Tetrahedron Letters 51 (2010) 6086–6089

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A simple, solvent and catalyst-free green synthesis of novel *N*-[(1*H*-indol-3-yl)arylmethyl]heteroarylamines

Abolfazl Olyaei [a,*], Bahareh Shams [a], Mahdieh Sadeghpour [b], Fatemeh Gesmati [a], Zeinab Razaziane [a]

[a] Department of Chemistry, Payame Noor University (PNU), Qazvin, Iran
[b] Department of Chemistry, Islamic Azad University, Takestan Branch, Qazvin, Iran

ARTICLE INFO

Article history:
Received 6 June 2010
Revised 18 July 2010
Accepted 30 July 2010
Available online 6 August 2010

ABSTRACT

One-pot, three-component coupling reactions of indole, aromatic aldehydes, and heteroaryl amines under solvent-free conditions lead to the formation of the corresponding novel 3-[(*N*-heteroaryl)-(aryl)methyl]indoles in moderate to high yields. The key features of this multi-component reaction are the simple reaction procedure, no organic solvent or acid catalyst, and easy product separation without further purification.

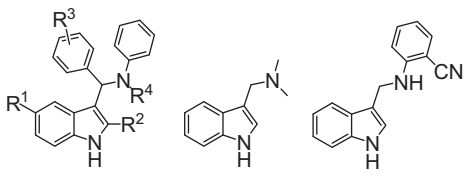
In recent years, significant interest has been devoted to the preparation of substituted indoles due to their varied biological activities including antioxidationantioxidant, antibacterial, and insecticidal.[1] They also act as colon cancer cell and tumor growth inhibitors[1d] and are employed as valuable antibiotics.[1a]

Among various derivatives of indoles, 3-substituted indoles have been much studied and several synthetic methods have been developed for the preparation of these compounds using indole or 3-indolecarboxaldehyde as starting materials. The Mannich reaction,[2] catalyzed Friedel–Crafts alkylation reactions of indoles,[3] conjugate addition of indoles to unsaturated carbonyl compounds, and the reaction of two equivalents of indoles with carbonyl groups in the presence of either protic[4,5] or Lewis acids[6–8] are considered as powerful carbon-carbon bond forming processes to afford 3-substituted indoles. Among 3-substituted indoles, 3-[(*N*-alkylanilino)(aryl)methyl]indoles have not been studied in detail and only a few synthetic methods have been developed for their preparation. These involve three-component reactions of indoles, benzaldehydes and *N*-alkylanilines or indole-3-carbaldehydes, and amines in the presence of an acid catalyst, such as phosphomolybdic acid (PMA) together with silica (SiO_2) or 2,4,6-trichloro-1,3,5-triazine (TCT) (Fig. 1).[9–11] 3-Indolylmethanamine derivatives are important intermediates for natural and natural-like products.[12]

To the best of our knowledge, the synthesis of 3-substituted indoles via condensation of heteroaryl amines, aromatic aldehydes, and indole has not previously been reported. In this article, in continuation of our work on the development of solvent-free conditions in one-pot, multi-component reactions,[13,14] we describe the synthesis of a series of novel 3-[(*N*-heteroaryl)(aryl)methyl]indoles via a simple three-component, one-pot method, using aromatic aldehydes, heteroaryl amines, and indole in the absence of an acid catalyst and under solvent-free conditions. As such, the utilization of environment-friendly conditions (absence of organic solvent) gives the product not only via an easy work-up procedure, but also in accordance with green chemistry principles.

As a model reaction, we initially examined the one-pot, three-component reaction of indole, 2-aminopyrimidine, and benzaldehyde in water in the presence of formic acid as the catalyst under reflux conditions. It was found that at least 12 h were needed for the reaction to be completed. After cooling, the pinkish precipitate was filtered. Analysis of the product indicated that pure 1*H*,1′*H*-3,3′-phenylmethanediyl-bis-indole (**1**) had been obtained. It should be noted that the reaction of indole and benzaldehyde in formic acid did not proceed under the reaction conditions (Scheme 1). Therefore, it might be concluded that *N*-[(1*H*-indole-3-yl)(phenyl)-methyl]pyrimidine-2-amine (**4a**) is initially formed as an intermediate. Then, in the presence of the acid catalyst, 2-aminopyrimidine is eliminated and the resulting intermediate **5** is attacked by indole to give the 3-substituted indole (**1**). The proposed mechanism is shown in Scheme 1.

When this reaction was carried out under solvent-free conditions at 70–120 °C, the reaction proceeded to completion in 2 h. The mixture was subjected to column chromatography (silica gel,

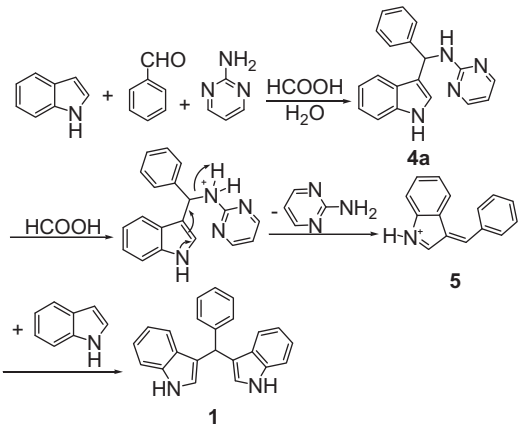


R^1: H, Br, OMe; R^2: H, Me; R^3: H, 4-NO_2, 4-Cl, 3-OH, 3,4-$(OMe)_2$, 3,4,5-$(OMe)_3$, 4-OMe, 3-OMe, 4-Me; R^4: Me, Et, Pr

Figure 1. Examples of 3-substituted indoles.

* Corresponding author. Tel.: +98 281 2224024; fax: +98 281 2226400.
E-mail address: Olyaei_a@pnu.ac.ir (A. Olyaei).

0040-4039/$ - see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2010.07.175



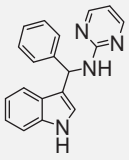
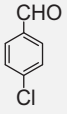
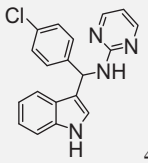
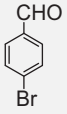
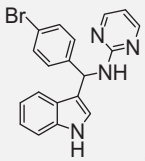
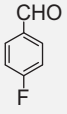
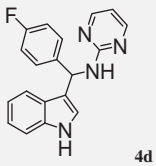
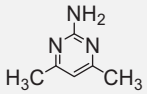
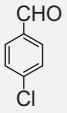
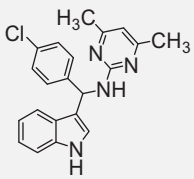
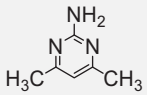
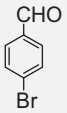
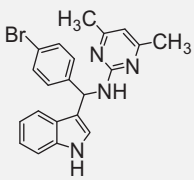
Scheme 1. Proposed mechanism for the synthesis of bis(indolyl)methane **1**.

hexane/EtOAc) to afford two products including bis(indolyl)methane **1** and compound **4a**. To avoid formation of compound **1**, the same reaction was repeated in the absence of the acid catalyst. Under these conditions, bis(indolyl)methane was formed 5% and the 3-[(*N*-heteroaryl)(aryl)methyl]indole was obtained as the major product. Our investigation demonstrated that the best result was obtained at 80 °C and the reaction was complete in 2 h.

One-pot, three-component coupling reactions of indole, aromatic aldehydes (benzaldehyde, 4-chlorobenzaldehyde, 4-bromobenzaldehyde, 4-fluorobenzaldehyde, 4-nitrobenzaldehyde, 2-chlorobenzaldehyde, and 2-chloro-6-fluorobenzaldehyde) **2a–g**, and heteroaryl amines (2-aminopyrimidine, 2-aminopyridine, and 2-amino-4,6-dimethylpyrimidine) **3a–c** at 80 °C afforded 3-[(*N*-heteroaryl)(aryl)methyl]indoles **4a–l** in moderate to high yields (Table 1, Scheme 2). After completion, ethanol was added to the reaction mixture and the solution was poured into water. The resulting colorless precipitate was filtered and dried.[15]

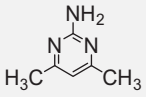
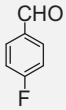
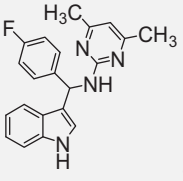
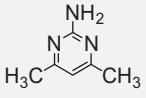
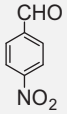
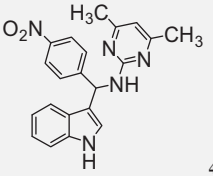
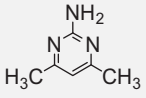
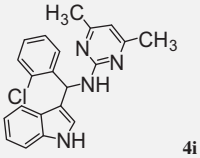
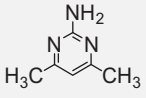
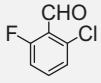
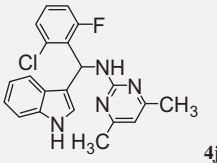
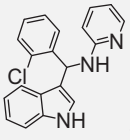
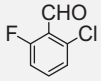
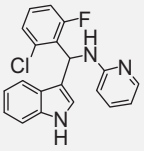
The crude product was stirred in boiling *n*-hexane and filtered to afford pure product. Mechanistically, we assume that when the heteroaryl amine is treated with an aldehyde, an imine intermediate is formed which is attacked by indole to give the 3-substituted indole. Identification of products **4a–l** was carried out on the basis of spectroscopic information. For example, the ^{1}H NMR spectrum of compound **4b** showed a sharp singlet for the indole-*NH* at δ 10.95. The methine proton and NH proton of the amine appeared

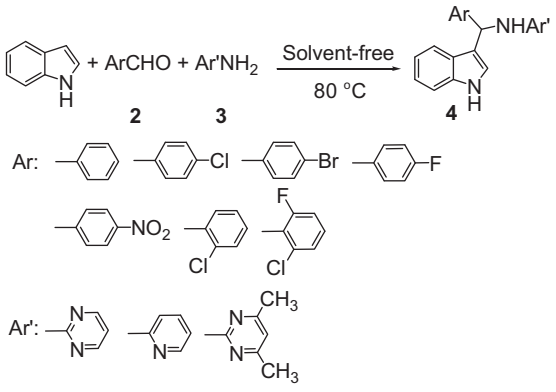
Table 1
Synthesis of 3-substituted indoles under solvent-free conditions at 80 °C

Entry	Amine	Aldehyde	Product	Time (h)	Yield (%)	Mp (°C)
1			 **4a**	3	90	182–183
2			 **4b**	4	87	161–163
3			 **4c**	6	75	155–157
4			 **4d**	2.5	89	180–182
5			 **4e**	3.5	80	214–216
6			 **4f**	4	88	219–220

(*continued on next page*)

Table 1 (*continued*)

Entry	Amine	Aldehyde	Product	Time (h)	Yield (%)	Mp (°C)
7			 **4g**	4	90	191–193
8			 **4h**	5	92	204–205
9			 **4i**	4	87	237–238
10			 **4j**	4	84	178–179
11			 **4k**	1.5	85	174–176
12			 **4l**	2	83	141–142



Scheme 2. Synthesis of 3-[(*N*-heteroaryl) (aryl)methyl]indoles **4**.

as two doublets at about δ 6.57 and 7.97 and the 4-substituted phenyl protons occurred as two well-resolved AB spin systems at δ 7.34 and 7.48. The pyrimidinyl moieties gave two well-resolved AB_2 spin systems at δ 6.59 and 8.30. Upon addition of D_2O, the NH signals disappeared and the methine proton collapsed to a singlet.

In summary, we have developed a convenient and environmentally green methodology for the synthesis of novel 3-substituted indoles in the absence of an acid catalyst under solvent-free conditions in moderate to high yields. The simple reaction procedure, generality, easy product separation, and purification make this protocol attractive. To the best of our knowledge, this is the first report on the synthesis of 3-[(*N*-heteroaryl)(aryl)methyl]indole derivatives.

Acknowledgment

The authors thank the Research Council of Payame Noor University of Qazvin for financial support.

Supplementary data

Supplementary data (spectroscopic data of products **4c**–**l**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.175.

References and notes

1. (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1996; (b) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970; (c) Jiang, B.; Yang, C. G.; Wang, J. *J. Org. Chem.* **2001**, *66*, 4865; (d) Zhang, H. C.; Bonaga, L. V. R.; Ye, H.; Derian, C. K.; Damiano, B. P.; Maryanoff, B. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2863.
2. (a) Snyder, H. R.; Smith, C. W.; Stewart, J. M. *J. Am. Chem. Soc.* **1944**, *66*, 200; (b) Dai, H. G.; Li, J. T.; Li, T. S. *Synth. Commun.* **2006**, *36*, 1829.

3. (a) Ke, B.; Qin, Y.; He, Q.; Huang, Z.; Wang, F. *Tetrahedron Lett.* **2005**, *46*, 1751; (b) Zhao, J. L.; Liu, L.; Zhang, H. B.; Wu, Y. C.; Wang, D.; Chen, Y. J. *Synlett* **2006**, 96.
4. (a) Szmuszkovicz, J. *J. Am. Chem. Soc.* **1957**, *79*, 2819; (b) Iqbal, Z.; Jackson, A. H.; Rao, K. R. N. *Tetrahedron Lett.* **1988**, *29*, 2577; (c) Reddy, A. V.; Ravinder, K.; Reddy, V. L. N.; Goud, T. V.; Ravikanth, V.; Venkateswarlu, Y. *Synth. Commun.* **2003**, *33*, 3687.
5. (a) Roomi, M.; MacDonald, S. *Can. J. Chem.* **1970**, *48*, 139; (b) Gregorovich, B.; Liang, K.; Clugston, D.; MacDonald, S. *Can. J. Chem.* **1968**, *46*, 3291.
6. (a) Harrington, P. E.; Kerr, M. A. *Synlett* **1996**, 1047; (b) Harrington, P. E.; Kerr, M. A. *Can. J. Chem.* **1998**, *76*, 1256.
7. (a) Babu, G.; Sridhar, N.; Perumal, P. T. *Synth. Commun.* **2000**, *30*, 1609; (b) Chen, D.; Yu, L.; Wang, P. G. *Tetrahedron Lett.* **1996**, *37*, 4467; (c) Mi, X.; Luo, S.; He, J.; Cheng, J. P. *Tetrahedron Lett.* **2004**, *45*, 4567; (d) Nagarajan, R.; Perumal, P. T. *Tetrahedron* **2002**, *58*, 1229; (e) Wang, L.; Han, J. H.; Sheng, T.; Fan, J. Z.; Tang, X. *Synlett* **2005**, 337.
8. (a) Bandini, M.; Cozzi, P. G.; Giacomini, M.; Melchiorre, P.; Selva, S.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 3700; (b) Yadav, J. S.; Abraham, S.; Subba Reddy, B. V.; Sabitha, G. *Tetrahedron Lett.* **2001**, *42*, 8063; (c) Yadav, J. S.; Abraham, S.; Subba Reddy, B. V.; Sabitha, G. *Synthesis* **2001**, 2165; (d) Manabe, K.; Aoyama, N.; Kobayashi, S. *Adv. Synth. Catal.* **2001**, 174; (e) Yadav, J. S.; Subba Reddy, B. V.; Murthy, V. S. R.; Mahesh Kumar, G.; Madan, C. *Synthesis* **2001**, 783; (f) Kumar, A.; Sharma, S.; Maurya, R. A. *Tetrahedron Lett.* **2009**, *50*, 5937; (g) Fridkin, G.; Boutard, N.; Lubell, W. D. *J. Org. Chem.* **2009**, *74*, 5603; (h) Kobayashi, K.; Shirai, Y.; Konishi, H. *Heterocycles* **2009**, *78*, 2033.
9. Bello, J. S.; Amado, D. F.; Kouznetsov, V. V. *Rev. Soc. Quim Peru* **2008**, *74*, 190.
10. Das, B.; Kumar, J. N.; Kumar, A. S.; Damodar, K. *Synthesis* **2010**, 914.
11. Srihari, P.; Singh, V. K.; Bhunia, D. C.; Yadav, J. S. *Tetrahedron Lett.* **2009**, *50*, 3763.
12. Wynne, J. H.; Stalick, W. M. *J. Org. Chem.* **2002**, *67*, 5850.
13. Shockravi, A.; Sadeghpour, M.; Olyaei, A. *Synth. Commun.* **2009**, *39*, 2347.
14. Shockravi, A.; Sadeghpour, M.; Olyaei, A. *J. Chem. Res.* **2009**, 556.
15. *General procedure for the synthesis of 3-substituted indoles* (**4**)*:* A mixture of heteroaryl amine (1 mmol) and aromatic aldehyde (1 mmol) was stirred in a preheated oil bath at 80 °C. Indole (1 mmol) was added after 10 min and the mixture was heated for the appropriate amount of time as indicated in Table 1. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion, the reaction mixture was cooled to room temperature and EtOH (5 mL) was added. The solution was poured into water (50 mL). The colorless precipitate that formed was filtered, washed with H_2O and dried. The crude product was stirred for 5 min in boiling *n*-hexane and the resulting white precipitate was filtered. The product **4** thus obtained was found to be pure upon TLC examination.

N-[(1H-Indole-3-yl)(phenyl)methyl]pyrimidine-2-amine (**4a**): IR (KBr): 3220, 3168, 1599, 1528, 1450, 1140 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ: 6.57 (t, 1H, *J* = 4.7 Hz, pyrimidine-H5), 6.62 (d, 1H, *J* = 9.0 Hz, *CH*), 6.91–7.52 (m, 10H, indole-H and Ph-H), 7.93 (d, 1H, *J* = 9.0 Hz, pyrimidine-NH), 8.29 (d, 2H, *J* = 4.7 Hz, pyrimidine-H4, H6), 10.92 (s, 1H, indole-NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 51.98, 111.12, 112.37, 117.94, 119.40, 119.65, 122.00, 124.23, 126.87, 127.38, 128.05, 128.90, 137.28, 144.61, 158.85, 162.48; MS (EI): *m/z* 300 [M^+], 221, 206, 204, 178, 118, 80; Anal. Calcd for $C_{19}H_{16}N_4$: C, 76.00; H, 5.33; N, 18.66. Found: C, 76.10; H, 5.29; N, 18.70.

N-[(1H-Indole-3-yl)(4-chlorophenyl)methyl]pyrimidine-2-amine (**4b**): IR (KBr): 3235, 1592, 1523, 1451, 1419, 1092 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ: 6.57 (d, 1H, *J* = 8.9 Hz, *CH*), 6.59 (t, 1H, *J* = 4.7 Hz, pyrimidine-H5), 6.92–7.41 (m, 5H, indole-H), 7.37 (d, 2H, *J* = 8.4 Hz, ph-H), 7.52 (d, 2H, *J* = 8.4 Hz, ph-H), 7.97 (d, 1H, *J* = 8.9 Hz, pyrimidine-NH), 8.30 (d, 2H, *J* = 4.7 Hz, pyrimidine-H4, H6), 10.95 (s, 1H, indole-NH); ^1H NMR (500 MHz, DMSO-d_6 + D_2O) δ: 6.52 (s, 1H, CH), 6.59 (t, 1H, *J* = 4.7 Hz, pyrimidine-H5), 6.91–7.36 (m, 5H, indole-H), 7.34 (d, 2H, *J* = 8.4 Hz, ph-H), 7.48 (d, 2H, *J* = 8.4 Hz, ph-H), 8.25 (d, 2H, *J* = 4.7 Hz, pyrimidine-H4, H6); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 51.48, 111.30, 112.42, 117.39, 119.49, 119.59, 122.09, 124.34, 126.74, 128.88, 129.92, 131.90, 137.29, 143.67, 158.86, 162.39; MS (EI): *m/z* 336 [M^+ (^{37}Cl)], 334 [M^+ (^{35}Cl)], 300, 255, 240, 218, 204, 176, 118, 95, 80. Anal. Calcd for $C_{19}H_{15}ClN_4$: C, 68.16; H, 4.48; N, 16.74. Found: C, 68.20; H, 4.50; N, 16.81.