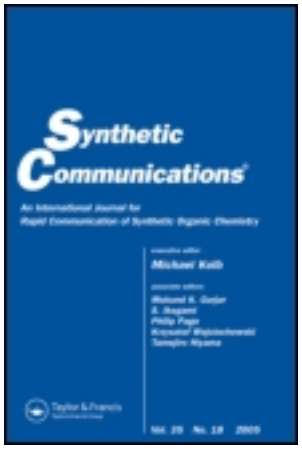

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A SHORT, NOVEL, AND PRACTICAL SYNTHESIS OF 3-ALKENYLATED INDOLES

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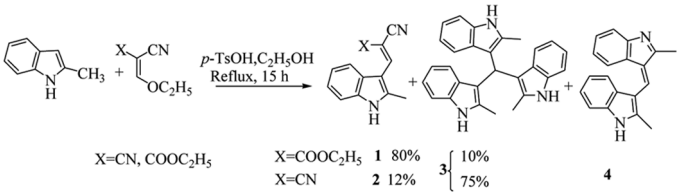
GRAPHICAL ABSTRACT



Abstract *Direct metal-free alkenylation of 2-methylindole via acid-mediated Michael addition–elimination reaction with ethoxymethylenemalononitrile or ethyl ethoxymethylenecyanoacetate affords 3-indolyl-2-cyanoacrylonitrile and ethyl 3-indolyl-2-cyanoacrylate. Behavior of 1H-indole is predictably different.*

Keywords Ethoxymethylenemalononitrile; ethyl ethoxymethylenecyanoacetate; indole alkenylation; Michael addition–elimination

INTRODUCTION

Ethoxymethylenemalononitrile and ethoxymethylenecyanoacetate belong to a special Michael acceptor group that is utilized extensively in organic synthesis, particularly in preparation of pharmacologically active substances.[1] They react with a variety of nucleophiles, and a broad range of their applications in the synthesis of chain, cyclic, heterocyclic, and fused heterocyclic structures has been reported and reviewed.[2]

Substituted indoles form the core skeletons of a wide range of pharmaceuticals and naturally occurring alkaloids.[3] [(2-Arylindol-3-yl)methylene]propanedinitriles inhibit the growth of breast cancer cells by cell cycle arrest in G2/M phase and apoptosis.[4] The 3-position of indoles is the preferred site for an electrophilic substitution reaction.[5]

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Although alkylation and arylation of indoles have been well documented,[6,7] there are only a few reports of their alkenylation.[8] These alkenylation reactions include palladium-catalyzed vinylation using alkenes,[8a] platinum- and nickel-catalyzed addition of indole to electron-poor alkynes,[8b,c] acid-promoted reaction,[8d] modified Heck reaction,[8e] reaction of indoles with electron-deficient ethoxyethylenes,[8f] and Knoevenagel condensation of indole-3-carbaldehyde with active methylene compounds.[4]

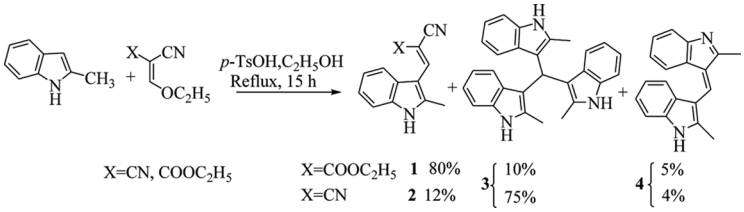
RESULTS AND DISCUSSION

Diethyl ethoxymethylenemalonate (DEEM), ethoxymethylenemalononitrile (EMMN), ethoxymethylenecyanoacetate (EMCA), and molecules with similar structures are ''push–pull olefins,'' variously referred to as β-alkoxyacrylate or β-akoxyolefins, none of which can truly and exclusively represent the structure. They can be considered functionalized C4 synthons, capable of adding a methylenemalonate-type moiety to the nucleophile attacking them. In contrast to most ordinary Michael acceptors, they usually form Michael monoadducts with retention of the double bond. The reactions of nucleophilic nitrogen atoms with the so-called alkoxyacrylate compounds prevail in literature, but there are also a few reports about reactions of nucleophilic carbons.[2]

To find new routes in application of these C4 synthons with carbon nucleophiles and a simple method for alkenylation of indole, we examined a novel and simple process of *p*-TsOH-catalyzed addition of 2-methylindole to EMMN or EMCA (Scheme 1). Needless to say, both the reagent and catalyst are easily available and low cost.

In our model experiment, *p*-TsOH-catalyzed reactions of EMCA and EMMN with 2-methylindole in refluxing ethanol afforded the 1:1 adducts **1** and **2**. In the case of EMMN, the main product is **3** (Scheme 1). Using a polar aprotic solvent such as CH_3CN increased the yield of compound **2** from 12% to 35%. Results of the solvent effect on the reaction are presented in Table1, and CH_3CN was found to be most suitable solvent. EMCA monoadduct **1** has previously been reported in the literature[9] to have been produced by the reaction of 3-formyl-2-methylindole with ethyl cyanoacetate.

A plausible mechanism for the formation of **3** is proposed in Scheme 2. In the first step, double Michael addition of 2-methylindole to EMMN leads to unisolated bis(3′-indolyl)methanes **5**, which undergoes a facile elimination reaction and loses a malononitrile group to produce the unisolated intermediate (**A**). Michael addition of



Scheme 1. Double Michael addition of 2-methyl indole to EMCA and EMMN.

Table 1. Study on the effect of the solvent on the preparation of **2**

Entry	Reaction conditions	Time	Product (Yield) %
1	CH_2Cl_2, reflux	2 d	**2a** (22), **3**(55)
2	C_2H_5OH, reflux	15 h	**2a** (12), **3** (75), **4** (4)
3	Toluene. reflux	22 h	**2a** (28), **3**(60)
4	CH_3CN, reflux	15 h	**2a** (35), **3** (50), **4** (5)

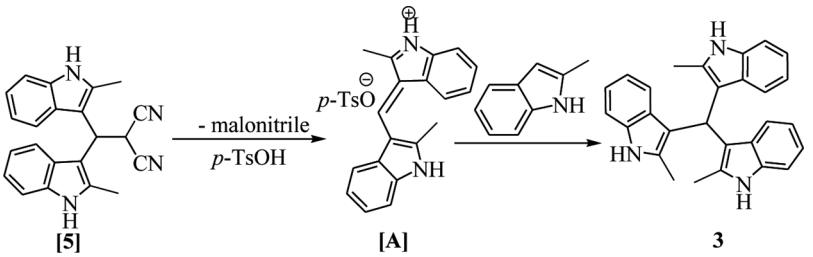
the third 2-methylindole to this intermediate affords tris(2-methylindolyl)methane **3** (Scheme 2).[10]

Curiously enough, 1*H*-indole itself did not lead to the corresponding 3-alkenylatedindole but furnished novel ethyl-3-({2-[2,2-bis(1*H*-indol-3-yl)ethyl]phenyl} amino)-2-cyanoprop-2-enoate **6** instead, in moderate yield (55%). In the case of EMMN, a similarly expected product **7** is not produced in tangible amounts (Scheme 3). A plausible explanation is that EMCA is a better Michael acceptor than EMMN under reaction conditions.

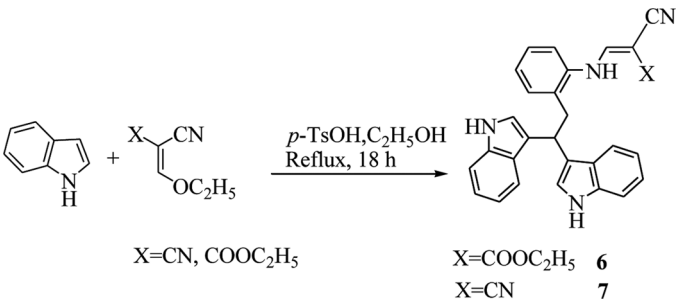
Under acidic conditions, 1*H*-indole is in equilibrium with 3-(indolin-2-yl) indole (indole dimer) (Scheme 4).[10c,11] Reaction of indoline NH group of indole dimer with an electrophile such as EMCA causes a drain of reaction equilibrium toward production of intermediate **B**. Addition of a third molecule of indole to **B** leads to the formation of novel substituted trimer **6** (Scheme 5).

In the mass spectrum, compound **6** shows a base peak at m/z 245, assignable to the bis-(indolyl)methyl moiety. The infrared (IR) spectrum shows two NH bands at 3416, 3354; two carbonyl bands at 1673, 1634, and CN at 2207 cm^{-1}. The ^1H NMR spectrum (500 MHz, DMSO-d_6) shows a singlet ascribable to two indolic NH group at δ_H 10.71, a doublet at 10.86 ($J = 13.4$, NH-CH), 14 aromatic protons [set *a* (δ 6.79, 6.96 and 7.03), set *b* (7.15, 7.21, 7.26, 7.33 and 7.38)], together with a triplet at 4.76 ($J = 7.7$, CH_2-CH), and a doublet at 3.54 ($J = 7.7$, CH_2-CH).^1H NMR signals of NH (δ_H 10.83) and CH (δ_H 8.04) for product **6** are coupled with $J = 13.4$ Hz. This was confirmed by spin-spin decoupling of NH signal at δ_H 10.84, which resulted in the appearance of the CH signal as a singlet.

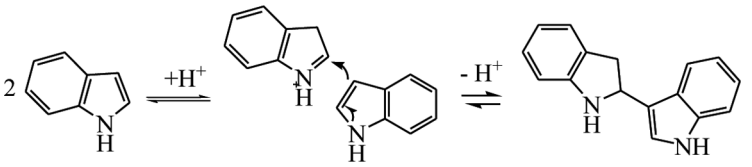
Compound **6** is a potential precursor of novel 4-[1,1-bis(3′)indolyl]quinoline-4-ole-3-cyanide, through a Gould–Jacobs reaction, and compounds **1** and **2** are potential precursors for bioactive fused pyran derivatives.[12]



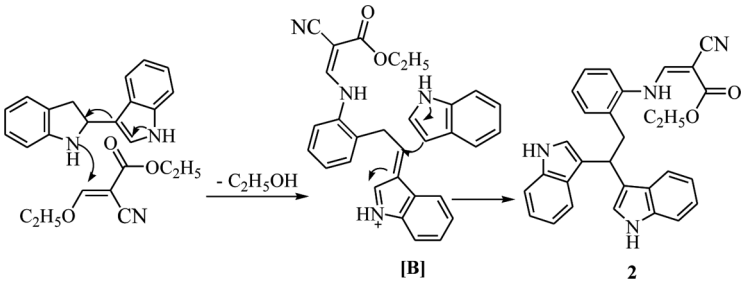
Scheme 2. A plausible mechanism for the formation of **3**.



Scheme 3. Reaction of 1H-indole with EMMN and EMCA.



Scheme 4. 1H-indole/indole dimer equilibrium.



Scheme 5. A plausible mechanism for the formation of **2**.

CONCLUSION

In conclusion, we have found a simple process for the synthesis of 3-alkenylindoles, using *p*-TsOH-catalyzed addition of 2-methylindole to EMMN or EMCA and also new application of a group of push–pull olefins (C4 synthons) with indole as carbon nucleophiles.

EXPERIMENTAL

Procedure for the Synthesis of 1, 2, 3, and 4

A 50-mL round-bottom flask was charged with a solution of 2-methylindole (30 mmol, 4 g) in 10 mL 96% ethanol, and a solution of EMCA (purity 98%)

(30 mmol, 5.1 g) in 10 mL 96% ethanol and *p*-TsOH (1 mmol, 0.2 g) was added. The reaction mixture was stirred at reflux for 15 h, until complete consumption of 2-methylindole was confirmed by thin-layer chromatography (TLC; petroleum ether: EtOAc; 3:1). TLC chromatogram showed two spots corresponding to compounds **1** and **3** with a trace of **4**. When the reaction mixture was cooled to room temperature, it deposited copiously, a solid which was separated by filtration. The filtrate showed traces of all three products, worthless for workup. The precipitate was dispersed in hot methanol to dissolve **3**, filtered hot, and cooled to obtain **1** as a yellow powder. Evaporation of the filtrate furnished compound **3** as a pinkish solid.

Exact replication of this reaction with EMMN in refluxing ethanol produced **2** in only poor yield, the major product being **3** in 38% yield. Performing the reaction in acetonitrile increased the yield of **2** to 35%.

Ethyl 2-cyano-3(2-methyl-1H indol-3-yl)prop-2-enoate ($C_{15}H_{14}N_2O_2$, 1)[9]. Yellow powder; yield 6 g (80%); mp: 245–246 °C.

[(2-Methylindol-3-yl)methylene]propanedinitriles ($C_{13}H_9N_3$, 2). Yellow powder; yield 2.1 g (35%); mp: 233.7–235 °C; IR (ν_{max}/cm^{-1}): 3446, 3328, 2214, 1569, 1514, 1458, 1388, 1350, 1253, 1166, 1098, 746; MS (70 eV): $m/z = 207$ (M^+, 18), 160 (11), 154 (65), 142 (15), 84 (25), 74 (39), 44 (100%); ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 2.50$ (3H, s, CH_3), 7.21 (2H, m, Ar*H*), 7.43 (1H, d, $J = 6.9$, Ar*H*), 8.08 (1H, d, $J = 7.1$, Ar*H*), 8.25 (1H, s, -CH=), 12.72 (1H, s, NH); ^{13}C NMR (125.7 MHz, DMSO-d_6): $\delta = 13.5$, 110.2, 112.1, 114.9, 117.2, 121.9, 123.2, 126.0, 131.8, 135.4, 150.2. Anal. calc. for $C_{13}H_9N_3$: C, 75.35; H, 4.38; N, 20.28. Found: C, 75.29; H, 4.31; N, 20.35.

3-[Bis(2-methyl-1H indol-3-yl)methyl]-2-methyl-1H-indole ($C_{28}H_{25}N_3$, 3)[13]. Pink powder; yield 6 g (50%); mp: 333–335 °C.

3-[3H-Indol-3-ylidenemethyl]-1H-indole ($C_{19}H_{18}N_2$, 4)[10c]. Orange powder; mp: 272 °C (decomp.).

Ethyl-3-({2-[2,2-bis(1H-indol-3-yl)ethyl]phenyl}amino)-2-cyanoprop-2-enoate ($C_{30}H_{26}N_4O_2$, 6). White powder; mp: 190 °C; yield: 5.2 g (55%); IR (KBr) (ν_{max}/cm^{-1}): 3354, 3324, 2207, 1673, 1634, 1599, 1456, 1416, 1379, 1250, 1172, 743; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 1.22$ (3H, t, $J = 7.0$ Hz, $OCH_2C\underline{H}_3$), 3.54 (2H, d, $J = 7.7$, CH-C$\underline{H}_2$), 4.15 (2H, q, $J = 7.1$, $OC\underline{H}_2CH_3$), 4.76 (1H, t, $J = 7.7$ Hz, C$\underline{H}$-CH_2), 6.79 (2H, t, $J = 7.6$ Hz), 6.96 (2H, t, $J = 7.5$ Hz), 7.03 (1H, t, $J = 7.4$ Hz), 7.15 (1H, t, $J = 8.3$ Hz), 7.21 (2H, d, $J = 2$ Hz, CH), 7.26 (3H, t, $J = 8.02$ Hz), 7.33 (1H, d, $J = 8.0$ Hz), 7.37 (2H, d, $J = 7.9$ Hz), 8.04 (1H, d, $J = 13.4$ Hz, C$\underline{H}$-NH), 10.71 (2H, s, $2NH_{indolic}$), 10.86 (1H, d, $J = 13.4$ Hz, CH-N-$\underline{H}$);^{13}C NMR (125.7 MHz, DMSO-d_6): $\delta = 15.0$, 15.2, 35.5, 37.3, 37.5, 60.9, 61.3, 74.1, 112.1, 112.2, 118.2, 118.5, 118.6, 118.7, 118.8, 118.9, 119.7, 121.4, 123.1, 123.2, 126.1, 127.3, 128.1, 131.8, 132.1, 137.1, 138.1, 155.2, 157.1, 167.8 ppm; MS (70 eV): $m/z = 474$ (M^+, 22), 358 (16), 311 (12), 282 (9), 245 (100), 218 (83), 189 (10), 155 (15), 117 (22), 90 (8%), Anal. calc. for $C_{30}H_{26}N_4O_2$: C, 75.93; H, 5.52; N, 11.81. Found: C, 75.89; H, 5.51; N, 11.83.

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