Tetrahedron Letters 50 (2009) 3959–3962

Contents lists available at ScienceDirect

Tetrahedron Letters

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

$InCl_3$-catalyzed efficient one-pot synthesis of 2-pyrrolo-3′-yloxindoles

Gnanamani Shanthi, Paramasivan T. Perumal *

Organic Chemistry Division, Central Leather Research Institute, Adyar, Chennai 600 020, India

ARTICLE INFO

Article history:
Received 2 December 2008
Revised 17 April 2009
Accepted 22 April 2009
Available online 3 May 2009

Keywords:
$InCl_3$
Three component
3-Phenacylideneoxindole
β-Keto ester
Paal–Knorr condensation

ABSTRACT

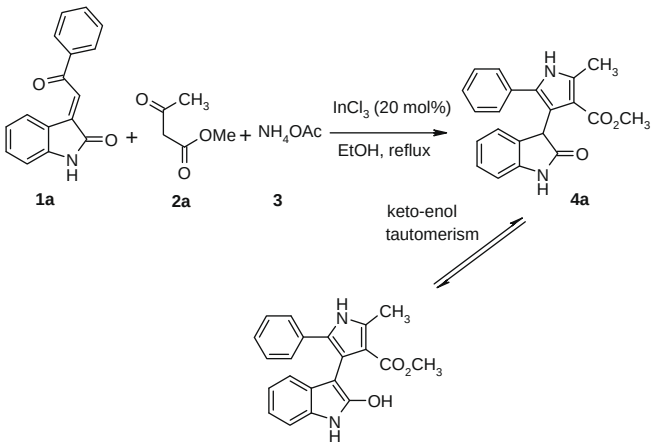
An $InCl_3$-catalyzed one-pot synthesis of 2-pyrrolo-3′-yloxindoles was achieved via three-component reaction of 3-phenacylideneoxindole, β-keto ester, and ammonium acetate at reflux by a sequential Michael addition followed by Paal–Knorr condensation.

© 2009 Elsevier Ltd. All rights reserved.

Multicomponent reactions (MCRs) are special types of synthetically useful organic reactions in which three or more different starting materials react to give a final product in a one-pot procedure. MCRs are powerful tools in the modern drug discovery process and allow the fast, automated, and high-throughput generation of organic compounds.[1] In the past decades, there have been tremendous developments in three- and four-component reactions and great efforts have been and still are being made to find and develop new MCRs.[2]

Pyrroles are one of the most prevalent heterocyclic compounds, which are present as the basic cores in many natural products,[3] potent pharmaceutical compounds,[4] and various kinds of functional materials.[5] Despite numerous diverse approaches toward the synthesis of pyrroles developed so far,[6] it is still challenging to prepare polysubstituted pyrroles with various substituents from readily available building blocks. In addition, oxindoles are attractive targets in organic synthesis because of their significant biological activities as well as wide-ranging utility as synthetic intermediates for alkaloids, drug candidates, and clinical pharmaceuticals.[7] To the best of our knowledge, there have been only two reports on the synthesis of pyrrolo oxindoles. Previously, Bergmann et al.[8] reported the synthesis of pyrrolo oxindoles from 3-acetonylideneoxindole and 3-amino crotonates in toluene under reflux for several hours. Muthusamy et al.[9] synthesized less substituted 2-pyrrol-3′-yloxindoles from 3-diazooxindoles and pyrroles in the presence of rhodium(II) acetate catalyst. In view of their importance, the development of a new and simple method for the synthesis of highly substituted pyrrole moiety is of importance.

Lately, the utility of indium(III) Lewis acids[10] in organic synthesis has received a great deal of interest due to their relatively low toxicity, stability in air and water and recyclability. As part of our current studies on the design of new routes for the preparation of biologically active heterocyclic compounds and in the application of $InCl_3$[11] in organic synthesis, we herein disclose a simple and improved method for the synthesis of 2-pyrrolo-3′-yloxindoles using a catalytic amount of $InCl_3$ (20 mol %) in ethanol at reflux in a shorter reaction time (10–15 min). To the best of our knowledge, this is the first report for the synthesis of 2-pyrrolo-3′-yloxindoles from 3-phenacylideneoxindole, β-keto ester, and ammonium acetate (Scheme 1).



Scheme 1.

* Corresponding author. Tel.: +91 44 24913289; fax: +91 44 24911589.
E-mail address: ptperumal@gmail.com (P.T. Perumal).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.04.089

Table 1
Catalytic activity of various Lewis acids on the three-component reaction[a]

Entry	Catalyst	Time (h)	Yield (%)
1	None	2.5	20
2	$SnCl_2.H_2O$	1.5	48
3	NH_2SO_3H	1.5	45
4	CAN	1.0	40
5	$Bi(OTf)_3$	1.0	56
6	$BiCl_3$	1.0	60
7	$In(OTf)_3$	0.50	85
8	$InCl_3$	0.25	92

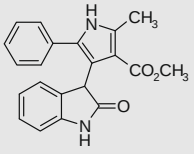
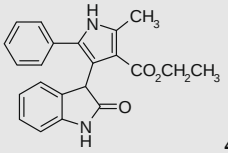
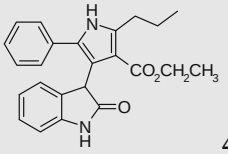
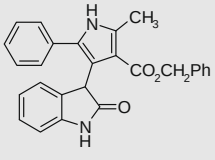
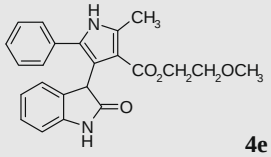
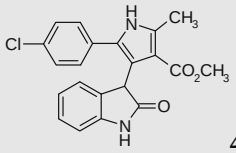
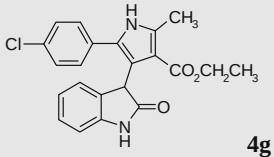
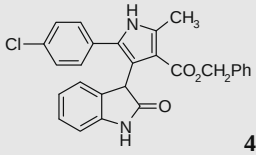
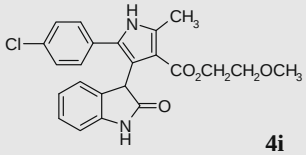
[a] Reaction of phenacylideneoxindole, methyl acetoacetate, and ammonium acetate in ethanol at reflux.

In order to study the scope and limitations of the three-component reaction, various Lewis acid catalysts, including $SnCl_2{\cdot}H_2O$, NH_2SO_3H, CAN, $Bi(OTf)_3$, $BiCl_3$, $In(OTf)_3$, and $InCl_3$ were investigated (Table 1). The best overall yield (92%) was obtained with $InCl_3$ in ethanol. Optimum results were obtained using 20 mol % of $InCl_3$.

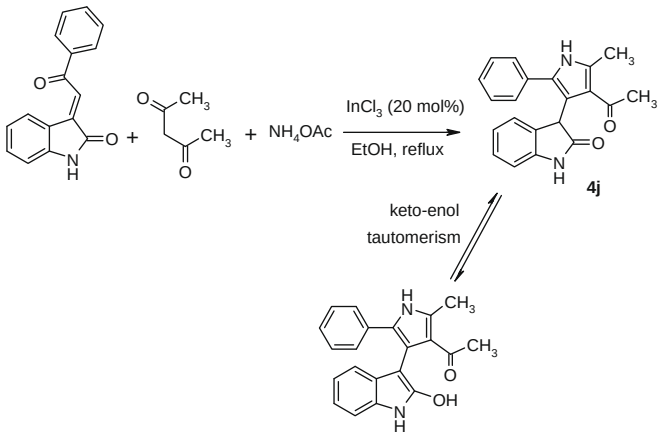
The reaction was carried out with 3-phenacylideneoxindole[12] **1** (1 equiv), β-keto ester **2** (1 equiv), and ammonium acetate **3** (2.5 equiv) catalyzed by $InCl_3$ (20 mol %) in ethanol and was refluxed for 10–15 min. The product precipitated from the reaction mixture.[13] This protocol is remarkably simple and requires no purification technique like column chromatography.

Table 2 summarizes our results on the one-pot reaction of various 3-phenacylideneoxindole and β-keto ester with ammonium acetate. All the reactions went smoothly and afforded the

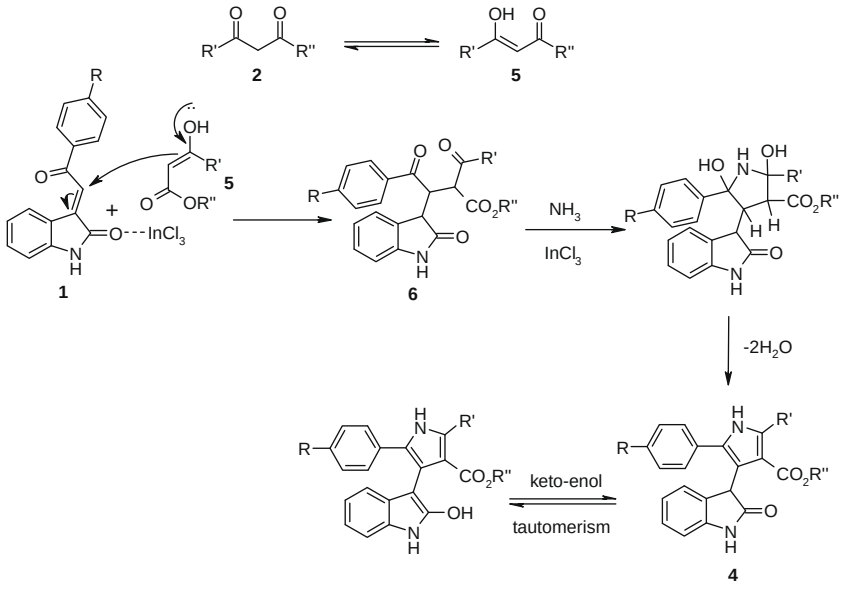
Table 2
Synthesis of 2-pyrrolo-3′-yloxindoles **4a–i**

S.no	Product (**4**) (keto:enol)[a]	Time (min)	Yield[b] (%)
1	 **4a** (10:1)	10	92
2	 **4b** (10:1)	10	93
3	 **4c** (8:1)	15	90
4	 **4d** (9:1)	10	94
5	 **4e** (7:1)	15	91
6	 **4f** (9:1)	10	93
7	 **4g** (8:1)	15	92
8	 **4h** (10:1)	15	88
9	 **4i** (8:1)	15	90

[a] Ratio obtained from ^1H NMR analysis of the NH protons.
[b] Isolated yield.



Scheme 2.



Scheme 3.

corresponding highly substituted 2-pyrrolo-3′-yloxindoles in good yields.

The structures of compounds **4a–i** were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis.[14] The IR spectrum of **4a** showed absorptions at 3356, 3207, 1694, and 1671 cm^{-1} indicating the presence of –NH and –C═O groups, respectively. In the ^{1}H NMR spectrum, aromatic signals were seen at δ 6.79–7.52, methyl and methoxy protons at δ 2.40 and 3.17, methine proton was observed at δ 4.55, and two broad singlets at δ 10.32 and 11.61 showed the presence of two –NH groups (D_2O exchangeable). Carbonyl carbons resonated at δ 164.4 (ester carbonyl) and 178.5 (oxindole carbonyl) in the ^{13}C NMR spectrum. The mass spectrum of **4a** displayed the molecular ion (M^+) peak at *m/z* 360.

This method offers several advantages such as milder reaction condition, shorter reaction time, high yield, and simple experimental and isolation procedures making it an efficient route to the synthesis of 2-pyrrolo-3′-yloxindoles.

To further explore the potential of this protocol for the synthesis of pyrrolo oxindoles, we also investigated the one-pot reaction involving 3-phenacylideneoxindole, acetylacetone, and ammonium acetate and the corresponding pyrrolo oxindole **4j** (keto:enol = 7:1) was obtained in 93% yield (Scheme 2).

The proposed mechanism involves the Michael addition of enol **5** onto the 3-phenacylideneoxindole **1** as shown in Scheme 3, then in situ generated 1,4-dicarbonyl compound **6** undergoes Paal–Knorr condensation with ammonium acetate to afford product **4**.

In summary, we have demonstrated an improved, one-pot, three-component reaction that offers a simple and clean method for the synthesis of 2-pyrrolo-3′-yloxindoles from 3-phenacylideneoxindole, 1,3-dicarbonyl, and ammonium acetate catalyzed by indium(III) chloride. Further, development of new multicomponent reactions using indium(III) chloride as a catalyst is in progress. Biological evaluation of these derivatives is underway.

Acknowledgment

One of the authors, G.S. thanks the Council of Scientific and Industrial Research, New Delhi, India, for the research fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.089.

References and notes

1. (a) Ugi, I.; Domling, A.; Werner, B. *J. Heterocycl. Chem.* **2000**, *37*, 647; (b) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321; (c) Ugi, I.; Heck, S. *Comb. Chem. High Throughput Screening* **2001**, *4*, 1.
2. (a) Shestopalov, A. M.; Emeliyanova, Y. M.; Shestiopolov, A. A.; Rodinovskaya, I. A.; Niazimbetova, A. I.; Evans, D. H. *Org. Lett.* **2002**, *4*, 423; (b) Bagley, M. C.; Cale, J. W.; Bower, J. *Chem. Commun.* **2002**, 1682; (c) Bora, U.; Saikia, A.; Boruah, R. C. *Org. Lett.* **2003**, *5*, 435; (d) Dallinger, D.; Gorobets, N. Y.; Kappe, C. O. *Org. Lett.* **2003**, *5*, 1205.
3. (a) Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. R. *Nat. Prod. Rep.* **2006**, *23*, 517; (b) Furstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582; (c) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753.
4. (a) Trofimov, B. A.; Sobenina, L. N.; Demenev, A. P.; Mikhaleva, A. I. *Chem. Rev.* **2004**, *104*, 2481; (b) Sayah, B.; Pelloux-Leon, N.; Vallee, Y. *J. Org. Chem.* **2000**, *65*, 2824; (c) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54.
5. (a) Plitt, P.; Gross, D. E.; Lynch, V. M.; Sessler, J. L. *Chem. Eur. J.* **2007**, *13*, 1374; (b) Zhao, W.; Carreira, E. M. *Chem. Eur. J.* **2006**, *12*, 7254; (c) Gale, P. A. *Acc. Chem. Res.* **2006**, *39*, 465; (d) Nadeau, J. M.; Swager, T. M. *Tetrahedron* **2004**, *60*, 7141.
6. (a) Dey, S.; Pal, C.; Nandi, D.; Giri, V. S.; Zaidlewicz, M.; Krzeminski, M.; Smentek, L.; Hess, B. A.; Gawronski, J.; Kwit, M.; Babu, N. J.; Nangia, A.; Jaishankar, P. *Org. Lett.* **2008**, *10*, 1373; (b) Khalili, B.; Jajarmi, P.; Eftekhari-Sis, B.; Hashemi, M. M. *J. Org. Chem.* **2008**, *73*, 2090; (c) Galliford, C. V.; Scheidt, K. A. *J. Org. Chem.* **2007**, *72*, 1811; (d) St. Cyr, D. J.; Martin, N.; Arndtsen, B. A. *Org. Lett.* **2007**, *9*, 449.
7. (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, *63*, 2209; (b) Dounay, A. B.; Hatanaka, K.; Kodanko, J. J.; Oestreich, M.; Overman, L. E.; Pfeifer, L. A.; Weiss, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 6261; (c) Xue, J.; Zhang, Y.; Wang, X.; Fun, H. K.; Xu, J.-H. *Org. Lett.* **2000**, *2*, 2583; (d) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209.
8. Rehn, S.; Bergman, J. *Tetrahedron* **2005**, *61*, 3115.
9. Muthusamy, S.; Gunanathan, C. *Synlett* **2002**, 1783.
10. (a) Frost, C. G.; Chauhan, K. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015; (b) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Curr. Org. Chem.* **2003**, *7*, 7; (c) Frost, C. G.; Hartley, J. P. *Mini-Rev. Org. Chem.* **2004**, *1*, 1.
11. (a) Shanthi, G.; Perumal, P. T. *Tetrahedron Lett.* **2008**, *49*, 7139; (b) Shanthi, G.; Perumal, P. T. *Tetrahedron Lett.* **2007**, *48*, 6785; (c) Shanthi, G.; Subbulakshmi, G.; Perumal, P. T. *Tetrahedron* **2007**, *63*, 2057; (d) Babu, G.; Nagarajan, R.; Natarajan, R.; Perumal, P. T. *Synthesis* **2000**, 661; (e) Babu, G.; Perumal, P. T. *Aldrichim. Acta* **2000**, *33*, 16; (f) Babu, G.; Perumal, P. T. *Tetrahedron* **1998**, *54*, 1627; (g) Babu, G.; Perumal, P. T. *Tetrahedron Lett.* **1997**, *38*, 5025.
12. Lindwall, H. G.; Maclennan, J. S. *J. Am. Chem. Soc.* **1932**, *54*, 4739.
13. *General procedure for the synthesis of 2-pyrrolo-3′-yloxindoles* **4a–j**: To a stirred mixture of 3-phenacylideneoxindole **1** (1 equiv), 1,3-dicarbonyl compound **2**

(1 equiv), and ammonium acetate **3** (2.5 equiv) in ethanol, catalytic amount of $InCl_3$ (20 mol %) was added and refluxed for 10–15 min as mentioned in Table 2. Upon cooling, the product precipitated from the reaction mixture, which was filtered, dried, and recrystallized from ethanol.

14. *Methyl 2-methyl-5-phenyl-4-(2-oxo-2,3-dihydro-1H-indol-3-yl)-1H-pyrrole-3-carboxylate* **4a**: White solid. mp: 316–317 °C. IR (KBr): 3357, 3207, 1694, 1671, 1463, 1103, 696 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 2.40 (s, 3H), 3.17 (s, 3H), 4.55 (s, 1H), 6.79 (m, 3H), 7.08 (m, 1H), 7.31 (t, 1H, J = 7.7 Hz), 7.42 (t, 2H, J = 7.7 Hz), 7.52 (d, 2H, J = 7.7 Hz), 10.32 (s, 1H, NH, D_2O exchangeable), 11.61 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6): δ 12.9, 44.6, 49.2, 108.6, 109.4, 113.9, 120.9, 122.4, 127.0, 127.3, 128.8, 131.5, 131.7, 131.8, 136.5, 142.9, 164.4, 178.5. MS (m/z): 346 (M^+). Anal. Calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.75; H, 5.16; N, 8.01.
Ethyl 2-methyl-5-phenyl-4-(2-oxo-2,3-dihydro-1H-indol-3-yl)-1H-pyrrole-3-carboxylate **4b**: White solid. mp: 317–318 °C. IR (KBr): 3354, 3211, 1700, 1668, 1465, 1100, 699 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 0.84 (t, 3H, J = 6.9 Hz), 2.46 (s, 3H), 3.69 (m, 2H), 4.59 (s, 1H), 6.76 (m, 3H), 6.97 (m, 1H), 7.09 (m, 5H), 10.35 (s, 1H, NH, D_2O exchangeable), 11.63 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.1, 13.9, 44.7, 57.8, 108.7, 109.7, 113.7, 120.8, 122.4, 126.9, 127.3, 127.7, 127.8, 128.8, 131.6, 131.7, 131.8, 136.6, 142.9, 163.9, 178.4. MS (m/z): 360 (M^+). Anal. Calcd for $C_{22}H_{20}N_2O_3$: C, 73.32; H, 5.59; N, 7.77. Found: C, 73.27; H, 5.52; N, 7.70.
2-Methyl-3-acetyl-5-phenyl-4-(2-oxo-2,3-dihydro-1H-indol-3-yl)-1H-pyrrole **4j** (Scheme 3): White solid. mp: 334–335 °C. IR (KBr): 3331, 3149, 1690, 1621, 1467, 1213, 697 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 2.08 (s, 3H), 2.50 (s, 3H), 4.44 (s, 1H), 6.74 (m, 3H), 7.05 (m, 1H), 7.31 (t, 1H, J = 6.9 Hz), 7.44 (t, 2H, J = 6.9 Hz), 7.47 (d, 2H, J = 7.7 Hz), 10.18 (s, 1H, NH, D_2O exchangeable), 11.54 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.6, 29.9, 44.8, 108.5, 114.2, 120.1, 120.5, 121.9, 126.7, 127.4, 127.8, 128.8, 131.0, 131.6, 131.9, 135.4, 143.4, 178.0, 191.7. MS (m/z): 330 (M^+). Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.27; H, 5.40; N, 8.41.