An Efficient Synthesis of New Aza-Substituted Indoles via Michael-Type Addition

Sinan Bayindir, Esra Erdogan, Haydar Kilic, Nurullah Saracoglu*

Department of Chemistry, Faculty of Sciences, Atatürk University, Erzurum 25240, Turkey
Fax +90(442)2360948; E-mail: nsarac@atauni.edu.tr

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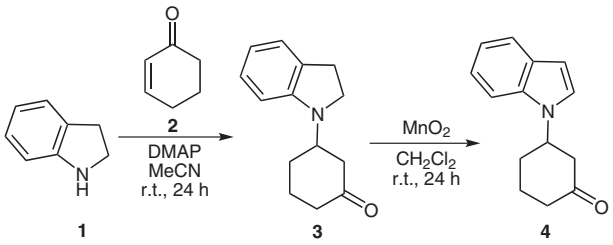
Abstract: An efficient method has been developed for the synthesis of new aza-substituted indoles. The methodology involves a two-step synthesis. The first step involves the Michael addition of indoline with various Michael acceptors. The other includes the oxidation of the indoline ring in the Michael adducts to an indole

Key words: alkylation, indoline, Michael addition, oxidation, catalyst

Indole subunits are of considerable interest both for the synthetic organic chemist and the medicinal chemist due to their remarkable range of biological and medicinal properties. Indole derivatives have been used to treat certain kinds of cancer, hypercholesterolemia, to prevent cardiovascular disease, or act as oral insulin mimics.[1–7] Other indole derivatives show antiviral activity against hepatitis or have applications as nonsteroidal anti-inflammatories.[8–12] This wide range of interesting properties has prompted the development of an efficient methodology for the synthesis of substituted indoles. In general, substituted indole synthesis is accomplished either by the construction of the indole ring from other substrates via Fischer indolization or by direct functionalizations of an existing indole via electrophilic substitution.[13,14] While the methods for the preparation of 3-substituted indoles are well established,[15–18] there is still a need for easier access to 2-substituted indoles and aza-substituted indoles. Furthermore, alkylation of indoles and their anions under extreme conditions usually gives N- and C-alkylation products nonregioselectively.[19–23] Although N-substituted indoles also represent an important subclass,[8,11,12,24,25] the synthesis of N-substituted indoles is more difficult than the other substituted indoles because of the low nucleophilicity of nitrogen atom. Michael-type addition is one of the most important indole functionalization reactions.[26] Recently, KF/Al_2O_3-mediated direct aza-Michael addition of indoles to electron-deficient olefins such as α,β-unsaturated ketones, amides, and nitriles has been reported.[27] However, the reaction failed with unsaturated esters and aldehydes. We herein report our results on the two-step synthesis of new aza-substituted indole derivatives via Michael-type addition reactions of indoline with various acceptors. Indoline fragments are both important moieties of a large number of natural products and medicinal agents[28] and key precursors for the synthesis of indole derivatives.[29–33]

Initially, cyclic unsaturated ketones were selected as Michael acceptors (Table 1, entries 1–3). The reaction of indoline (**1**) with cyclohex-2-enone (**2**) was examined in the presence of 4-dimethylaminopyridine (DMAP) as a catalyst in acetonitrile, and reaction was complete after 24 hours to afford 3-(indolin-1-yl)cyclohexanone (**3**, Scheme 1). The indoline ring was then oxidized to 3-(1*H*-indol-1-yl)cyclohexanone (**4**)[37] with MnO_2 in CH_2Cl_2 in 90% yield (Scheme 1 and Table 1, entry 2). Moreover, we successfully isolated the corresponding N-alkylated indoles by starting with cyclopent-2-enone and cyclohept-2-enone (entries 1 and 3).



Scheme 1

Next, the scope of the method was broadened to include the reaction between indoline and acyclic unsaturated ketones and esters (Table 1, entries 4–9). Reaction of chalcone with indoline catalyzed by KF–Al_2O_3 in acetonitrile provided aza-alkylated indole derivative followed by MnO_2 oxidation (entry 4). Michael addition of the other acceptors such as (*E*)-4-phenylbut-3-en-2-one, (*E*)-methyl but-2-enoate, (*E*)-pent-3-en-2-one, and methyl propiolate with indoline, followed by the oxidation of indoline rings gave the corresponding aza-substituted indoles in high yield (Table 1, entries 5–8). NMR spectroscopic studies allowed the assignment of the configuration of the vinyl groups for both the Michael adduct obtained from methyl propiolate and oxidation product (entry 8).[34,35] Coupling constants (^3J = 13.0 and 13.9 Hz) are in good agreement with the *E*-configuration for both compounds.

Michael addition of indoline to nitrostyrene catalyzed by $Bi(NO_3)_3{\cdot}5H_2O$ gave 1-(2-nitro-1-phenylethyl)indoline in high yield. Oxidation of the indoline moiety to indole with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in CH_2Cl_2 led to a new alkylated indole derivative in 95% yield (entry 10). We also used 1,1-bis(phenylsulfonyl)ethylene as

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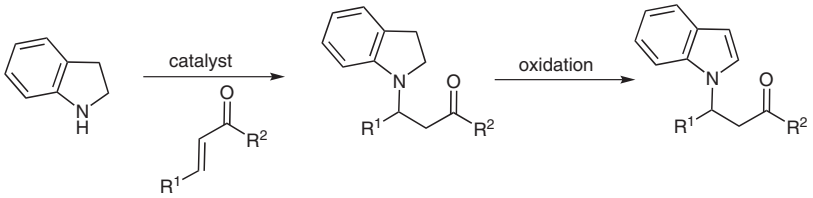
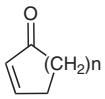
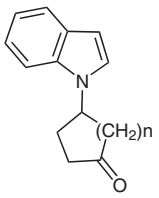
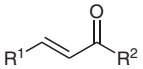
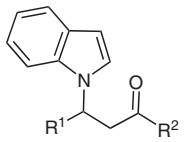
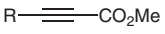
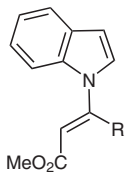
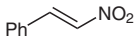
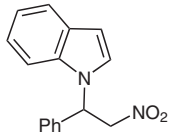
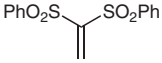
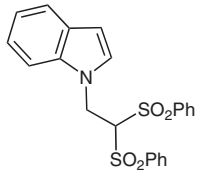
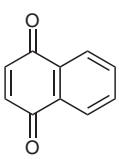
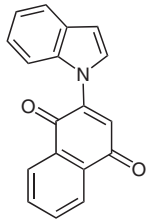
the alkylation reagent in CH_2Cl_2 in the presence of bismuth nitrate for 5 hours. Oxidation of the resultant Michael adduct with DDQ gave the novel N-alkylated indole derivative (entry 11).

After the successful application of this protocol with cyclic unsaturated ketones and acyclic unsaturated ketones and esters, we investigated the conjugate–addition reactions of indoline to symmetrical Michael acceptors such as dimethyl acetylenedicarboxylate (DMAD), 1,4-naphthoquinone, and 1,1,2,2-tetracyanoethylene (TCNE). After bismuth nitrate catalyzed reaction of indoline with DMAD in CH_2Cl_2, the Michael product was oxidized with MnO_2 to give N-vinyl-substituted indole derivative (entry 9).[36] The nuclear Overhauser effect difference experiment for DMAD addition product **5** revealed that vinyl group has the *E*-geometry (Figure 1).

The reaction of indoline with 1,4-naphthoquinone was performed in the presence of catalytic DMAP. Naphthoquinone was used in two equivalents instead of one since a complex mixture was formed with a stoichiometric

Table 1 The Catalysts and Oxidation Reagents for the Synthesis of New Aza-Substituted Indoles



Entry	Acceptor		Catalyst[a]	Oxidation reagent[b]	Product	Yield (%)
1		n = 1	DMAP	MnO_2		92
2		n = 2				90
3		n = 3				97
4		R^1 = Ph, R^2 = Ph	$KF–Al_2O_3$	MnO_2		60
5		R^1 = Ph, R^2 = Me				96
6		R^1 = Me, R^2 = OMe				95
7		R^1 = Me, R^2 = Me				92
8		R = H	$Bi(NO_3)_3·5H_2O$	MnO_2		95
9		$R = CO_2Me$				84
10			$Bi(NO_3)_3·5H_2O$	DDQ		95
11			$Bi(NO_3)_3·5H_2O$	DDQ		98
12			DMAP	MnO_2		51

[a] Catalyst for Michael addition.
[b] Reagent for oxidation of Michael adduct to corresponding indole.

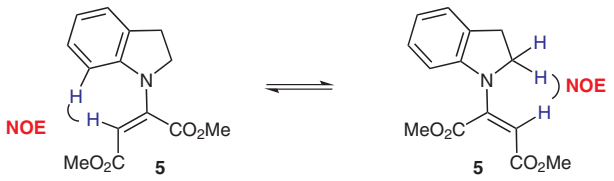
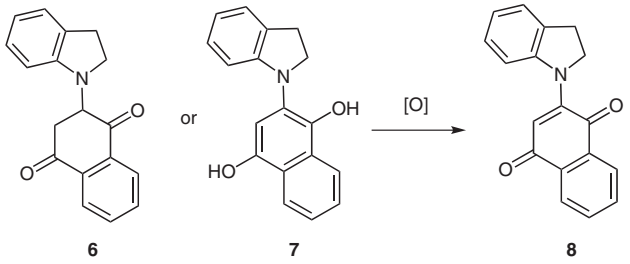


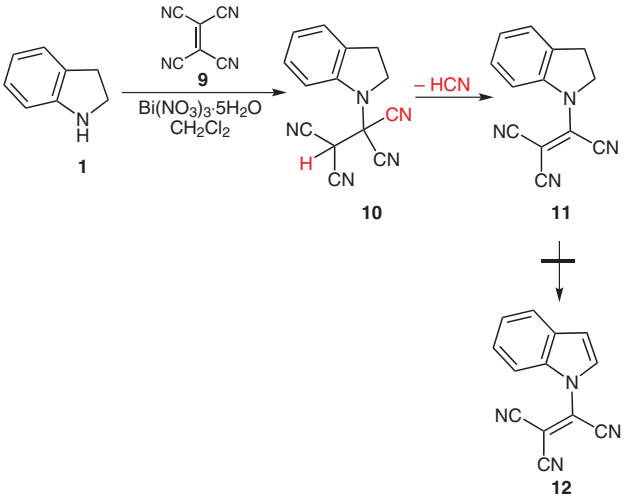
Figure 1

amount. Examination of the ^{1}H NMR and ^{13}C NMR spectra of the reaction mixture revealed the formation of oxidation product **8**, instead of the expected Michael adduct **6** or tautomeric form **7** (Scheme 2). We assume that the second mol of naphthoquinone oxidizes Michael adduct **6** or tautomer **7** to yield naphthoquinone derivative **8**. The indoline ring of **8** was oxidized with MnO_2 to afford the aza-substituted indole derivative in 51% yield (entry 12).



Scheme 2

TCNE is one of the most powerful electron acceptors. Reaction of indoline with TCNE was carried out in the presence of bismuth nitrate in CH_2Cl_2 at room temperature for five hours. This reaction provided a single product with an excellent yield of 95% (Scheme 3). The ^{1}H NMR and ^{13}C NMR spectra of the isolated product indicated that elimination of hydrogen cyanide from the primary Michael adduct **10** had occurred to form trinitrile adduct **11**. However, all attempts at oxidation of the indoline ring in **11** failed.



Scheme 3

In conclusion, a facile, efficient, and regioselective synthesis of N-alkylated indoles has been accomplished in which the key step involves Michael addition reactions of indoline.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(35) McNab, H.; Tyas, R. G. *J. Org. Chem.* **2007**, *72*, 8760.
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(37) **Representative Procedure – Synthesis of 3-(1*H*-Indol-1-yl)cyclohexanone (4)**
To a solution of indoline (500 mg, 4.19 mmol) and cyclohex-2-enone (429 mg, 4.19 mmol) in MeCN (15 mL) was added DMAP (25 mg, 0.05 mmol). The mixture was stirred at r.t. for 24 h. After evaporation of the solvent, the crude product 3-(indolin-1-yl)cyclohexanone (**3**) was purified by crystallization from EtOAc–hexane (pale yellow crystals, 850 mg, 94%, mp 235–236 °C).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08–7.03 (m, =CH, 2 H), 6.64 (t, *J* = 7.6 Hz, =CH, 1 H), 6.42 (d, *J* = 7.6 Hz, =CH, 1 H), 3.82–3.75 (m, CH, 1 H), 3.49–3.43 (m, CH_2, 1 H), 3.38–3.31 (m, CH_2, 1 H), 2.98 (t, *J* = 8.2 Hz, CH_2, 2 H), 2.60–2.57 (m, CH_2, 1 H), 2.56–2.50 (m, CH_2, 1 H), 2.47–2.41 (m, CH_2, 1 H), 2.33–2.25 (m, CH_2, 1 H), 2.16–2.07 (m, CH_2, 2 H), 1.86–1.70 (m, CH_2, 1 H), 1.69–1.60 (m, CH_2, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.0, 150.2, 130.1, 127.6, 124.8, 117.9, 107.3, 55.0, 46.7, 43.9, 41.3, 28.5, 28.4, 22.9.
To a solution of 3-(indolin-1-yl)cyclohexanone (1.00 g, 4.65 mmol) in CH_2Cl_2 (10 mL) was added activated MnO_2 (869 mg, 10 mmol). The mixture was then stirred at r.t. for 24 h. After filtration, the mixture was evaporated in vacuo to give 3-(1*H*-indol-1-yl)cyclohexanone (**4**) as yellow oil (890 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (dd, *J* = 7.8, 2.0 Hz, =CH, 1 H), 7.35 (d, *J* = 8.4 Hz, =CH, 1 H), 7.26–7.20 (m, =CH, 2 H), 7.16–7.12 (m, =CH, 1 H), 6.57 (d, *J* = 2.9 Hz, =CH, 1 H), 4.72–4.66 (m, CH, 1 H), 2.94–2.91 (m, CH_2, 1 H), 2.90–2.77 (m, CH_2, 1 H), 2.56–2.40 (m, CH_2, 2 H), 2.35–2.30 (m, CH_2, 1 H), 2.25–2.10 (m, CH_2, 2 H), 1.85–1.78 (m, CH_2, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.2, 135.7, 128.9, 124.0, 122.0, 121.5, 120.1, 109.6, 102.6, 54.4, 48.4, 41.1, 31.6, 22.5.