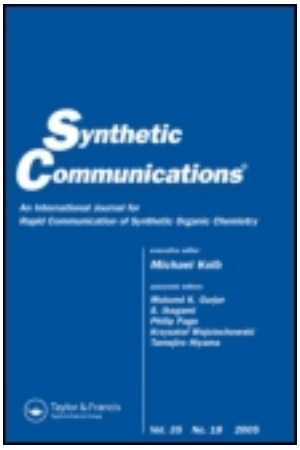


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Facile and Inexpensive Entry to Indeno[2,1-b]indol-6-one Nucleus

Giorgio Abbiati [a], Valentina Canevari [a], Elisabetta Rossi [a] & Alberto Ruggeri [a]
[a] Istituto di Chimica Organica "Alessandro Marchesini," Facoltà di Farmacia, Università degli Studi di Milano, Milan, Italy
Published online: 15 Aug 2006.

To cite this article: Giorgio Abbiati , Valentina Canevari , Elisabetta Rossi & Alberto Ruggeri (2005) Facile and Inexpensive Entry to Indeno[2,1-b]indol-6-one Nucleus, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 35:13, 1845-1850, DOI: 10.1081/SCC-200063981

To link to this article: http://dx.doi.org/10.1081/SCC-200063981

Synthetic Communications®, 35: 1845–1850, 2005

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1081/SCC-200063981

Facile and Inexpensive Entry to Indeno[2,1-*b*]indol-6-one Nucleus

Giorgio Abbiati, Valentina Canevari, Elisabetta Rossi, and Alberto Ruggeri
Istituto di Chimica Organica "Alessandro Marchesini," Facoltà di Farmacia, Università degli Studi di Milano, Milan, Italy

Abstract: Starting from simple indole, a straightforward and inexpensive four-step synthetic approach to indeno[2,1-*b*]indol-6-one nucleus is described.

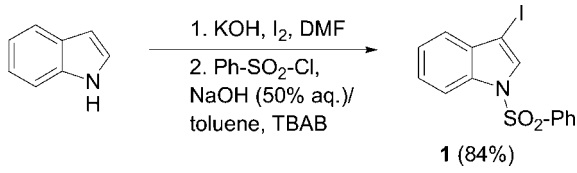
Keywords: Indeno[2,1-*b*]indol-6-ones, polycyclic indoles, Ullmann coupling

INTRODUCTION

Indeno[2,1-*b*]indol-6-ones are an interesting class of compounds structurally related to ellipticine,[1] a natural alkaloid characterized by a significant antitumor activity.[2,3] Recently, some hydroxy indeno[2,1-*b*]indol-6-one derivatives were investigated for their potential antioxidative properties,[4] and a patent concerning these compounds was recently filed.[5]

The synthesis of some indeno-indolones was previously achieved by means of a Japp–Klingemann reaction combined with the Fischer indole synthesis,[6] through two different palladium-catalyzed intramolecular reactions (the cyclisation of 2-(2-bromobenzoyl)-1-methyl-indole[7] and the cyclocarbonylation of 2-iodo-3-phenyl-indoles[8]), and finally by a double lithiation of 3-phenyl-indoles followed by treatment with ethyl *N*,*N*-dimethyl-carbamate.[9] Despite the usefulness and neatness of these approaches, some of them suffer from a few drawbacks, such as the high cost of the reagents

Received in Poland February 14, 2005
Address correspondence to Giorgio Abbiati, Istituto di Chimica Organica "Alessandro Marchesini," Facoltà di Farmacia, Università degli Studi di Milano, Via Venezian 21-20133, Milan, Italy. Tel.: +39 +2 50.31.44.74; Fax: +39 +2 50.31.44.76; E-mail: giorgio.abbiati@unimi.it



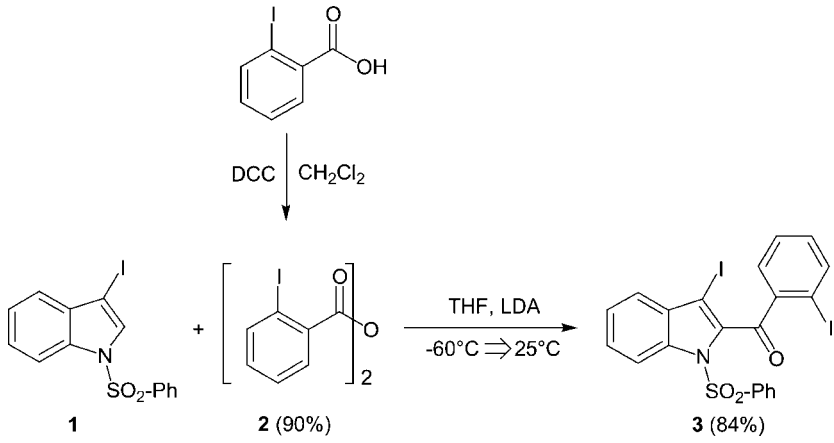
Scheme 1.

employed, multistep procedures, and less-than-satisfactory overall reaction yields. In connection with our ongoing interest in the synthesis of polycyclic indole derivatives,[10] in this article we present an alternative, simple, and inexpensive approach to the indeno[2,1-*b*]indol-6-one nucleus starting from indole.

RESULTS

The 3-iodo-1-phenylsulfonylindole **1** was prepared in good yields according to Sakamoto's procedure,[11] sequential alkaline iodination/nitrogen protection of indole (Scheme 1). The product was easily purified by crystallization with a mixture of petroleum ether/ethyl acetate.

The derivative **1** was transformed in the intermediate **3** by lithiation with lithium diisopropylamide (LDA) in THF at -60°C followed by reaction with the 2-iodo-benzoic acid-anhydride **2**; after the usual workup, the reaction mixture was purified by flash chromatography over silica gel, yielding the diiododerivative **3** in 84% yield (Scheme 2). The anhydride **2** was prepared in 90% yields by treatment of 2-iodobenzoic acid with dicyclohexyl-carbodiimide (DCC) in diethyl ether.



Scheme 2.

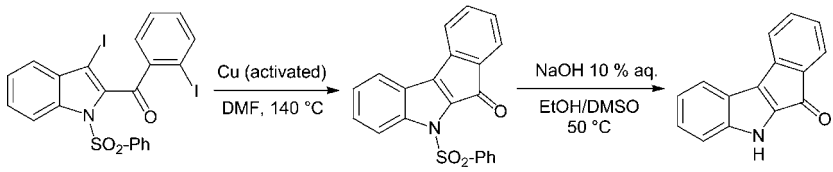
The cyclisation of derivative **3** was performed through a Ullmann-type coupling[12] in the presence of activated copper in DMF at 140°C, yielding quantitatively the *N*-protected indeno-indolone **4**. Finally, the desired product **5** was obtained in almost quantitative yields through alkaline hydrolysis of **4** in ethanol/dimethylsulfoxide at 50°C and purifying the reaction crude by flash chromatography over silica gel (Scheme 3). All structures were assigned on the basis of analytical and spectral data.

In summary, we developed an alternative synthetic route to indeno[2,1-*b*]indol-6-one nucleus starting from simple indole. The method offer several advantages, such as relatively cheap reagents, effortless experimental operation, and high overall process yield.

EXPERIMENTAL

All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents. Fluka silica gel F_{254} thin-layer plates were employed for thin-layer chromatography (TLC). Davisil silica gel LC 60A was employed for flash column chromatography. Melting points, measured with a Stuart Scientific SMP3 apparatus, are uncorrected. Infrared spectra were recorded on a FT-IR Perkin Elmer Spectrum One spectrophotometer using KBr tablets. Proton and carbon NMR spectra were recorded at room temperature, on Varian-Gemini 200 spectrometer. The APT or DEPT sequences were used to distinguish the methine and methyl carbon signals from those resulting from methylene and quaternary carbons. "PE" refers to the fraction of petroleum ether with boiling point of 40–60°C. "EtOAc" means ethyl acetate. Indole and 2-iodobenzoic acid were purchased respectively from Lancaster Synthesis Ltd. and Avocado Research Chemical Ltd.

3-Iodo-1-phenylsulfonylindole 1: To a well-stirred mixture of indole (2.95 g, 25.2 mmol) and powdered potassium hydroxide (5.65 g, 100.7 mmol) in DMF (13 mL) a solution of iodine (6.71 g, 26.5 mmol) in DMF (13 mL) was added dropwise. The reaction mixture was stirred at room temperature for 15 min



3 **4** (100%) **5** (98%)

Scheme 3.

and than poured into a stirred mixture of sodium bisulfite (2.00 g, 10.7 mmol) and 2% aqueous ammonia (350 mL). The light precipitate obtained was rapidly filtered off and added to a mixture of 20% aqueous sodium hydroxide (60 mL) and tetrabutylammonium bromide (0.8 g, 2.5 mmol). A solution of benzenesulfonylchloride (5.33 g, 30.2 mmol) in benzene (40 ml) was slowly added and the reaction mixture was vigorously stirred at room temperature for 2 h. After that, the organic layer was separated, washed with water (1 × 40 mL), dried over sodium sulfate, and filtered, and the solvent removed at reduced pressure. The resulting crude was recrystallized from PE/EtOAc, yielding the 3-iodo-1-phenylsulfonylindole **1** as a pale yellow solid (8.1 g, 84%). Mp: 126°C (lit.[10] 127–128). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.32–7.60$ (m, 6H, arom.), 7.73 (s, 1H, C2-H arom.), 7.89–8.02 (m, 3H, arom.) ppm.

2-Iodo-benzoic acid-anhydride 2: A mixture of 2-iodobenzoic acid (2.00 g, 8.06 mmol) and DCC (0.832 g, 4.03 mmol) in dry diethyl ether (10 mL) was vigorously stirred at rt for 2 h under a nitrogen atmosphere. The white precipitate was filtered off over a double layer of filter paper and washed with cold, dry diethyl ether (2 × 10 mL). The ethereal phase was evaporated under reduced pressure, yielding the 2-iodo-benzoic acid-anhydride **2** as a white solid (1.73 g, 90%). Mp: 68–72°C (lit.[11] 71–75). IR: $\nu = 1792$ (C═O), 987 (C–O) cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.24$ (dt, 1H, arom., $J = 8.1$, 1.8 Hz), 7.47 (dt, 1H, arom., $J = 7.5$, 1.1 Hz), 8.01 (dd, 1H, arom., $J = 8.1$, 1.8 Hz), 8.10 (dd, 1H, arom., $J = 7.5$, 1.1 Hz) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): $\delta = 128.5$, 132.5, 134.4, 142.4 (C-H arom.), 95.6, 132.7 (C quat. arom.), 161.5 (C═O) ppm. ESI-MS m/z (%): 478 [M$^+$] (20), 477 (100).

(1-Benzenesulfonyl-3-iodo-1*H*-indol-2-yl)-(2-iodo-phenyl)-methanone 3: LDA (0.78 mL, 2 M solution in heptane/THF/ethylbenzene, 1.56 mmol) was slowly added to a well-stirred solution of 3-iodo-1-phenylsulfonylindole **1** (0.30 g, 0.78 mmol) in dry THF at −60°C under a nitrogen atmosphere. The solution was stirred for 1.5 h, and after that a solution of 2-iodo-benzoic acid–anhydride **2** (0.75 mg, 1.56 mmol) in dry THF (3 ml) was added dropwise. The reaction mixture was allowed to warm at room temperature and the stirring was proceeded until no more starting product was detectable by TLC analysis. After 36 h the reaction mixture was concentred under reduced pressure, poured into water (40 mL), and extracted with dichloromethane (2 × 25 mL). The combined organic layers, dried over sodium sulfate, were evaporated to dryness and the crude purified by flash chromatography over a silica-gel column ($PE/CH_2Cl_2 = 8:2$), yielding **3** as a light yellow solid (0.41 g, 84%). Mp: 195–200°C (dec.). IR: $\nu = 1662$ (C═O), cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.21$ (dt, 1H, arom., $J = 7.3$, 1.5 Hz), 7.32–7.60 (m, 9H, arom.), 7.97–8.14 (m, 3H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): $\delta = 115.1$, 123.8, 125.2, 127.8, 128.2, 128.3, 129.5, 133.2, 133.6, 134.5, 142.3 (C-H arom.), 95.2, 110.9, 132.1, 136.4, 137.4,

137.5, 140.1 (C quat. arom.), 188.4 (C═O) ppm. ESI-MS m/z (%): 636 [$M^+ + Na$] (100).

5-Benzenesulfonyl-5*H*-indeno[2,1-*b*]indol-6-one 4: A stirred solution of **3** (0.20 g, 0.32 mmol) and activated copper powder[13] (0.060 g, 0.96 mmol) in DMF (6 mL) was heated at 140°C for 3 h. After cooling, the reaction mixture was poured into water (200 mL) and extracted with diethyl ether (2 × 50 mL). The organic layers were dried over sodium sulfate, filtered, and evaporated to dryness to afford crude **4** as a dark orange solid (0.116 g, 100%). NMR analysis demonstrated that the product obtained was sufficiently pure to be used without further purification. Mp: 198°C. IR: $\nu = 1709$ (C═O), cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 7.15$ (dt, 1H, arom., $J = 7.0$, 1.5 Hz), 7.22–7.60 (m, 8H, arom.), 7.73 (d, 1H, arom., $J = 7.3$), 8.15 (d, 2H, arom., $J = 7.5$), 8.31 (d, 1H, arom., $J = 8.4$) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): $\delta = 115.8$, 120.3, 122.0, 124.3, 125.1, 127.5, 128.8, 129.2, 129.6, 133.9, 134.6 (C-H arom.), 122.9, 134.8, 136.0, 137.1, 138.5, 142.8, 142.9 (C quat. arom.), 180.5 (C═O) ppm. ESI-MS m/z (%): 382 [$M^+ + Na$] (100).

5*H*-Indeno[2,1-*b*]indol-6-one 5: To a solution of **4** (0.100 g, 0.28 mmol) in EtOH (10 mL) and DMSO (1.5 mL), 10% aq. NaOH (0.6 mL) was slowly added. The reaction mixture was stirred at 50°C for 40 min. Thus, the reaction mixture was concentrated at reduced pressure, poured into water (100 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers, dried over sodium sulfate, were filtered and evaporated to dryness. The crude was purified by flash chromatography over a silica-gel column ($PE/CH_2Cl_2 = 3:1$), yielding **5** as a dark red solid (0.060 g, 98%). Mp: 257–259°C. IR: $\nu = 1694$ (C═O), 3434 (NH) cm^{-1}. ^1H NMR (DMSO, 200 MHz): $\delta = 7.00$ (dt, 1H, arom., $J = 7.2$, 1.7 Hz), 7.09–7.38 (m, 6H, arom.), 7.80 (d, 1H, arom., $J = 8.1$), 12.04 (bs, 1H, NH) ppm. ^{13}C NMR (DMSO, 200 MHz): $\delta = 115.0$, 120.1, 122.1, 122.4, 123.8, 126.9, 127.4, 134.9 (C-H arom.), 121.3, 134.6, 137.1, 137.2, 140.8, 143.7 (C quat. arom.), 184.3 (C═O) ppm. APCI(+)-MS m/z (%): 220 [$M^+ + Na$] (100).

REFERENCES

1. Goodwin, S.; Smith, A. F.; Horning, E. C. Alkaloids of *Ochrosia elliptica*. *J. Am. Chem. Soc.* **1959**, *81*, 1903–1908.
2. Dalton, L. K.; Demerac, S.; Elmes, B. E.; Loder, J. W.; Swan, J. M.; Telei, T. Synthesis of the tumor-inhibitory alkaloids, ellipticine, 9-methoxyellipticine, and related pyrido[4,3-b]carbazoles. *Aust. J. Chem.* **1967**, *20*, 2715–2727.
3. Svoboda, G. H.; Poore, G. A.; Montfort, M. L. Alkaloids of *Ochrosia maculata* Jacq. (*Ochrosia borbonica* Gmel.). Isolation of the alkaloids and study of the antitumor properties of 9-methoxyellipticine. *J. Pharm. Sci.* **1968**, *57*, 1720–1725.

4. Ostrovidov, S.; Franck, P.; Joseph, D.; Mattarello, L.; Kirsch, G.; Belleville, F.; Nabet, P.; Dousset, B. Screening of new antioxidant molecules using flow cytometry. *J. Med. Chem.* **2000**, *43*, 1762–1769.
5. Nifant'ev, I. E.; Kashulin, I. A.; Ivchenko, P. V.; Klusener, P. A. A.; Korndorffer, F. M.; De Kloe, K. P.; Rijsemus, J. J. H. Preparation of hetero-cyclopentadiene derivatives. PCT Int. Appl. WO2002092564, 2002.
6. Martarello, L.; Kirsch, G.; Wierzbicki, M. Synthesis of some new indeno-indoles. *Heterocycl. Commun.* **1997**, *3*, 51–56.
7. Kozikowski, A. P.; Ma, D. Palladium-catalyzed synthesis of annelated indoles. *Tetrahedron Lett.* **1991**, *32*, 3317–3320.
8. Campo, M. A.; Larock, R. C. Synthesis of fluoren-9-ones by the palladium-catalyzed cyclocarbonylation of *o*-halobiaryls. *J. Org. Chem.* **2002**, *67*, 5616–5620.
9. Kashulin, I. A.; Nifant'ev, I. E. Efficient method for the synthesis of hetarenoindanones based on 3-harylhetarenes and their conversion into hetarenoindenes. *J. Org. Chem.* **2004**, *69*, 5476–5479.
10. (a) Abbiati, G.; Beccalli, E. M.; Marchesini, A.; Rossi, E. Synthesis of β-carbolines from 2-acyl-1-benzensulfonil-3-iodo-1*H*-indoles. *Synthesis* **2001**, *16*, 2477–2483; (b) Abbiati, G.; Beccalli, E.; Arcadi, A.; Rossi, E. Novel intramolecular cyclization of N-alkynyl heterocycles containing proximate nucleophiles. *Tetrahedron Lett.* **2003**, *44*, 5331–5334; (c) Abbiati, G.; Beccalli, E. M.; Broggini, G.; Zoni, C. Regioselectivity on the palladium-catalyzed intramolecular cyclization of indole derivatives. *J. Org. Chem.* **2003**, *68*, 7625–7628; (d) Rossi, E.; Abbiati, G. Intramolecular palladium-catalyzed annulations: Advances in azapolycyclic indole synthesis. In *Targets in Heterocyclic Systems–Chemistry and Properties*; Attanasi, O. A., Spinelli, D., Eds.; Società Chimica Italiana: Rome, **2003**; Vol. 7, 86–107.
11. Sakamoto, T.; Kondo, Y.; Takazawa, N.; Yamanaka, H. Preparation and palladium-catalyzed arylation of indolylzinc halides. *J. Chem. Soc., Perkin Trans. 1* **1996**, *16*, 1927–1934.
12. Newman, M. S.; Cella, J. A. Intramolecular aromatic and aliphatic Ullmann reactions. *J. Org. Chem.* **1974**, *39*, 2084–2087.
13. Furniss, B. S.; Hannaford, A. J.; Rogers, B.; Smith, P. W. G.; Tatchell, A. R. Solventi e reagenti. In *Vogel Chimica Organica Pratica*, 2nd Ed. Ambrosiana: Milano, 1988; p. 322.