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A New Method for the Synthesis of 3-Substituted Indoles

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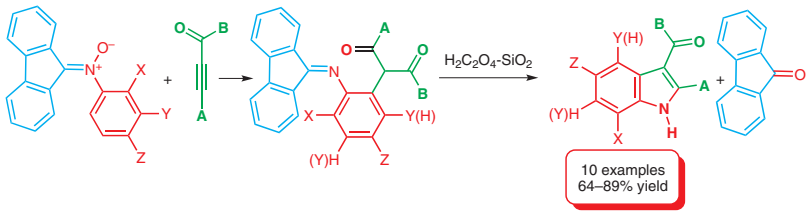

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Abstract Starting from readily accessible nitrones and electron-deficient acetylenes, a highly efficient and versatile synthetic protocol for 3-substituted indoles has been developed.

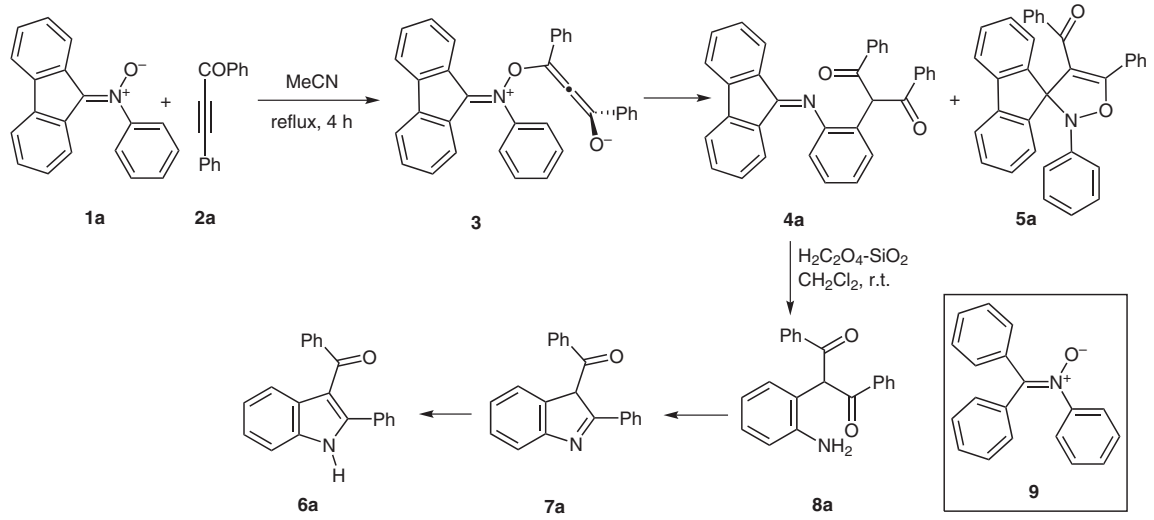
Key words indoles, nitrones, electron-deficient acetylenes, nucleophilic addition, 1,3-dipolar additions

Indole derivatives are valued for their wide range of applications.[1] Ever since the pioneering synthesis by Fischer,[2] indoles have remained attractive synthetic targets. Numerous methods are reported for the synthesis of indoles and several excellent reviews summarize synthesis protocols developed for indoles.[3,4] In a recent review, Taber assembled strategies for indole synthesis into nine groups.[3p] We now report a simple, highly versatile, and mechanistically appealing one-pot synthesis of 3-substituted indoles that can be fitted into the type 5 indole synthesis formulated by Taber.[3p]

While examining the mechanism of 1,3-dipolar additions, we observed the formation of unusual 1:1 adduct **4a** arising through an aza-Cope rearrangement in the reaction between *N*-(9*H*-fluoren-9-ylidene)aniline oxide **1a** and phenylbenzoylacetylene (**2a**, Scheme 1).[5,6] Acid-catalyzed hydrolysis of imine **4a** followed by in situ cyclization via an intramolecular amine–carbonyl condensation reaction of intermediate **8a** should give 3*H*-indole **7a** that will subsequently rearrange to 3-substituted indole **6a** (Scheme 1). In a preliminary experiment, we treated nitrone **1a** with **2a** to give **4a** in good yield (64%) along with isoxazoline **5a** in minor amounts (19%).[5a,c] From the reaction mixture, **4a** was isolated in pure form by usual chromatographic techniques. On treatment with oxalic acid adsorbed on silica gel, as expected, **4a** underwent hydrolysis and in situ cyclization to give phenyl(2-phenyl-1*H*-indol-3-yl)methanone (**6a**) in quantitative yield. Though this method represents a simple approach to indole synthesis,[7] we surmised that a practical alternative would be to hydrolyze **4a** without separation from the product mixture. In a repeat run, we treated nitrone **1a** with acetylene **2a** in acetonitrile. When all of the starting materials were consumed, solvent was removed, and the residue, redissolved in dichloromethane, was treated with oxalic acid adsorbed on silica gel. Hydrolysis of **4a** was completed in one hour, and the indole **6a** generated could be separated easily from other byproducts (such as fluorenone and isoxazoline **5a**) in higher yields vis-à-vis the two-step method mentioned earlier. This result was quite encouraging, and we adopted this as the general strategy for subsequent reactions. Though triphenylnitrone **9** also gave similar results, yield of the desired indole product was higher with fluorenylidene nitrone **1a**. So, we employed fluorenylidene nitrones for all optimization studies described in this article. The more easily accessible aldonitrones follow a different reaction course with electron-deficient acetylenes and hence are not suitable precursors for indole synthesis.[5a,c]

Close examination of the indole product **6** reveals that it retains most of the atoms present in the *N*-aryl substituent and acetylene used. Substitution pattern of putative indole products is dependent on substrate structure and hence is easily predicted. This points towards the potential of our method of indole synthesis to selectively synthesize indoles having desired substituents at the 2-, 3-, 4-, 5-, 6-, and 7-positions. Such flexibility makes indole synthesis reported here unique and potentially useful.

In order to establish generality and wide applicability of this novel indole synthesis, we repeated the reaction of **1a** with electron-deficient acetylenes **2b**–**e** (Figure 1).



Scheme 1 Reaction between nitrone **1a** and acetylene **2a**

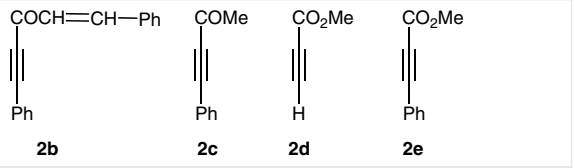
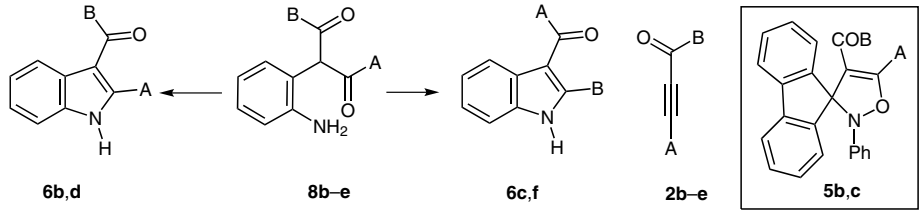


Figure 1 Acetylenes used in indole synthesis

In all cases, the corresponding indole derivatives were formed in good yields. With unsymmetrical intermediates **8b**–**e**, two regioisomeric indole isomers could be generated. The major product formed in such cases is easily predicted on the basis of relative reactivity of the two carbonyl groups. For example, in the reaction between nitrone **1a** and 4-phenylbut-3-yn-2-one (**2c**), (2-methyl-1*H*-indol-3-yl)(phenyl)methanone (**6c**) was generated along with the isoxazoline derivative and fluorenone. In this case, the more reactive acetyl group undergoes condensation with the amine functionality in preference to the less reactive benzoyl group. Similarly, in the reaction between **1a** and **2e**, **6f** was formed as the major product. Formation of **6f** may be explained on the basis of intramolecular nucleophilic substitution reaction at the ester carbonyl with the amino group as nucleophile and the methoxy group as the nucleofuge. On the other hand, in the reaction between nitrone **1a** and acetylenes **2b**,**d**, indoles **6b**,**d** were exclusively generated in high yields (Scheme 2). The cyclization step is highly selective, and the other possible isomer was not formed in detectable amounts in any of those reactions. In the case of acetylenes **2a**–**c** the corresponding isoxazoline byproducts **5a**–**c** were formed in minor amounts. In the case of acetylenes **2d**,**e**, the corresponding indoles and fluorenone were the only isolable products. Product distribution in the reaction between nitrone **1a** and acetylenes **2a**–**e** is summarized in Table 1.[8] Best results are obtained with methyl propiolate (**2d**).

In order to extend the scope of indole synthesis, we examined the reaction of fluorenylidene nitrones having a methyl substituent at different positons of the *N*-aryl group with methyl propiolate (**2d**). Pattern revealing regioselec-



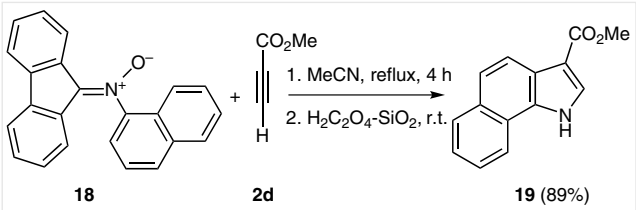
Scheme 2 Indoles formed in the reaction between **1a** and **2b**–**e**

Table 1 Product Distribution in the Reaction between Nitrone **1a** and Acetylenes **2a–e**[8]

Entry	Nitrone	Acetylene	Indole (%)	Isoxazoline (%)
1	**1a**	**2a**	**6a** (64)9a	**5a** (19)5a,c
2	**1a**	**2b**	**6b** (67)9b	**5b** (16)10
3	**1a**	**2c**	**6c** (66)9c	**5c** (18)10
4	**1a**	**2d**	**6d** (84)9d–g	–
5	**1a**	**2e**	**6f** (82)9h	–

tivity in the indole formation reaction is presented in Scheme 3. Nitrone **10**, having a substituent at the 4-position of the *N*-aryl ring, gave the corresponding 5-substituted indole **13**[9d,e] exclusively. Similarly, nitrone **11** with the methyl substituent at the 2-position gave the corresponding 7-substituted indole **14**.[9d,f] On the other hand, nitrone **12**, having methyl substituent at the 3 position of the *N*-aryl ring, gave a mixture of 4- and 6-substituted indoles (**15**[9d] and **16**[9g]) in a 3:1 ratio. Regioselectivity in this case could be explained on the basis of an unequal rotomer population of intermediate **17** involved in the nitrone–acetylene reaction.[5c]

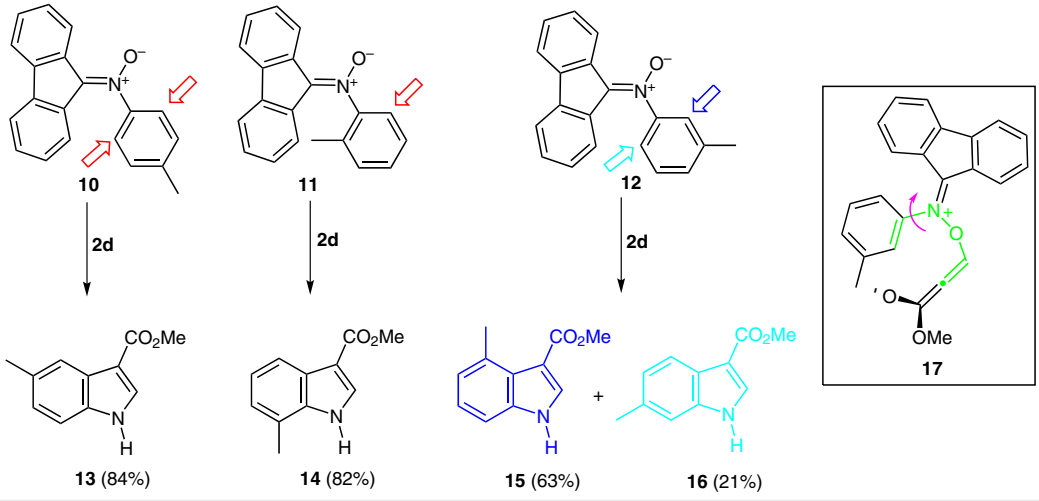
The versatility of our method was further demonstrated by near-quantitative generation of benzo[*g*]indole **19**[9i,j] in the reaction between **2d** and *N*-(9*H*-fluoren-9-ylidene)naphthalen-1-amine oxide (**18**)[5a] (Scheme 4). Benzo[g]indole derivatives are important for their biological activity and potential application as fluorescent probes.[11] Our method provides easy access to benzo[g]indole **19** in high yields.



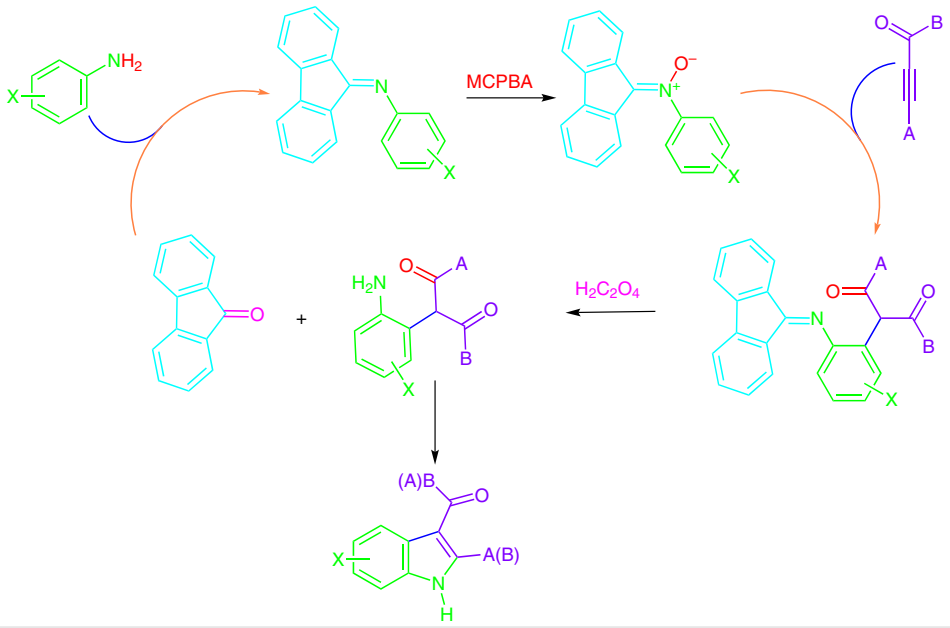
Scheme 4 Reaction between nitrone **18** and acetylene **2d**

Yet another advantage of this method is that the fluorenone, generated as a byproduct in the indole-forming step, can subsequently be recycled for the generation of a fresh batch of fluorenylidene nitrone that can then be converted into indole. As stated earlier, most atoms present in the acetylene and *N*-aryl substituent are retained in the indole product. Based on these, we complete the reaction cacle for a flexible yet highly atom-efficient synthesis of 1*H*-indoles (Scheme 5). Common methods for indole synthesis[3,4,9] fail to meet the simplicity and atom efficiency achieved by this approach.

Efficient methods are available for the synthesis of nitrones,[12] and several electron-deficient acetylenes are easily accessible. Oxalic acid adsorbed on silica gel is one of the cheapest, safest, and most easily handled acid catalysts. Expensive catalysts are not required, and the reaction conditions are mild. More importantly, the method is flexible enough to introduce a desired group at a predetermined position. These advantages make our indole synthesis unique for its efficiency, flexibility, wide applicability, and mechanistic appeal. Shortcomings of the strategy include the fact that indoles generated will, by default, have an electron-withdrawing substituent at the 3-position, it is not possible



Scheme 3 Regioselectivity in nitrone–acetylene reactions; arrows point to potential sites for aza-Cope rearrangement in intermediates analogous to **17**[5a]



Scheme 5 Reaction cycle for indole formation

to introduce a substituent specifically at positions 4 and 6, and, in some cases, it may not be possible to predict 2- and 3-substituents.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560210.

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(8) **General Procedure**

A 1:1 mixture (1 mmol each) of nitrone and acetylene in MeCN (10 mL) was stirred under reflux for 4 h. After complete consumption of starting materials, solvent was evaporated off, and the residue was redissolved in CH_2Cl_2 (10 mL) in the same flask. Oxalic acid (1 mmol) adsorbed on silica gel (1 g) was added to the same pot, and the mixture was stirred at r.t. for 1 h. After completion of the reaction, the solvent was removed, and the products were isolated by column chromatography over silica gel using mixtures of hexane and EtOAc as eluents. In all reactions, fluorenone was formed as a byproduct in yields comparable to those cited for the indoles. Nitrones were prepared by recycling the fluorenone.

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(10) **Characterization Data for 5b and 5c**

(*E*)-1-{2′,5′-Diphenyl-2′*H*-spiro[fluorene-9,3′-isoxazole]-4′-yl}-3-phenylprop-2-en-1-one (5b)

Yellow solid, yield 16%; mp 105 °C. IR (KBr): ν_{max} = 3058 (=CH stretch), 1649 (C=O stretch) cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.89–7.86 (m, 2 H), 7.67 (d, *J* = 7.6 Hz, 2 H), 7.64–7.60 (m, 1 H), 7.57–7.53 (m, 4 H), 7.36–7.32 (m, 2 H), 7.27–7.16 (m, 6 H), 6.99–6.91 (m, 4 H), 6.81–6.76 (m, 1 H), 6.61–6.58 (m, 2 H), 6.36 (d, *J* = 15.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.9, 163.1, 145.9, 144.9, 140.8, 140.7, 134.9,131.7, 130.2, 129.8, 129.4, 128.8, 128.6, 128.1, 128.0, 127.9, 127.0, 125.4, 124.7, 123.6, 120.1, 118.3, 117.0, 84.9. MS: *m/z* = 503 [M^+]. Anal. Calcd for $C_{36}H_{25}NO_2$: C, 85.86; H, 5.00, N, 2.78. Found: C, 85.82; H, 4.98; N, 2.75.

1-{2′,5′-Diphenyl-2′*H*-spiro[fluorene-9,3′-isoxazole]-4′-yl}ethanone (5c)

Yellow solid, yield 18%, mp 124 °C. IR (KBr): ν_{max} = 3058 (=CH stretch), 1649 (C=O stretch) cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.84–7.81 (m, 2 H), 7.65–7.52 (m, 6 H), 7.37–7.33 (m, 2 H), 7.26–7.22 (m, 3 H), 6.93–6.89 (m, 2 H), 6.79–6.75 (m, 1 H), 6.56–6.53 (m, 2 H), 2.28 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.4, 163.4, 145.9, 144.9, 140.6, 131.4, 129.7, 129.4, 128.6, 128.3, 128.0, 127.9, 125.5, 123.6, 120.2, 117.3, 117.1, 84.5, 28.7. MS: *m/z* = 415 [M^+]. Anal. Calcd for $C_{29}H_{21}NO_2$: C, 83.83; H, 5.09; N, 3.37. Found: C, 83.78; H, 5.05; N, 3.35.

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