Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters 47 (2006) 4683–4686
Tetrahedron Letters

A novel one-pot synthesis of highly diverse indole scaffolds by the Ugi/Heck reaction

Cédric Kalinski,[a,b,*] Michael Umkehrer,[a] Jürgen Schmidt,[a] Günther Ross,[a] Jürgen Kolb,[a] Christoph Burdack,[a] Wolfgang Hiller[b] and Stephan D. Hoffmann[b]

[a]*Priaton GmbH, Bahnhofstr. 9-15, D-82327 Tutzing, Germany*
[b]*Technical University Munich, Lichtenbergstr. 4, D-85747 Garching, Germany*

Received 21 March 2006; revised 18 April 2006; accepted 26 April 2006
Available online 19 May 2006

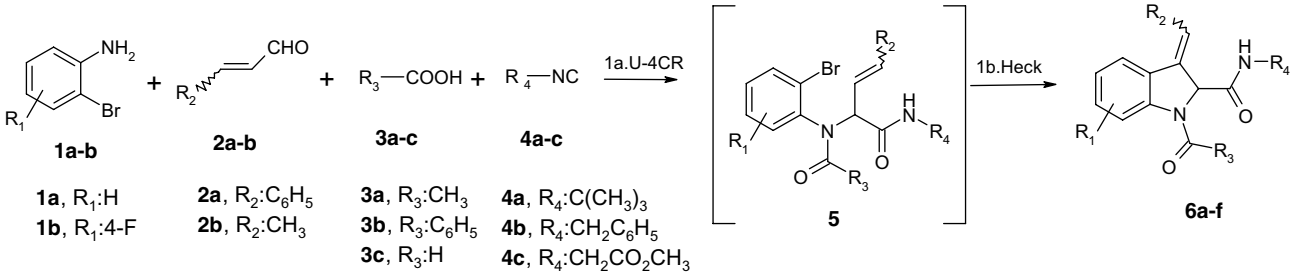
Abstract—A novel one-pot two-step multi component reaction of acrylic aldehydes, bromoanilines, acids and isocyanides yielding polysubstituted indoles is described. The reaction is based on the combination of an Ugi four-component reaction followed by an intramolecular Heck-reaction. The simultaneous use of formic acid and cinnamaldehydes affords in situ generation of 1H-indoles. Convertible isocyanides can also be used with success in this Ugi/Heck strategy and enable synthesis of 1H-indole-2-carboxylic acid building blocks.

Multi-component reactions (MCRs) are widely employed for the rapid assembly of compound arrays with high molecular diversity. Coupled with a post-condensation modification, their utility is increased even further, giving rise to numerous pharmacologically important scaffolds.[1–3]

In the course of our ongoing research on new post-condensation modifications, we recently reported that the combination of the Ugi-four component reaction and the Heck reaction yields highly substituted indol-2-ones in a one-pot solution phase procedure.[4] The potential of the Ugi–Heck reaction developed at the same time by Gracias[5] and Xiang[6] is very wide and enables many new applications.

Thus, we present herein the synthesis of new substituted dihydro-indoles involving 2-bromoanilines **1a**–**b** and acrylic aldehydes **2a**–**b** as starting materials in the Ugi-reaction (Scheme 1).

The formation of the acyclic products (**5**) was originally reported by Ugi et al. and the final ring-closing was performed by a classical intramolecular Heck-reaction[7–11] (Scheme 1). These two reaction steps were combined in a new one-pot synthesis.



Scheme 1. Ugi–Heck synthesis of substituted indoles.

Keywords: Ugi–reaction; Ugi–Heck reaction; Indole; Isocyanide-based multi-component reactions (IMCRs); Combinatorial chemistry.
* Corresponding author. Tel.: +49815890400; fax: +498158904022; e-mail addresses: kalinski@priaton.de; umkehrer@priaton.de

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.04.127

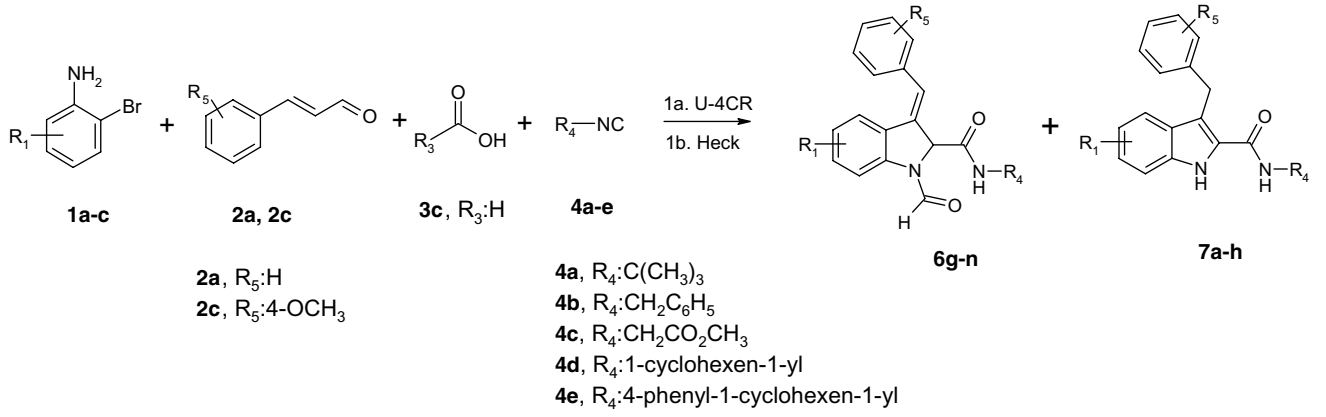
The Ugi–Heck reaction was performed in a typical procedure,[12] whereby the starting materials were mixed in equimolar amounts and stirred for 24–48 h at room temperature. Afterwards solvent was changed from polar protic to polar aprotic and 10% of Pd-catalyst was added. The reaction mixture was stirred for additional 24 h at 80 °C. The expected compounds (**6a**–**f**) were isolated as isomeric mixtures with moderate to good yields (Table 1). They were characterized by ^{1}H NMR, ^{13}C NMR and HPLC-MS data. All the synthesized compounds had purities >95%. The used bromoanilines, acids, acrylic aldehydes and isocyanides could be varied broadly, producing products with four potential points of diversity.

To our delight, we also found a new access to the synthesis of substituted 1H-indoles by involving cinamaldehydes **2a** and **2c** and formic acid **3c** in our one-pot procedure (Scheme 2). Under the conditions of the Heck-reaction, the resulting formic group was partially cleaved. Successive isomerisation led to 1H-indoles with moderate to good yields. Following this new reaction strategy, we synthesized different 1H-indoles (**7a**–**h**) from substituted 2-bromoanilines **1a**–**b**, cinnamaldehydes **2a,c** and diverse isocyanides **4a**–**e** (Table 2). The resulting compounds were successfully isolated with moderate to good yields and their assignments were made on the basis of ^{1}H NMR, ^{13}C NMR and HPLC-MS data. All the synthesized compounds had purities >95%. Scheme 3 shows the result of the X-ray crystal structure analysis of compound **7a** which confirms the spectroscopic results.[15b]

This versatile reaction offers many advantages. The use of substituted 2-bromoanilines allows further derivatisation of the 1H-indole scaffold. Particularly, the reaction-sequence tolerates the use of 'convertible' isocyanides **4d**–**e**. These isocyanides originally reported by Armstrong et al.[18,19] are cleavable under acidic conditions and can generate a plethora of outgoing products via a münchnone mechanism. As illustrated, we cleaved the isocyanide moiety of compounds (**7g**–**h**) to synthe-

Table 1. Ugi–Heck synthesis of substituted indoles

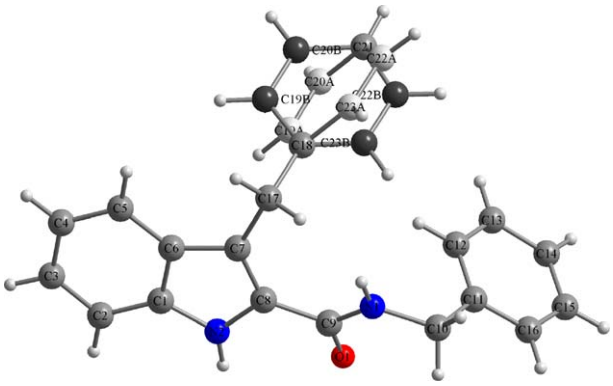
Bromoanilines **1**	Acrylic aldehydes **2**	Carboxylic acids **3**	Isocyanides **4**	(%)	Product
1a	**2a**	**3a**	**4a**	43	**6a**[13]
1a	**2a**	**3a**	**4b**	27	**6b**
1a	**2a**	**3a**	**4c**	25	**6c**[14]
1a	**2a**	**3b**	**4a**	33	**6d**
1a	**2b**	**3a**	**4a**	19	**6e**
1b	**2b**	**3c**	**4a**	48	**6f**



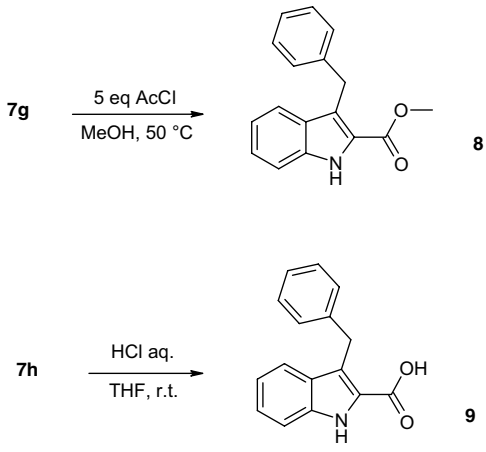
Scheme 2. 1H-Indoles **7a**–**h** synthesized from cinnamaldehydes and formic acid by the Ugi–Heck reaction.

Table 2. Synthesized 1H-indoles

Bromoanilines **1**	Cinnamaldehydes **2**	Isocyanides **4**	(%)	Product
1a	**2a**	**4b**	21	**7a**[15a]
1a	**2a**	**4a**	17	**7b**
1a	**2a**	**4c**	15	**7c**
1a	**2c**	**4a**	23	**7d**
1c	**2a**	**4b**	31	**7e**[16]
1b	**2a**	**4b**	38	**7f**
1a	**2a**	**4d**	29	**7g**[17]
1a	**2a**	**4e**	32	**7h**



Scheme 3. Result of the X-ray analysis of compound **7a**.



Scheme 4. Synthesis of 1H-indole building blocks by the use of convertible isocyanides.

size the corresponding carboxylic acid[20] **9** and ester **8** (Scheme 4).

The resulting 1H-indole-2-carboxylic acid derivatives constitute pharmacologically relevant building blocks due to their diverse expansion potential by alkylation or amide formation.

In summary, a novel one-pot two-step solution phase procedure based on the combination of the Ugi- and the Heck-reaction for the preparation of highly substituted dihydro-indoles, 1H-indoles and 1H-indole-2-carboxylic acid building blocks has been reported.

Current efforts are now focused on the development of new pharmacological scaffolds based on the combination of combinatorial and classical chemistry.

References and notes

1. Dömling, A. *Combinat. Chem. High Throughput Screening* **1998**, *1*, 1.
2. Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2004**, *39*, 3168.
3. Dömling, A. *Chem. Rev.* **2006**, *106*, 17.
4. Umkehrer, M.; Kalinski, C.; Kolb, J.; Burdack, C. *Tetrahedron Lett.* **2006**, *47*, 2391.
5. Gracias, V.; Moore, J. D.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 417.
6. Xiang, Z.; Luo, T.; Lu, K.; Cui, J.; Shi, X.; Fathi, R.; Chen, J.; Yang, Z. *Org. Lett.* **2004**, *6*, 3155.
7. Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.
8. Krause, N. Metallorganische Chemie, 1996; Spektrum Akad. Verl.
9. Dounay, A. B.; Overmann, L. E. *Chem. Rev.* **2003**, *103*, 2945.
10. Terpko, M. O.; Heck, R. F. *J. Am. Chem. Soc.* **1979**, *101*, 5281.
11. Mori, M.; Ban, Y. *Tetrahedron Lett.* **1979**, *20*, 1133.
12. Typical Procedure: Aldehyde (3 mmol) and amine (3 mmol) were stirred in 5 ml 2,2,2-trifluoroethanol for 1 h at room temperature. Then 3 mmol acid and 3 mmol isocyanide were added. The reaction mixture was stirred for 1–3 days at room temperature until the reaction was completed (Indication by TLC). After the reaction was completed, the solvent was evaporated and the resulting residue was dissolved in 5 ml acetonitrile and 0.3 mmol $Pd(OAc)_2$ and 0.6 mmol PPh_3 were added. The reaction mixture was stirred for additional 16–24 h at 80 °C. Afterwards, the solvent was evaporated again, the resulting residue was dissolved in ethyl acetate and filtered through a pad of silica. The resulting crude product was purified by crystallisation from ethanol or by column chromatography on silica gel (hexane/ethyl acetate).
13. Compound **6a** was isolated in 43% yield as a beige solid. ^{1}H (DMSO, 250.13 MHz): 0.89 (s, 9H, C–(CH_3)$_3$, 2.20 (s, 3H, CH_3–C=O), 5.75 (s, 1H, C*H*–C=O), 6.08 (s, 1H, C=C*H*–C_6H_5), 7.05–7.45 (m, 7H, ar), 7.62–7.65 (m, 2H, ar). ^{13}C (DMSO, 62.89 MHz): 23.87 (CH_3–C=O), 27.38 (C–(CH_3)$_3$), 50.30 (*C*–(CH_3)$_3$), 65.38 (*C*H), 116.32 (C=*C*H–C_6H_5), 119.20, 119.94, 123.38, 127.23, 128.46, 128.54, 129.32, 130.48, 134.79, 135.94, 144.87 (ar), 165.00 (CH_3–*C*=O), 168.37 (*C*ONH). MS (ESI): $m/z = 349$ $[M+H]^+$, 371 $[M+Na]^+$. Mp: 194.6 °C.
14. Compound **6c** was isolated in 19% yield as a brown solid. ^{1}H (DMSO, 250.13 MHz): 2.36 (s, 3H, CH_3–C=O), 3.54 (s, 3H, COOCH_3), 3.64 (d, 2H, $^3J = 5.53$ Hz, NH–CH_2–$COOCH_3$), 5.72 (s, 1H, C*H*–C=O), 6.10 (s, 1H, C=C*H*–C_6H_5), 7.09–7.42 (m, 9H, ar), 8.28 (t, 1H, $^3J = 5.53$ Hz, N*H*–CH_2–$COOCH_3$). MS (ESI): $m/z = 365$ $[M+H]^+$, 387 $[M+Na]^+$.
15. (a) Compound **7a** was isolated in 21% yield as a white solid. ^{1}H ($CDCl_3$, 250.13 MHz): 4.33 (s, 2H, Ph–CH_2–C=C), 4.48 (d, 2H, $^3J = 5.37$ Hz, NH–CH_2–C_6H_5), 6.12 (s, 1H, N*H*–CH_2–C_6H_5), 7.04–7.09 (m, 4H, ar–H), 7.14–7.16 (m, 4H, ar–H), 7.19–7.35 (m, 4H, ar–H); 7.43 (d, 1H, $^3J = 8.22$ Hz, ar–H), 7.65 (d, 1H, $^3J = 8.06$ Hz, ar–H), 9.29 (s, 1H, N*H*). ^{13}C ($CDCl_3$, 62.89 MHz): 30.21 (C_6H_5–*C*H_2–C=C), 43.95 (NH–*C*H_2–C_6H_5), 111.85, 114.65, 119.98, 120.36, 124.80, 126.78, 127.52, 127.76, 127.99, 128.04, 128.70, 129.01, 129.06, 135.16, 137.49, 139.22 (ar), 161.84 (*C*=O). MS (ESI): $m/z = 341$ $[M+H]^+$, 364 $[M+Na]^+$. Mp: 171.6 °C. (b) A colourless needle of **7a**, $1.00 \times 0.05 \times 0.05$ mm, was analyzed with a Oxford-Diffractions Excalibur3 diffractometer with Mo-K_α source (0.71073 Å). π- and ω-scans with $\Delta\pi/\Delta\omega = 1°$ with a $2\theta_{max} = 40.5°$ were used. The data collection was performed at 120 ± 2 K. Compound **5a** crystallizes in the monoclinic space group *C*2/*c*. The unit cell parameters are: $a = 28.419(2)$, $b = 4.8960(3)$, $c = 27.529(2)$ Å, $\beta = 112.32(1)°$, $V = 3543.4(4)$ Å^3, $Z = 8$, $\rho_{calc} = 1.276$ g cm^{-3}, $F(000) = 1440$. The data were collected in the *h k l* range −27 to 27, −4 to 4, −26 to 26; 1727 reflections with $I > 2\sigma(I)$ were measured. Non-hydrogen atoms were refined anisotropically by full-matrix least-squares methods on F^2. The positions of the hydrogen atoms were

determined geometrically and refined using the riding model. One phenyl group is disordered and was refined using a split model for the atomic positions (C19, C20 C22, C23). Final $R = 0.066$, $R_w = 0.141$ for all observed reflections. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 600942. Further details on the crystal structure investigation may be obtained from the Cambridge Crystallographic Data Centre free of charge, on application to CCDC, 12 Union Road, Cambridge CB12EZ, UK (fax: (+44) 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk), quoting the depository number.

16. Compound **7e** was isolated in 31% yield as a white solid. ^{1}H ($CDCl_3$, 215.13 MHz): 2.44 (s, 3H, C_6H_5–CH_3), 4.30 (s, 2H, C_6H_5–CH_2–C═C), 4.48 (d, 2H, $^3J = 5.52$ Hz, NH–CH_2–C_6H_5), 6.11 (s, 1H, NH–CH_2–C_6H_5), 7.04–7.08 (m, 4H, ar–H), 7.12–7.16 (m, 4H, ar–H), 7.25–7.33 (m, 4H, ar–H), 7.42 (s, 1H, ar–H), 9.36 (s, 1H, NH). ^{13}C ($CDCl_3$, 62.89 MHz): 21.58 (CH$_3$–C_6H_5), 30.19 (C_6H_5–CH$_2$–C═C), 43.95 (NH–CH$_2$–C_6H_5), 111.61, 114.17, 119.26, 126.71, 126.74, 127.50, 127.75, 128.06, 128.70, 129.00, 129.27, 129.66, 133.66, 137.57, 139.36 (ar), 162.00 (C═O). MS (ESI): $m/z = 355$ $[M+H]^+$, 377 $[M+Na]^+$. Mp: 196.1 °C.
17. Compound **7g** was isolated in 29% yield as a white solid. ^{1}H ($CDCl_3$, 215.13 MHz): 1.49–1.64 (m, 4H, cyclohexenyl), 1.77–1.79 (m, 2H, cyclohexenyl), 2.06–2.09 (m, 2H, cyclohexyl), 4.39 (s, 2H, CH_2–C_6H_5), 5.25 (t, 1H, $^3J = 4.03$ Hz, C═CH cyclohexenyl), 6.68 (s, 1H, C(O)–NH), 7.09–7.31 (m, 7H, ar), 7.44 (d, 1H, $^3J = 8.22$ Hz, ar), 7.62 (d, 1H, $^3J = 8.06$ Hz, ar), 9.68 (s, 1H, NH). ^{13}C ($CDCl_3$, 62.89 MHz): 21.88, 22.42, 24.01, 27.65 (CH$_2$ cyclohexenyl), 30.07 (CH$_2$–C_6H_5), 111.99, 113.32, 113.74 (Cq), 119.90, 120.29, 124.72, 127.04, 128.23, 128.91 (Cq), 129.10 (Cq), 129.13, 132.42 (Cq), 135.46 (Cq), 139.13 (Cq) (ar), 160.12 (C═O). MS (ESI): $m/z = 331$ $[M+H]^+$, 353 $[M+Na]^+$.
18. Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574.
19. Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1995**, *117*, 7842.
20. Compound **9** was prepared as follows: 60 mg (0.15 mmol) of **7h** were dissolved in 4 mL of a solution of THF/water 9/1. The mixture was stirred over night at room temperature. Then, 15 mL methylene chloride were added and the resulting organic layer was washed with brine and dried over magnesium sulfate. The crude product was washed with cold chloroform to yield **9** (29 mg, 77%) as a white solid. ^{1}H (DMSO, 250.13 MHz): 4.45 (s, 2H, CH_2–C_6H_5), 6.98 (dt, 1H, $^3J = 7.18$, $^4J = 0.63$ Hz, ar), 7.09–7.40 (m, 7H, ar), 7.55 (d, 1H, $^3J = 8.05$ Hz, ar), 11.22 (s, 1H, NH). ^{13}C (DMSO, 62.89 MHz): 24.52 (CH_2–C_6H_5), 106.93, 113.31 (Cq), 114.26, 115.08, 118.81, 120.51, 122.22 (Cq), 122.41 (Cq), 123.05, 123.29, 130.30 (Cq), 136.72 (Cq), 158.59 (C═O). MS (ESI): $m/z = 250$ [M−H].