83%		90%
2			84%		80%
3			85%		90%
4			90%		91%
5			90%		92%
6			88%		85%
7			89%		75%
8			85%		87%

the palladium in this sequential process would obviate the tedious separation and purification of intermediates **11** and **16**. Scheme 1 illustrates the retrosynthetic analysis applied to this process. Accordingly, we believed that compounds **10** and **15** could be made by Ugi reaction from their precursors **6**−**9** and **6**, **7**, **13**, and **14**, respectively.

To actualize this design, we first screened the commercially available amines, aldehydes, carboxylic acids, and isocyanide to identify the proper substrates that can generate the Ugi products with the structural features of compounds **10** and **15** (Scheme 1). After screening a variety of combinations of different four components, we found that

methanol is the best solvent for the Ugi reaction, and sequential addition of the four components in the Ugi reaction is essential to achieve the high yield.[8] As a result, compound **21** was made from **7** and **18**−**20** in 91% yield, and compound **26** was generated from **7**, **18**, **24**, and **25** in 90% yield (Scheme 2). Importantly, both **21** and **26** have the functionalities to effect the subsequent Pd-catalyzed Heck reactions.

We then began to investigate the possibility to synthesize the products **23** and **28** directly from compounds **21** and **26** by the Pd-catalyzed intramolecular Heck and double-bond isomerization reactions. To this end, a systematic evaluation of a variety of reaction conditions was conducted, and we found that the catalytic system ($Pd(OAc)_2$, PCy_3, and *N*-methyldicyclohexylamine in DMA) is essential to ensure the desired reactions. The products **23** and **28** were obtained in 96 and 94% yields, respectively, at 60 or 100 °C for 4−18 h. In this synthetic transformation, *N*-methyldicyclohexylamine is a unique base, and the double-bond isomerization (from **22**, **27** to **23**, **28**) is presumably mediated by the Pd-catalyzed reversible β-hydride elimination process (Scheme 2).

It is interesting to note that microwave technology[9] could not be applied to the above-mentioned transformation, because the double-bond isomerization did not proceed completely under the tested conditions, although the rate of intramolecular Heck reaction increased dramatically under the irradiation of microwave.

With optimized reaction conditions in hand, we next examined the scope and generality of this method to make diversified isoquinolines.

(8) To a solution of allylamine (1.0 mmol) in MeOH (1.0 mL) was added aldehyde (1.0 mmol), and the reaction mixture was stirred at room temperature for 10 min. Acid (1.0 mmol) was added to the reaction mixture. After the mixture was stirred for another 5 min, isocyanide (1.0 mmol) was added. The reaction mixture was stirred overnight. Solvent was removed under reduced pressure, and the residue was purified by flash chromatography (petroleum ether/EtOAc/CH_2Cl_2) to give the corresponding Ugi product.

(9) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH Press: Weinheim, 2002.

First, we used commercially available isocyanide and substituted iodobenzoic acids and aldehydes to do the Ugi reactions. Good to excellent yields of coupling products **1aa**−**10aa** were obtained when allylamine was employed under the optimized conditions (Table 1).

We then started to evaluate the Pd-catalyzed reactions to make compounds **1ab**−**10ab** from compounds **1aa**−**10aa**. Fortunately, the desired products were obtained in high yields (entries 1−10 in Table 1).

Encouraged by these results, we started to apply the experience gained from the above study to synthesize type II isoquinolines. Accordingly, the commercially available allylamine, two isocyanides, four aryl acids, and two aryl aldehydes were divided into eight groups to do the Ugi reactions. To our satisfaction, good results of Ugi products **1ba**−**8ba** were obtained (entries 1−8 in Table 2).

By applying the prescribed reaction conditions to make the type I isoquinolines, we have synthesized compounds **1bb**−**8bb** from **1ba**−**8ba** in high yields (entries 1−8 in Table 2). It is noteworthy that the aryl bromide-based Ugi products **6ba**−**8ba** can also undergo the desired Pd-catalyzed reactions to give the products **6bb**−**8bb**, albeit in slightly lower yields (entries 6−8 in Table 2).

In summary, we have developed a highly efficient approach to synthesizing diversity-based isoquinolines via the Ugi−Heck reaction sequence. This two-step synthetic route allows us to make a variety of isoquinolines easily, and application of this method to generate isoquinoline-based libraries is currently under investigation in our laboratory.

Acknowledgment. Financial support from the NSFC (Grants 20142004 and 20242002) and the sponsored research program of VivoQuest, Inc., is gratefully acknowledged.

Supporting Information Available: Experimental procedure and ^1H NMR and ^{13}C NMR spectra for the known product compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048791N