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Preparation of 3,3-disubstituted oxindoles by addition of malonates to 3-halo-3-oxindoles

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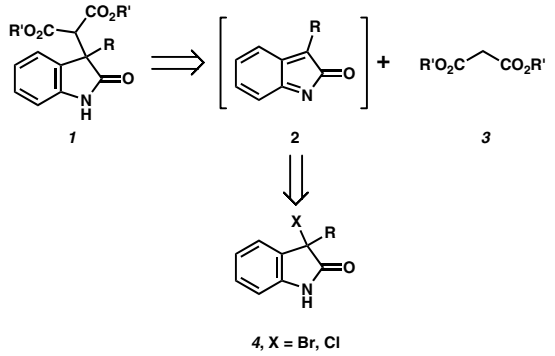
Abstract—A method for the synthesis of 3,3-disubstituted oxindole derivatives is described. This involves the base-mediated addition of malonate esters to 3-halo-3-alkyloxindoles. The addition is tolerant of a range of alkyl substituents at position 3 of the oxindole. Addition to an aryl chloro-oxindole is also described.

Oxindoles are ubiquitous in their presence in nature as well as in pharmaceutically relevant substances.[1] Methods for functionalization of the oxindole nucleus are thus of value in medicinal chemistry and natural product synthesis.

During the course of our studies on the synthesis of alkaloid natural products we sought a convenient preparation of functionalized 3,3-disubstituted oxindoles. To this end we envisioned the formation of **1** via alkylation of a highly reactive electrophilic *o*-azaxylylene intermediate **2** with a suitable nucleophile precursor such as malonate ester **3** (Scheme 1). Compound **2** can in turn be conveniently generated in situ from 3-halo-3-oxindole **4** by base-mediated dehydrohalogenation.

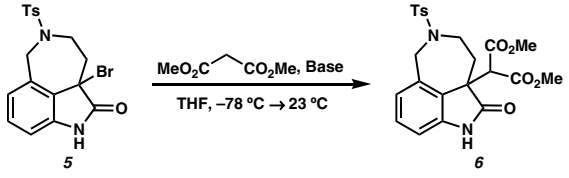


Scheme 1.

Since the first reports of Hinman and Baumann[2] in 1964, the potential of 3-bromo-oxindoles as electrophiles has been realized to only a limited extent.[3] We sought to expand the scope of these electrophiles by employing malonate nucleophiles for the formation of a carbon–carbon bond at C-3 of the oxindole.

We initially chose bromooxindole **5** as a test substrate. On screening a number of bases employing dimethyl malonate as the pro-nucleophile, we discovered that amidine and phosphazene bases promoted the alkylation in high yield (Table 1). We decided to employ

Table 1. Influence of base on bromo-oxindole alkylation



Entry	Base	Yield (%)
1	NaHMDS	27
2	DBU	87
3	P_4-^{t}Bu phosphazene	89
4	BEMP	60
5	Et_3N	Trace

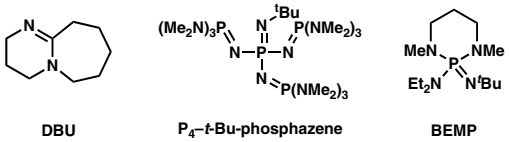


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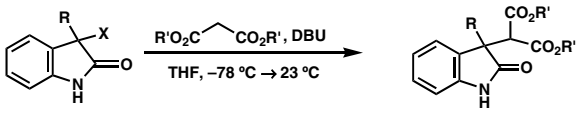
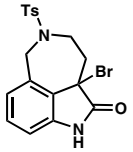
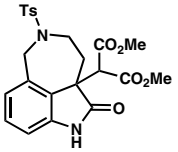
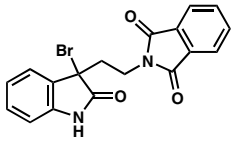
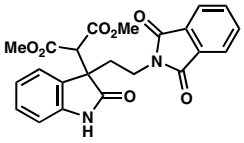
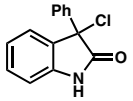
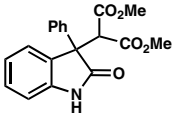
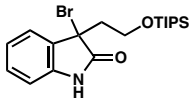
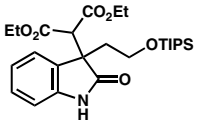
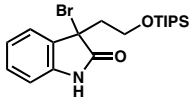
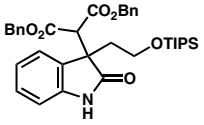
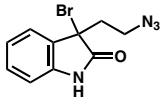
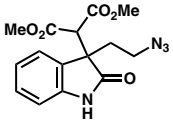
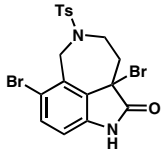
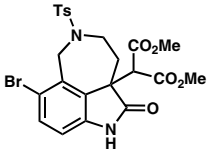
Table 2. Base-promoted addition of malonates to halo-oxindoles



Entry	Halo-oxindole	R′	Product	Yield[a]
1		Me		87
2		Me		79
3		Me		47[b]
4		Et		60
5		Bn		79
6		Me		87
7		Me		68

[a] Isolated yield.
[b] 66% yield obtained when Cs_2CO_3 was employed as base.

1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in our subsequent studies due to its ready availability.

We were able to achieve smooth additions of malonate esters to a variety of 3-bromo-3-alkyloxindoles to generate 3,3-disubstituted oxindoles under mild reaction conditions (Table 2). In addition to dimethyl malonate, diethyl, and dibenzyl malonates delivered the corresponding alkylated products efficiently (entries 4 and 5). A 3-aryl-3-chloro-oxindole could also be employed as the electrophilic component in the reaction (entry 3).

A representative procedure is as follows: Bromo-oxindole **5** (48.2 mg, 0.1144 mmol) was dissolved in THF (1 mL) in the presence of dimethyl malonate (0.3432 mmol, 39 μL). The solution was cooled to −78 °C and DBU (0.3432 mmol, 51 μL) was added dropwise. The reaction mixture was then allowed to warm to 23 °C and quenched by the addition of saturated aqueous NH_4Cl (1 mL), diluted with water (30 mL) and extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine (1 × 30 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield a residue that was purified by silica gel chromatography (1:1 hexanes–EtOAc) to yield adduct **6**[4] as a colorless oil (46.7 mg, 87% yield).

In summary, we have expanded the scope and utility of 3-halooxindoles as electrophiles and have demonstrated their ability to undergo the addition of malonates under mild conditions to generate 3,3-disubstituted oxindoles. We anticipate the utility of this transformation to access biologically relevant oxindoles.

Acknowledgments

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References and notes

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4. $R_f = 0.16$ (1:1 hexanes–EtOAc); IR (film, cm^{-1}): 3339, 2951, 2925, 1731, 1328, 1155, 724; ^1H NMR (300 MHz, $CDCl_3$): 8.02 (br s, 1H, N–*H*), 7.49 (d, *J* 8 Hz, 2H, Ar-*H*), 7.20–7.14 (m, 3H, Ar-*H*), 6.91 (d, *J* 7.5 Hz, 1H, Ar-*H*), 6.79 (d, *J* 7.5 Hz, 1H, Ar-*H*), 4.75 (dd, *J* 15.5, 1 Hz, 1H, ArCH*H*′NTs), 4.43 (s, 1H, C*H*(CO_2Me)$_2$), 4.23 (d, *J* 15.5 Hz, 1H, ArC*H*H′NTs), 4.18 (m, 1H, TsNCH*H*′CH_2–), 3.80 (s, 3H, CO_2CH_3′), 3.65 (m, 1H, TsNC*H*H′CH_2–), 3.37 (s, 3H, CO_2CH_3), 2.51 (m, 1H, ArCH*H*′CH_2NTs), 2.38 (s, 3H, Ar-CH_3), 1.49 (m, 1H, ArC*H*H′CH_2NTs); ^{13}C NMR (75 MHz, $CDCl_3$): 177.6, 166.53, 166.47, 143.4, 141.0, 136.6, 135.7, 129.7, 129.3, 128.9, 127.0, 122.4, 109.6, 52.9, 52.4, 51.44, 51.38, 51.2, 46.6, 30.3, 21.5. MS (FAB) *m*/*z* Calcd for $C_{23}H_{25}N_2O_7S$ (MH^+) 473.1382; found: 473.1402.