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Regioselective synthesis of 1-hydroxycarbazoles via anionic [4+2] cycloaddition of furoindolones: a short synthesis of murrayafoline-A

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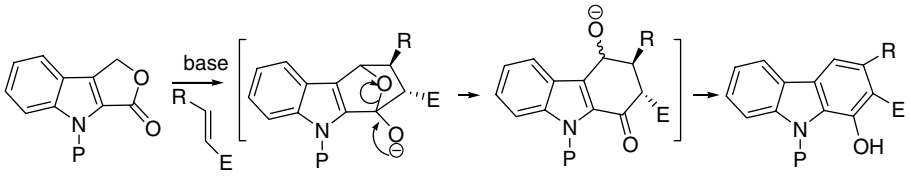
Abstract—Suitably N-protected furoindolones react regioselectively with a variety of Michael acceptors in the presence of LDA to give 1-hydroxycarbazoles in a single-pot process and in good yields. The methodology has been applied to the synthesis of murrayafoline-A.

Carbazoles are ubiquitous structural subunits of numerous naturally occurring compounds as well as synthetic materials. Over the past four decades, a wide range of biologically active carbazole alkaloids have been isolated from plant sources. Many of these natural products display biological properties such as antitumor, psychotropic, anti-inflammatory, antihistaminic, antibiotic and antioxidative activities.[1] As synthetic materials, many carbazole derivatives exhibit photoreactive, photoconductive and light emitting properties.[2] Carbazoles have also been recognized as a useful scaffold in anion binding studies.[3] Consequently, the synthesis of carbazoles has been a vigorously active area of study.[4]

The conventional applications of electrophilic substitutions of simple carbazoles are limited to the preparation of 3- and 6-substituted carbazoles. Accordingly, considerable efforts have been devoted to the development of regioselective routes to functionalized/substituted carbazoles from nitrogen substituted biaryls via a pyrrole ring-formation approach and from benzene/indole derivatives by the benzannulation approach or by thermal electrocyclization methodology.[5] Recently, Knolker and Reddy extensively reviewed the synthesis of biologically active carbazole alkaloids.[6] We now report a new synthesis of 1-oxygenated carbazoles by benzannulation of furoindolones with several Michael acceptors. This methodology provides a simple and straightforward regioselective route for the preparation of 1-oxygenated multi-substituted carbazoles.

Our continued interest in the application of anionic [4+2] cycloaddition[7] of isobenzofuranones prompted us to investigate the anionic reactivity of furoindolones (Scheme 1) towards the synthesis of 1-hydroxy carbazoles.



Scheme 1. Proposed methodology for the synthesis of substituted carbazoles.

Keywords: Carbazole; Cycloaddition; Furoindolone; Murrayafoline-A.
* Corresponding author. Tel.: +91 3222 283318; fax: +91 3222 282252; e-mail: dmal@chem.iitkgp.ernet.in

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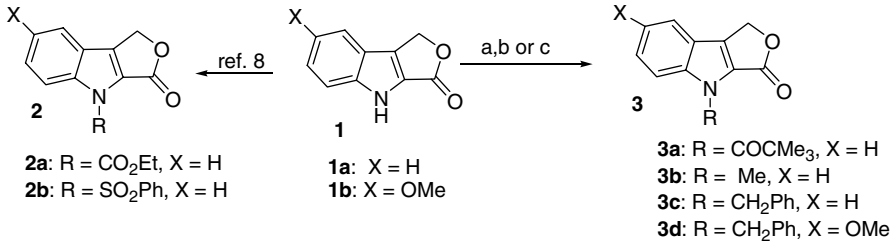
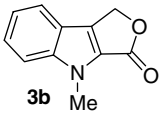
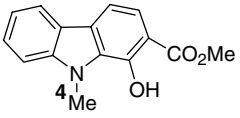
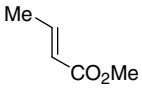
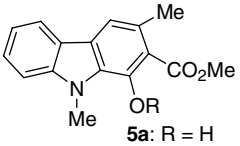
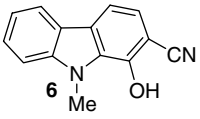
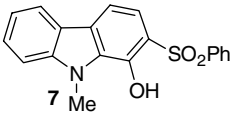
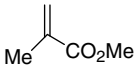
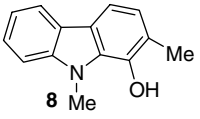
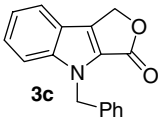
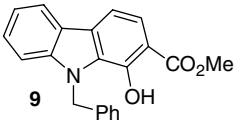
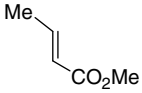
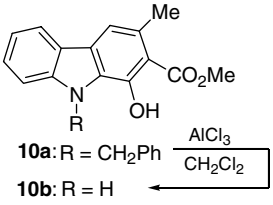
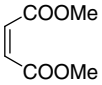
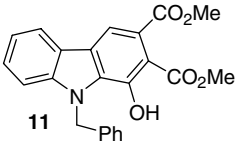
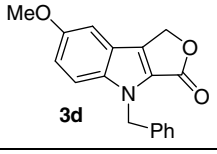
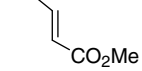
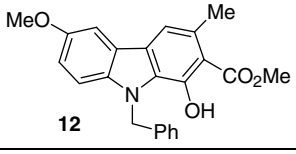


Scheme 2. Reagents and conditions: (a) *n*-BuLi, Me_3COCl , dry THF, 71% for **3a**; (b) LDA, MeI, dry THF, 84% for **3b**; (c) K_2CO_3, $PhCH_2Cl$, NaI, dry acetone, 62% for **3c** and 69% for **3d**.

Table 1. Preparation of N-protected carbazoles using furoindolones and Michael acceptors

Entry	Furoindolone	Michael acceptor	Carbazole	Yield (%)
1	 **3b**		 **4**	72
2	**3b**		 **5a**: R = H **5b**: R = Me	78 (**5a**) 76 (**5b**)
3	**3b**		 **6**	81
4	**3b**		 **7**	65
5	**3b**		 **8**	55
6	 **3c**		 **9**	64
7	**3c**		 **10a**: R = CH_2Ph **10b**: R = H	67 (**10a**) 81 (**10b**)
8	**3c**		 **11**	85
9	 **3d**		 **12**	58

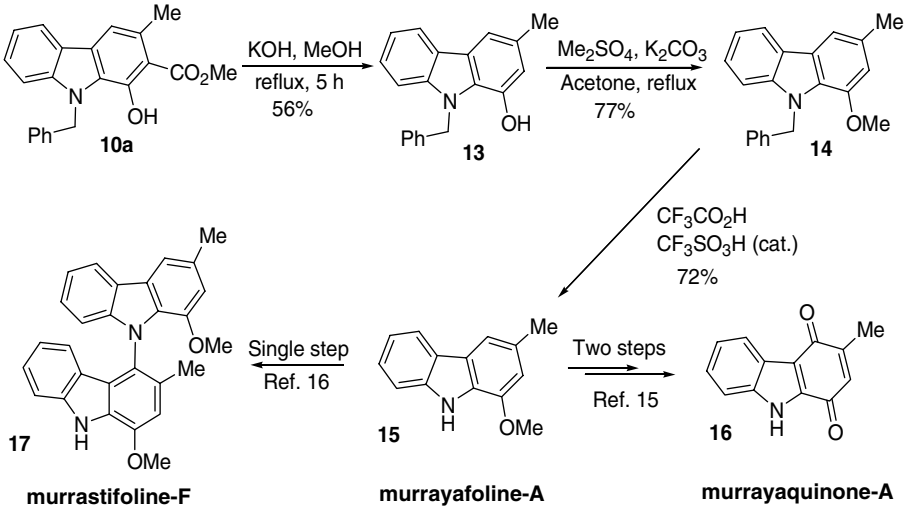
Our previous study with *N*-ethoxycarbonyl derivative **2a** and *N*-phenylsulfonyl derivative **2b** prepared from furoindolones **1a** was fairly successful in providing a route to indoloquinones.[8] However, these synthons were not reactive with Michael acceptors like acrylates and crotonates, thus eluding entry to simple carbazole derivatives. Nevertheless, this study gave us an important cue for further investigations. We observed that both *N*-ethoxycarbonyl and *N*-phenylsulfonyl groups were cleaved during the course of the reaction in the presence of LDA at temperatures below ambient temperature. We, therefore, decided to examine LDA-stable N-protection of compound **1a** for the proposed cycloaddition (Scheme 1).

Since the *N*-pivaloyl group of an indole is stable[9] to LDA below 40–45 °C, our initial studies began with compound **3a** (Scheme 2), which was readily prepared in 71% yield from the parent furoindolone **1a** by pivaloylation with *n*-BuLi and pivaloyl chloride at −78 °C. When compound **3a** was treated with lithium diisopropylamide (3.0 equiv), followed by methyl acrylate at −78 °C and the resulting mixture worked-up in the usual manner, the expected carbazole was not obtained. Compound **1a** was recovered in a substantial amount, indicating that the pivaloyl group of **3a** was removed in the presence of LDA before the desired cycloaddition could take place. We then proceeded to examine the reactivity of *N*-methylfuroindolone **3b**. This was prepared in 84% yield from compound **1a** by methylation with LDA and iodomethane. Treatment of **3b** with LDA, followed by methyl acrylate gave, after work-up, compound **4** in 72% yield. It was evident from this result that the stability of the N-protection towards LDA was crucial to the success of the benzannulation. Although the Sammes annulation[10] of phthalides is known to involve the intermediacy of hydroxytetralones, no such intermediate could be isolated from the reaction with **3b**. In order to generalize the observations, we performed similar annulations with several Michael acceptors for the preparation of N-protected carbazoles. The results are summarized in Table 1.

For the access to 1,2,3-trisubstituted carbazoles, methyl crotonate was reacted with **3b** in the presence of LDA at −78 °C and the desired product **5a** was obtained in 78% yield. To confirm its structure, it was converted to the *O*-methyl derivative **5b**. In striking contrast, ethyl cinnamate did not undergo annulation with **3b** under similar conditions. Both *N*-methylfuroindolone **3b** and ethyl cinnamate were recovered, after work-up of the reaction. Similarly, methyl vinyl ketone and mesityl oxide were not compatible for the reaction with **3b**. Both ketones were destroyed during the reaction. On the other hand, cyano-containing and sulfone-containing Michael acceptors (entries 3 and 4) underwent smooth annulations with compound **3b**. The reaction of **3b** with methyl methacrylate (entry 5) is noteworthy. It proceeded through a cascade of reactions to give 1-hydroxy-2-methylcarbazole **8**.

In order to increase the utility of the products **4**–**8**, demethylation of the carbazole nitrogen of compound **8** was examined. The literature procedures[11] tested on **8** resulted in formation of complex mixtures of products. Consequently, we chose benzyl derivative **3c** as an annulating agent. Annulation of compound **3c** with methyl acrylate in the presence of LDA gave compound **9** in 64% yield. We then carried out the same type of annulation reaction with several Michael acceptors for the preparation of N-benzylated carbazoles. Compound **3d**, prepared from **1b** also responded to the annulation reaction with methyl crotonate and produced tetrasubstituted carbazole compound **12**. We performed the N-debenzylation of **10a** with $AlCl_3$ in dichloromethane to give carbazole **10b** in 81% yield.[12]

Having recognized the potential use of compound **10a** in the synthesis of murrayafoline-A **15**, we proceeded as shown in Scheme 3. For the crucial demethoxycarbonylation of **10a**, different literature methods[13] were investigated. When subjected to aq NaOH, the reaction stopped after hydrolysis of the ester group to the corresponding acid derivative. The reaction of **10a** with HBr in AcOH returned the starting material even after



Scheme 3. Synthesis of murrayafoline-A.

extended reflux and a similar outcome was obtained when **10a** was treated with DBU in toluene at reflux. Finally, we achieved demethoxycarbonylation of **10a** with concentrated KOH solution in methanol to give **13** in moderate yield. The low yield may be attributed to the sensitivity of 1-hydroxy-3-methylcarbazole **13** to aerial decomposition during its isolation. Compound **13** was converted to the *O*-methyl derivative **14** (77%) by refluxing with a mixture of K_2CO_3 and Me_2SO_4 in acetone. It was observed that compound **14** was stable and easy to handle with respect to **13**. However, debenzylation of compound **14** proved problematical. A wide range of literature methods[14] were investigated for the debenzylation but without success. Finally, debenzylation was successfully accomplished by refluxing *N*-benzylmurrayafoline-A (**14)** in TFA with a catalytic amount of TfOH for 20–25 min to produce **15**. This synthesis of **15** is a formal synthesis of murrayaquinone-A **16**[15] and murrastifoline-F **17**,[16] as they have both been previously reported from compound **15**.

In conclusion, the anionic [4+2] cycloaddition of furoindolones has been introduced as a regioselective route for synthesizing 1-oxygenated carbazoles. Further applications of this methodology for the synthesis of other highly substituted carbazoles and biscarbazoles are underway.

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12. *Selected data:* Compound **3b**: Mp: 147 °C; FT-IR: 1747, 1571, 1456, 1321. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.64 (d, 1H, $J = 8.2$); 7.40–7.50 (m, 2H); 7.15–7.30 (m, 1H); 5.39 (s, 2H); 3.95 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.82, 144.33, 133.87, 128.65, 126.17, 121.07, 120.18, 111.30, 66.98, 30.03; (one signal could not be identified due to overlapping). HRESIMS (*m*/*z*): 188.0709, calcd for $C_{11}H_9NO_2$: 188.0712.
Compound **4**: Mp: 99 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.68 (s, 1H); 8.04 (d, 1H, $J = 7.8$); 7.50–7.66 (m, 3H); 7.40 (d, 1H, $J = 8.1$); 7.21–7.24 (m, 1H); 4.23 (s, 3H); 3.97 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.96, 150.80, 142.29, 128.58, 128.52, 126.42, 122.15, 120.86, 119.48, 119.22, 110.96, 109.09, 107.71, 52.11, 31.94; ESIMS $[M+H]^+$: 256.0979, $[M-OMe]^+$: 224.0728.
Compound **10a**: Mp: 123 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 12.34 (s, 1H); 8.03 (d, 1H, $J = 7.8$); 7.36–7.45 (m, 3H); 7.15–7.26 (m, 6H); 5.94 (s, 2H); 4.00 (s, 3H); 2.68 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.46, 151.92, 150.75, 142.20, 138.94, 130.71, 128.47, 127.56, 127.07, 126.99, 126.48, 122.22, 120.93, 119.37, 113.79, 109.83, 108.18, 52.0, 48.45, 24.57; HRESIMS (*m*/*z*): 346.1442 calcd for $C_{22}H_{19}NO_3$: 346.1443.

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