Preparation of 3-Alkyl-Oxindoles by Copper(II)-Mediated C–H, Ar–H Coupling Followed by Decarboxyalkylation

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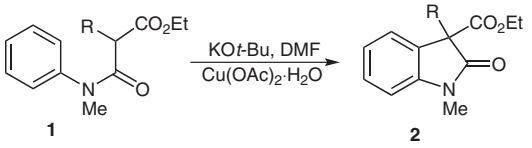
Dedicated to Professor Saverio Florio in celebration of his 70th birthday

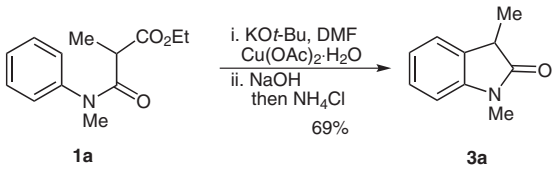
Abstract: A novel route for the conversion of anilides into 3-alkyl-oxindoles is described in which a copper(II)-mediated cyclization process is followed by an acid-mediated decarboxyalkylation. Scope and limitation studies are reported together with a telescoped variant which incorporates in situ *N*-deprotection.

Key words: oxindoles, 3-alkyl-oxindoles, anilides, cyclisation, copper(II) catalysis, C–H activation, decarboxyalkylation

We recently developed a novel copper(II)-mediated route for the conversion of anilides **1** into 3-alkyl-3-carboethoxy-oxindoles **2** by a formal C–H, Ar–H coupling process as shown in Scheme 1.[1,2] In the case of the 3-methylated example **1a** it proved possible to carry out a 'one-pot' cyclisation–decarboxyalkylation process to produce 3-methyl-oxindole (**3a**) in reasonable yield (Scheme 2).[1]



Scheme 1



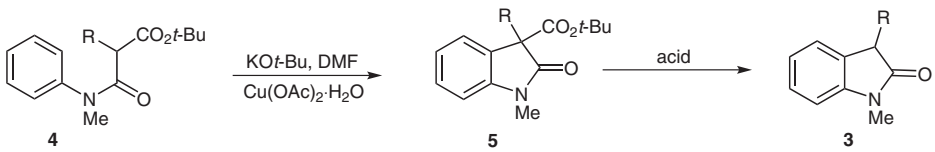
Scheme 2

In view of the utility of 3-alkylated oxindoles as synthetic building blocks[3] and as drug candidates,[4] and given the low yields often observed in the 3-alkylation of oxindoles,[3f] we attempted to generalize this procedure. Unfortunately, the base-mediated saponification–decarboxylation sequence proved to be unsuccessful with other 3-alkyl-3-carboethoxy-oxindoles **2** (e.g., 3-allyl and 3-benzyl analogues); such problems during basic procedures are precedented.[3g,h] As shown in Scheme 3, we therefore proposed the use of the corresponding *tert*-butyl esters **4** to evaluate their utility[5] in the copper(II)-mediated cyclization process with a view to exploring an acid-mediated route to 3-alkyl-oxindoles **3**.

To test this approach, anilide **4a** (R = Me) was prepared as shown in Scheme 4.[6] Thus, Mukaiyama coupling[7] of *N*-methylaniline (**6**) and *tert*-butyl malonate (**7**) gave amide **8** in essentially quantitative yield. Alkylation using methyl iodide also proceeded efficiently to give cyclization precursor **4a**. The key copper(II)-mediated cyclization was investigated next using the $Cu(OAc)_2 \cdot H_2O$–DMF procedure developed earlier.[1] We were delighted to observe the formation of oxindole **5a** in good yield using these conditions. The second crucial step in this sequence, the acid-mediated decarboxyalkylation to produce 3-methyl-oxindole (**3a**), proved to be relatively straightforward (Scheme 4). This transformation could be achieved using several acids but neat TFA (with anisole as a cation trap)[8] at room temperature proved to be the most effective.

Having established the viability of the copper(II)-mediated cyclization route on *tert*-butyl ester **4a** and the decarboxyalkylation of *tert*-butyl ester **5a**, we went on to explore the scope of this cyclisation–decarboxyalkylation sequence with a range of anilides **4**[9] (Table 1).

As can be seen, this cyclisation–decarboxyalkylation sequence was used to prepare a range of 3-substituted oxindoles including those with saturated alkyl substituents (entries 1–3), allyl, benzyl, phenethyl, and naphthylmethyl substituents (entries 4–7), as well as the benzyloxypro-



Scheme 3

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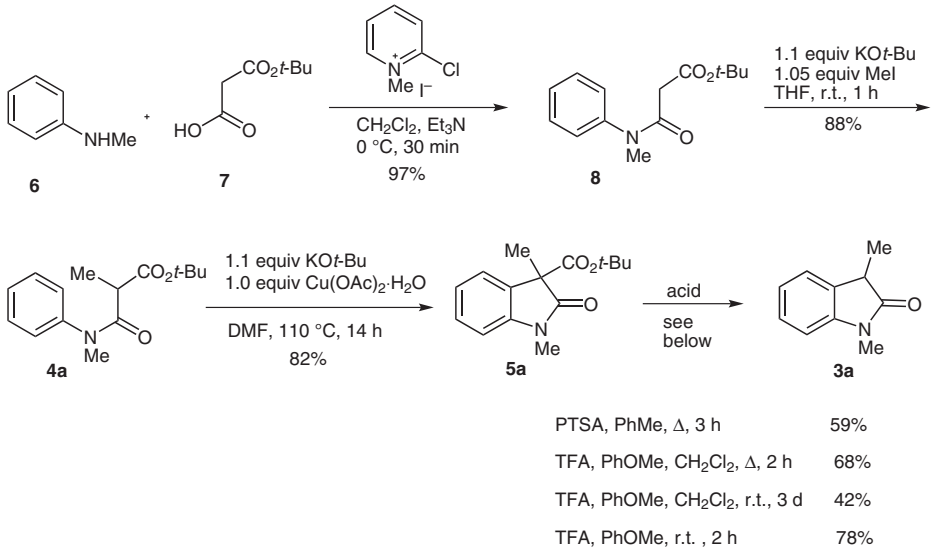
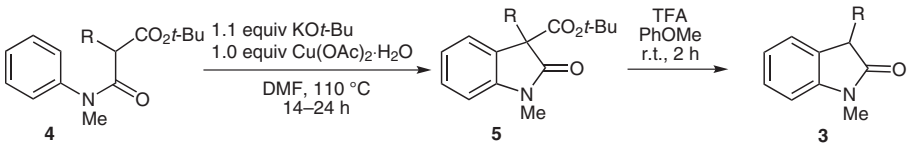


Scheme 4

pyl (entry 8) and 4-pyridylmethyl (entry 9) examples. All reactions proceeded in the expected manner in fair to excellent yield. The conditions devised for **4a** and **5a** (Scheme 4) were employed in all examples; it is likely that the lower yields could be improved with further optimization studies. One notable observation from this study is the profound steric effect observed for the cyclization of the isopropyl system with oxindole **5c** being obtained in only 42% yield after a reaction time of 72 hours.

Table 1 Scope of the Cyclisation–Decarboxyalkylation Sequence



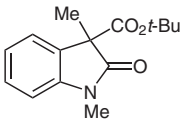
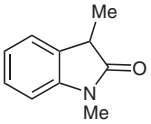
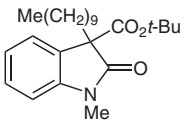
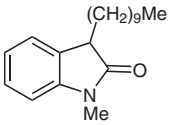
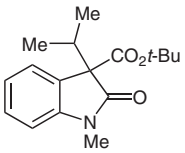
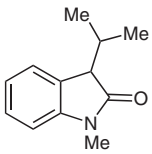
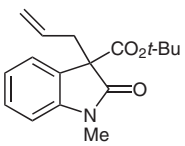
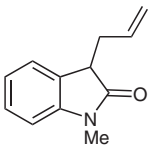
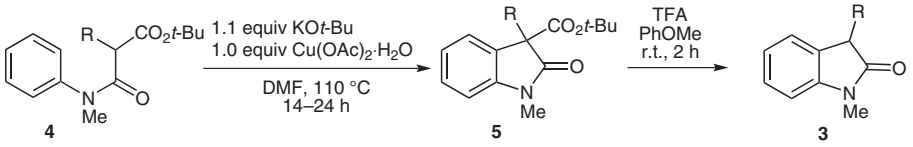
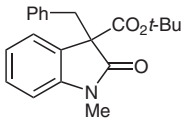
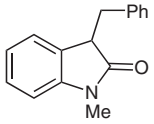
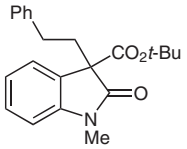
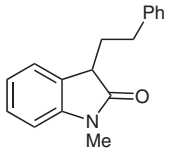
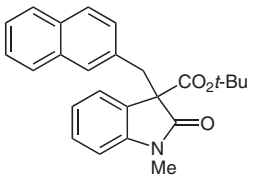
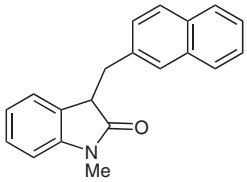
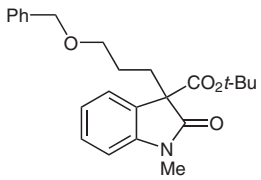
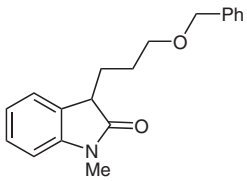
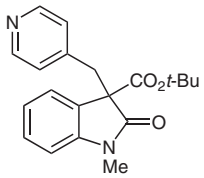
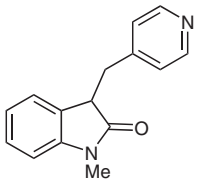
Entry	Cyclisation product **5**	Yield **5** (%)	3-Alkyl-oxindole **3**	Yield **3** (%)
1	 **5a**	82	 **3a**	78
2	 **5b**	76	 **3b**	90
3	 **5c**	46[a]	 **3c**	68
4	 **5d**	59	 **3d**	92

Table 1 Scope of the Cyclisation–Decarboxyalkylation Sequence (continued)



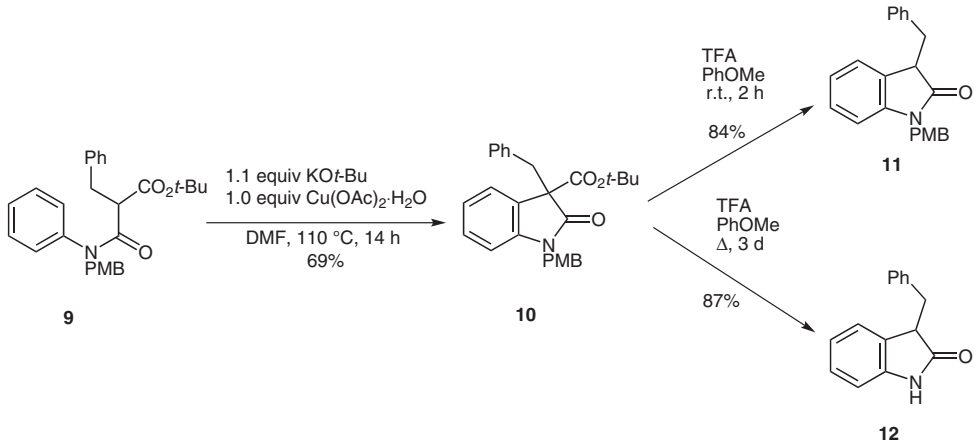
Entry	Cyclisation product **5**	Yield **5** (%)	3-Alkyl-oxindole **3**	Yield **3** (%)
5	 **5e**	93	 **3e**	98
6	 **5f**	71	 **3f**	62
7	 **5g**	73[10]	 **3g**	93[11]
8	 **5h**	65	 **3h**	86
9	 **5i**	68	 **3i**	92

[a]A reaction time of 72 h was required.

Finally, we briefly explored the utility of this methodology for the preparation of unprotected oxindoles (Scheme 5). Thus, we established that *p*-methoxybenzyl (PMB) protection is compatible with the copper(II)-mediated cyclization (**9** → **10**) and then investigated deprotection protocols.

Treatment of oxindole **10** using the TFA and room temperature conditions developed earlier, for 2 hours, gave efficient decarboxyalkylation producing the *N*-PMB-protected 3-benzyl-oxindole **11** in excellent yield. The use of a higher temperature and a longer reaction time gave both decarboxyalkylation and *N*-deprotection producing 3-benzyl-oxindole **12** in 87% yield. The complementarity of these deprotection procedures should be of value when the product oxindoles are required for further synthetic elaboration.

In summary, an inexpensive and operationally straightforward sequence for the conversion of readily available anilides **4** into 3-substituted-*N*-methyl-oxindoles **3** has been developed, based on a copper(II)-mediated C–H, Ar–H coupling process followed by decarboxyalkylation. This procedure is compatible with alkyl, arylalkyl, and functionalized substituents and can also be utilized to prepare 3-substituted oxindoles in the N–H form. We are currently applying this new methodology in natural product areas.



Scheme 5

Acknowledgment

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(9) Prepared by the alkylation of amide **8** using the route shown in Scheme 4; all yields were greater than 88% with the exceptions of *i*-Pr (**5c**, 55%), $PhCH_2CH_2$ (**5f**, 63%), $PhCH_2O(CH_2)_3$ (**5h**, 69%), and 4-$PyCH_2$ (**5i**, 46%).

(10) **Representative Procedure for the Copper-Mediated Cyclisation: *tert*-Butyl 1-Methyl-3-(naphthalen-2-yl-methyl)-2-oxoindoline-3-carboxylate (5g)**
A 100 mL round-bottomed flask fitted with a condenser and stirrer-bar was charged with *tert*-butyl ester **4g** (R = naphthalen-2-yl-methyl, 195 mg, 0.50 mmol) and DMF (10 mL). KO*t*-Bu (62 mg, 0.55 mmol) was added in a single portion, followed by copper(II) acetate monohydrate (100 mg, 0.50 mmol). The green-black suspension was heated to 110 °C (oil bath temperature) over 15 min. After stirring at 110 °C for 18 h, the reaction was cooled to r.t. and quenched with a sat. solution of NH_4Cl (10 mL), diluted with H_2O (20 mL), and extracted with EtOAc (20 mL). The organic layer was washed with a sat. brine solution (2 × 20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to give an orange oil. Purification by flash column chromatography (SiO_2, 7:2:1 PE–CH_2Cl_2–EtOAc) gave product **5g** (141 mg, 73%) as a colorless gum; R_f = 0.44 (3:1 PE–EtOAc). IR (film): ν_{max} = 3056, 2978, 2932, 1734, 1715, 1610, 1493, 1471, 1370, 1351, 1306, 1251, 1155, 1086, 997, 909, 750 cm^{-1}. ^1H NMR (400 MHz, $CHCl_3$-d_1): δ = 1.41 (9 H, s, CMe_3), 2.89 (3 H, s, NMe), 3.64 (1 H, d, *J* = 13.5 Hz, CH_2), 3.69 (1 H, d, *J* = 13.5 Hz, CH_2), 6.50 (1 H, d, *J* = 7.5 Hz, ArH), 6.98 (1 H, dd, *J* = 8.5, 2.0 Hz, ArH), 7.06 (1 H, ddd, *J* = 7.5, 7.5, 1.0 Hz, ArH), 7.17 (1 H, ddd, *J* = 7.5, 7.5, 1.5 Hz, ArH), 7.33–7.37 (3 H, m, ArH), 7.38 (1 H, ddd, *J* = 7.5, 1.5, 0.5 Hz, ArH), 7.48 (1 H, d, *J* = 8.5 Hz, ArH), 7.60 (1 H, dd, *J* = 6.0, 3.5 Hz, ArH), 7.67 (1 H, dd, *J* = 6.0, 3.5 Hz, ArH). ^{13}C NMR (100 MHz, $CHCl_3$-d_1): δ = 26.1 (NMe), 27.8 (CMe_3), 39.7 (CH_2), 61.8 (C), 82.6 [$OC(CH_3)_3$], 108.1 (ArH), 122.3 (ArH), 123.6 (ArH), 125.4 (ArH), 125.5 (ArH), 126.9 (ArH), 127.3 (ArH), 127.7 (ArH), 127.8 (Ar), 128.3 (ArH), 128.8 (2 × ArH), 132.1 (Ar), 132.5 (Ar), 132.9 (Ar), 144.1 (Ar), 168.1 (C=O), 173.8 (C=O). ESI-MS: *m/z* = 410 $[MNa]^+$. ESI-HRMS: *m/z* calcd for $C_{25}H_{25}NNaO_3$: 410.1727; found: 410.1731 $[MNa]^+$; 0.6 ppm error.

(11) **Representative Procedure for Decarboxyalkylation: 1-Methyl-3-(naphthalen-2-ylmethyl) indolin-2-one (3g)**
A 10 mL round-bottomed flask with stirrer bar was charged with *tert*-butyl ester **5g** (97 mg, 0.25 mmol) and anisole (82 μL, 0.75 mmol), a septum was fitted and the flask purged with argon(balloon). TFA (1 mL) was added, and the resulting brown solution was stirred for 2 h. The reaction mixture was concentrated in vacuo to give a yellow gum. Purification by flash column chromatography (SiO_2, 4:1 PE–EtOAc) gave oxindole **3g** (67 mg, 93%) as a yellow solid.

R_f = 0.39 (3:1 PE–EtOAc); mp 91–93 °C. IR (film): ν_{max} = 3053, 2920, 2853, 1709, 1612, 1493, 1469, 1422, 1375, 1350, 1256, 1127, 1089, 750, 732 cm^{-1}. ^1H NMR (400 MHz, $CHCl_3$-d_1): δ = 3.04 (1 H, dd, *J* = 13.5, 9.5 Hz, CH_2), 3.17 (3 H, s, NMe), 3.67 (1 H, dd, *J* = 13.5, 4.5 Hz, CH_2), 3.84 (1 H, dd, *J* = 9.5, 4.5 Hz, CH), 6.71–6.77 (2 H, m, *J* = 7.5 Hz, ArH), 6.88 (1 H, ddd, *J* = 7.5, 7.5, 1.0 Hz, ArH), 7.21 (1 H, dd, *J* = 8.0, 8.0 Hz, ArH), 7.34 (1 H, dd, *J* = 8.5, 1.5 Hz, ArH), 7.43–7.47 (2 H, m, ArH), 7.60 (1 H, br s, ArH), 7.73–7.82 (3 H, m, ArH). ^{13}C NMR (100 MHz, $CHCl_3$-d_1): δ = 26.2 (NMe), 37.0 (CH_2), 46.9 (CH), 107.9 (ArH), 122.1 (ArH), 124.5 (ArH), 125.5 (ArH), 126.0 (ArH), 127.6 (3 × ArH), 127.9 (2 × ArH), 128.0 (ArH), 128.3 (Ar), 132.3 (Ar), 133.3 (Ar), 135.5 (Ar), 144.1 (Ar), 177.0 (C=O). ESI-MS: *m/z* = 310 $[MNa]^+$. ESI-HRMS: *m/z* calcd for $C_{20}H_{17}NNaO$: 310.1202; found: 310.1196 $[MNa]^+$; 1.6 ppm error.