Diels–Alder and Michael addition reactions of indoles with masked *o*-benzoquinones: synthesis of highly functionalized hydrocarbazoles and 3-arylindoles

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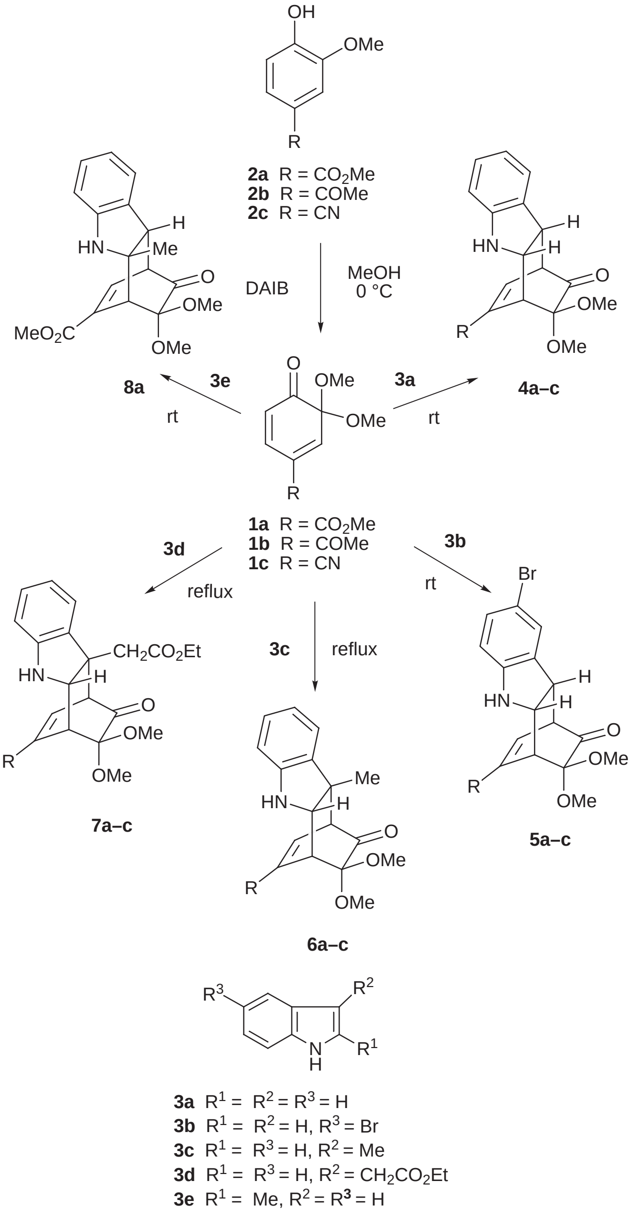
Highly functionalized hydrocarbazoles and 3-arylindoles are prepared from commercially available 2-methoxyphenols and indoles.

The chemistry of indole[1] has been extensively investigated because of the wide-spread occurrence of its skeleton as a basic structural unit of various types of natural products with interesting and useful physiological properties.[2] It is well-known that indole behaves as an enamine towards electrophiles and undergoes Michael addition to electron-deficient alkenes.[1] In contrast, its dienophilic behavior has been reported only on a few occasions.[3–8] Indoles have been found to react as dienophiles in formal [4 + 2] cycloaddition reactions with 3,6-disubstituted 1,2,4,5-tetrazines,[3] tetrachlorothiophene 1,1-dioxide,[4] isoprene,[5] buta-1,3-diene,[5] cyclohexa-1,3-dienes[6] and quinodimethanes.[7] Indole magnesium salts were found to undergo facile cycloaddition reactions with 2-phenylsulfonyl-1,3-dienes.[8] However, indole participates in other types of cycloadditions as an electron-rich alkene.[1]

Masked *o*-benzoquinones (MOBs) are one of the most readily accessible types of cyclohexa-2,4-dienones with immense synthetic potential.[9,10] MOBs have been shown to be efficient dienes and they have been extensively used in this capacity in our laboratory.[9] Following our studies on Diels–Alder reactions of furans with MOBs,[11] we turned our attention to indoles. It was envisioned that if indoles could react with MOBs by cycloaddition, easy access to a variety of potentially useful hydrocarbazoles could be achieved. On the other hand, if indoles add to MOBs by a Michael addition a facile synthesis of highly substituted 3-arylindoles could be achieved. Accordingly, the reactions of selected MOBs **1a**–**c**, generated from phenols **2a**–**c** with a variety of indoles, were examined. We herein report that indoles **3a**–**e** undergo Diels–Alder or Michael addition to MOBs **1a**–**c** depending on the reaction temperature and substitution pattern, to furnish Diels–Alder adducts **4**–**8** or aromatized Michael adducts **9**–**11** in good yields.

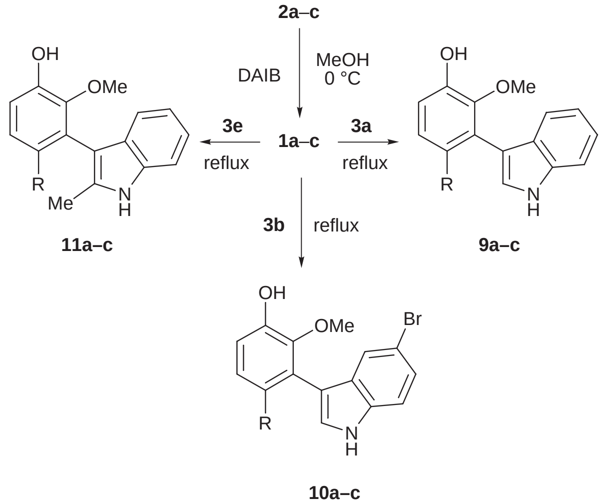
In order to avoid their dimerization, MOBs were usually generated *in situ* from the corresponding 2-methoxyphenols in the presence of a reactive dienophile at a suitable temperature using (diacetoxyiodo)benzene (DAIB) in MeOH. Since indoles are known to react with DAIB,[12] an alternative procedure needed to be developed. Consequently, **1a**–**c** were generated from **2a**–**c** in MeOH by adding DAIB (1.0 equiv.) at 0 °C in MeOH and then an indole derivative was added. After the addition of an indole derivative, the temperature was elevated either to room temperature or to reflux (Schemes 1 and 2, Table 1).[13]

3-Methylindole (**3c**) reacted efficiently only at reflux to furnish the Diels–Alder adducts **6a**–**c** and products which could result *via* Michael addition were not descernible. The reactions of **3d** with **1a**–**c** were found to be sluggish and only Diels–Alder adducts **7a**–**c** were obtained in poor yields. At both room temperature and reflux, 2-methylindole (**3e**) underwent Michael addition to MOBs **1b** and **1c** followed by aromatization of the adducts to provide compounds **11b** and **11c** exclusively in excellent yields. Intriguingly, indole (**3a**) underwent cycloaddition at room temperature to furnish Diels–Alder adducts **4a**–**c** and Michael addition at reflux temperature to afford aromatized Michael adducts **9a**–**c** in good yields. 6-Bromoindole exhibited the same behavior as indole albeit with low efficiency.



Scheme 1

The gross structures of all the products were determined by their IR, ^{1}H and ^{13}C NMR, DEPT, low- and high-resolution mass spectral analysis. The majority of these products provided satisfactory elemental analyses. The regioselectvity of the Diels–Alder reactions was determined by ^{1}H–^{1}H decoupling



Scheme 2

Table 1 Diels–Alder and Michael addition reactions of indoles **3a**–**c** with MOBs **1a**–**c**

Entry	Indole derivative	MOB	Diels–Alder adduct	Yield (%)	Michael[b] adduct	Yield (%)
1	**3a**	**1a**	**4a**[a]	65	**9a**	96
2	**3b**	**1a**	**5a**[a]	50	**10a**	92
3	**3c**	**1a**	**6a**[b]	71	—	—
4	**3d**	**1a**	**7a**[b]	15	—	—
5	**3e**	**1a**	**8a**[a]	24	**11a**	86
6	**3a**	**1b**	**4b**[a]	70	**9b**	91
7	**3b**	**1b**	**5b**[a]	[c]	**10b**	90
8	**3c**	**1b**	**6b**[b]	54	—	—
9	**3d**	**1b**	**7b**[b]	37	—	—
10	**3e**	**1b**	—	—	**11b**	96
11	**3a**	**1c**	**4c**[a]	45	**9c**	53
12	**3b**	**1c**	**5c**[a]	23	**10c**	67
13	**3c**	**1c**	**6c**[b]	39	—	—
14	**3d**	**1c**	**7c**[b]	8	—	—
15	**3e**	**1c**	—	—	**11c**	75

[a] Add indole **3** to a solution of **1** in MeOH at 0 °C, then stir for 1 h at rt. [b] Add indole **3** to a solution of **1** in MeOH at 0 °C, then reflux for 1 h. [c] Not isolable.

experiments in all cases. Their stereoselectivity was predicted to be as shown based on our earlier results with furans[11] and is confirmed in the case of the adduct **7b** by its single crystal X-ray diffraction analysis.[14] Since in all cases the reactions furnished adducts resulting from *endo*-addition, these cycloaddition reactions appear to have followed all the ground rules of Diels–Alder reactions. On the other hand, the Michael addition appears to be highly regioselective. In all cases, only 1,6-addition took place. This result was confirmed by the NMR spectra of the aromatic Michael adducts **9**–**11** and by single crystal X-ray analysis in the case of **10a**.[14]

The exclusive cycloaddition of 3-substituted indoles **3c**,**d** and exclusive Michael addition of 2-methylindole to MOBs at both temperatures is probably due to steric factors. The dual reactivity of indoles lacking substituents needs to be understood. It was reasoned that the initially formed Diels–Alder adducts rearrange to the observed products **9**–**11** at high temperature. In order to test this hypothesis, the Diels–Alder adduct **4a** was refluxed in MeOH in the presence of indole and AcOH but only a complex mixture of products which contained no trace of **9a** was obtained. Hence an alternative mechanism, with **9**–**11** being produced *via* a Michael addition–aromatization sequence, is proposed. This concept has also gained support from the substitution pattern required for the success of these reactions. The presence of electron-withdrawing groups on C-4 of MOBs is essential for the success of these reactions. On the other hand, the presence of electron-withdrawing substituents on the 2- or 3-position of indole prevents both cycloaddition and Michael addition.

In conclusion these reactions are mechanistically interesting and help unravel a new class of dienes that can force indoles to act as dienophiles. These reactions provided easy access to a variety of multifunctional tetracyclic compounds and 3-arylindoles whose synthesis is otherwise difficult. The Diels–Alder adducts of indoles could potentially be useful starting materials in the total synthesis of indole monoterpenoid alkaloids and ellipticine-type compounds with antitumor activity.

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13 Procedure for Diels–Alder or Michael addition reactions of indoles **3** with **1a**–**c**. To a solution of **2** (1.0 mmol) in MeOH (10 ml) at 0 °C was added DAIB (1.0 mmol). After 10 min of stirring, an indole derivative **3** (5–20 mmol) was added at that temperature and the flask was rapidly warmed up to room temperature or to that of reflux by either removing the ice bath or transferring the reaction vessel to a preheated (100 °C) oil bath. The reaction mixture was stirred at either temperature for 1 h. Then MeOH was removed and the residue obtained was purified by flash chromatography on silica gel using 20% of ethyl acetate in hexanes as eluent to obtain Diels–Alder adducts or aromatized Michael adducts.

14 *Crystal data* for **7b**: $C_{22}H_{25}NO_6$, M = 399.43, monoclinic, a = 10.6487(1), b = 22.172(3), c = 8.588(2) Å, β = 95.726(1)°, V = 2017.5(5) Å^3, T = 293(2) K, space group $P2_1/c$, Z = 4, μ(Mo-Kα) = 0.096 mm^{-1}, 3545 reflections measured, 3545 unique (R_{int} = 0.0000). Final R indices [$I > 2\sigma(I)$] $R1$ = 0.0430, $wR2$ = 0.1261. For **10a**: $C_{17}H_{14}BrNO_4$, M = 376.20, triclinic, a = 9.0176(2), b = 9.4144(2), c = 10.3637(1) Å, α = 90.7060(1), β = 96.9180(1), γ = 117.1930(1)°, V = 774.62(2) Å^3, T = 293(2) K, space group $P\bar{1}$, Z = 2, μ(Mo-Kα) = 2.673 mm^{-1}, 7349 reflections measured, 3317 unique (R_{int} = 0.0347). Final R indices [$I > 2\sigma(I)$] $R1$ = 0.0349, $wR2$ = 0.0893. CCDC 182/1310. See http://www.rsc.org/suppdata/cc/1999/1441/ for crystallographic data in .cif format.

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