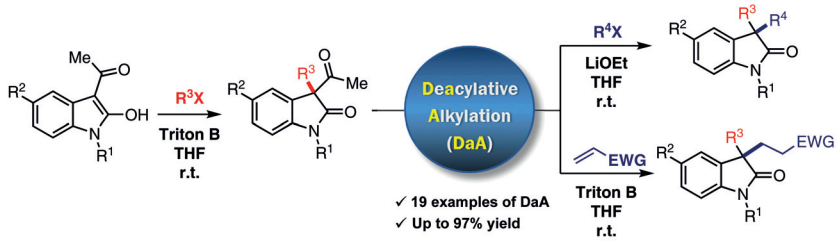
Synthesis A. Ortega-Martínez et al. Paper

Synthesis of 3,3-Disubstituted 2-Oxindoles by Deacylative Alkylation of 3-Acetyl-2-oxindoles

Aitor Ortega-Martínez[a,b]
Cynthia Molina[a,b]
Cristina Moreno-Cabrerizo[a,b]
José M. Sansano[*a,b]
Carmen Nájera[*a]

[a] Departamento de Química Orgánica and Centro de Innovación en Química Avanzada (ORFEO-CINQA), Facultad de Ciencias, Universidad de Alicante, 03080-Alicante, Spain
jmsansano@ua.es
cnajera@ua.es
[b] Instituto de Síntesis Orgánica, Facultad de Ciencias, Universidad de Alicante, 03080-Alicante, Spain



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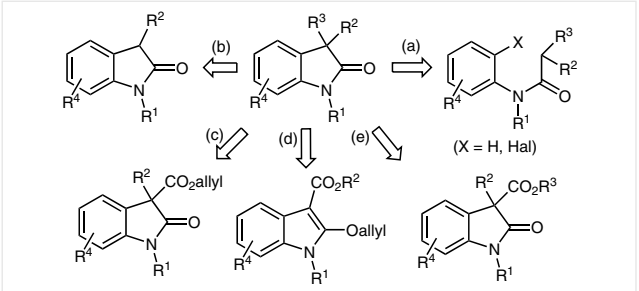
Abstract An innovative and efficient monoalkylation and nonsymmetrical 3,3-dialkylation of oxindoles has been achieved. First, the monoalkylation of 3-acetyl-2-oxindoles can be performed in good yields under mild reaction conditions using alkyl halides and benzyltrimethylammonium hydroxide (Triton B) as base at room temperature. This methodology is applied to construct the synthetically challenging compound 1,3-dimethyl-2-oxindole. Subsequent deacylative alkylation (DaA) of the alkylated 3-acetyl-2-oxindoles with alkyl halides takes place efficiently using LiOEt or by conjugate addition with electron-deficient alkenes in the presence of Triton B at room temperature under argon, affording the corresponding unsymmetrically 3,3-disubstituted 2-oxindoles. This simple methodology has been applied to the synthesis of precursors of horsfiline, esermethole, physostigmine, and phenserine alkaloids.

Key words deacylation, alkylation, 2-oxindoles, Michael addition, Triton B

In the last years, the family of 3,3-disubstituted 2-oxindoles has attracted attention because this unit is present in many natural products and synthetic drugs.[1] Two main synthetic strategies have been developed for the synthesis of these compounds based on: (a) intramolecular coupling reactions such as Heck reactions,[2] arylations of *o*-halogenated[3] and unsubstituted[4] anilides, and (b) alkylation of 3-substituted 2-oxindoles[5] (Scheme 1). Recently, (c) Pd-catalyzed decarboxylative allylation and benzylation reactions,[6] (d) the Meerwein–Eschenmoser–Claisen rearrangement,[7] and (e) Pd-catalyzed deacylative allylation[8] have also been employed for the generation of a quaternary stereocenter at the 3-position of 2-oxindoles.

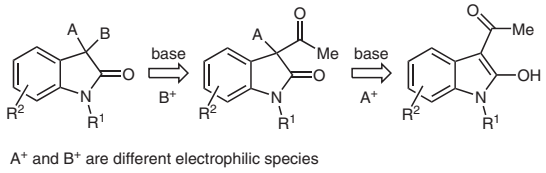
The deacylative alkylation (DaA) reaction employs the acetyl group as protecting, activating, and leaving group for the alkylation of enolates and has been performed mainly under Pd-catalyzed conditions for the introduction of allyl groups.[9] Detrifluoroacetylative reactions have been studied for the generation of fluoroenolates[10] and applied to the synthesis of 3-fluoro-2-oxindole enolates for subsequent Mannich reactions.[11]



Scheme 1 Retrosynthetic analysis for the synthesis of 3,3-disubstituted 2-oxindoles

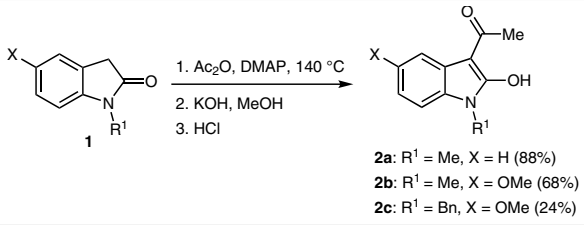
However, direct and selective successive alkylation of 2-oxindoles with different electrophiles is not an easy synthetic strategy because the first monoalkylation step is difficult to control and requires strong bases for the generation of the corresponding enolate. We envisaged that DaA could be an excellent strategy for the synthesis of 3,3-dialkylated 2-oxindoles. In this work, we describe a base-mediated monoalkylation of 3-acetyl-2-oxindoles followed by a DaA as a simple process for the synthesis of 3,3-dialkylated oxindoles (Scheme 2).

Monoacylated *N*-methyloxindole **2a** was prepared from the corresponding 2-oxindole **1a**, which is commercially available, by reaction with acetic anhydride in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) at 140 °C for 5 h.[12] Due to the concomitant acylation at the C3 carbon and at the oxygen atom, the reaction mixture was treated with KOH in MeOH followed by concentrated aqueous HCl



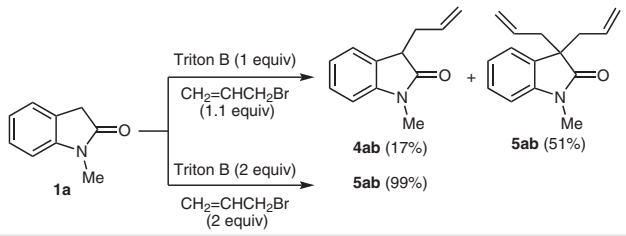
Scheme 2 Our proposal for the synthesis of 3,3-disubstituted 2-oxindoles

to afford compound **2a** in 88% yield (Scheme 3). For the synthesis of oxindoles **2b** and **2c**, 5-methoxyisatin was transformed into the corresponding 2-oxindoles **1b**[13] and **1c**[14,15] according to reported procedures. Further acylation of **1b** and **1c** gave **2b** and **2c** in 68% and 24% overall yield, respectively.



Scheme 3 Synthesis of 3-acetyl-2-oxindoles **2**

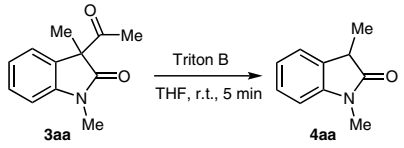
When these reaction conditions were assayed with unsubstituted *N*-methyl-2-oxindole (**1a**) and allyl bromide, the formation of a mixture of monoallylated **4ab** and diallylated **5ab** oxindole in 17% and 51% yield, respectively, was observed (Scheme 4). Upon increasing the amount of base and allyl bromide to 2 equiv, only diallylated compound **5ab** was formed quantitatively.



Scheme 4 Allylation of *N*-methyl-2-oxindole **1a**

However, when compound **3aa** was treated with Triton B it was possible to prepare 3-monomethylated oxindole **4aa** in 67% yield (Scheme 5), which is an important starting compound for the synthesis of alkaloids (see below). Therefore, this methodology can be applied to the selective synthesis of 3-monoalkylated oxindoles **4**.

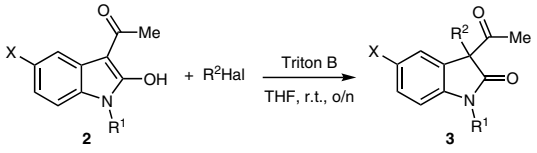
The alkylation of **2** was initially performed with LiOEt as base and allyl bromide, affording the allylated product **3ab** in less than 5% yield. However, when Triton B (40wt% in MeOH) was used as base in tetrahydrofuran (THF), at room

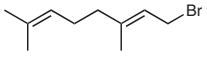


Scheme 5 Synthesis of 1,3-dimethyl-2-oxindole **4aa**

temperature, the corresponding allylated product **3ab** was obtained in 84% yield (Table 1, entry 2). These reaction conditions were employed for the alkylation of **2** with different alkyl halides to give the desired products **3** in good yield (Table 1). Under these reaction conditions the alkylation took place regioselectively at the 3-position of the oxindole. Only in the case of *n*-pentyl bromide the reaction needed to be carried out under reflux (entry 6). In the case of methyl bromoacetate, the methyl ester was used to avoid transesterification with MeOH (entry 7). Compounds **3** were sensitive to deacylation during the purification by flash chromatography, affording the monoalkylated 2-oxindoles **4** in less than 10% (entries 2–7).

Table 1 Monoalkylation of 3-Acetyl-2-oxindoles **2**[a]



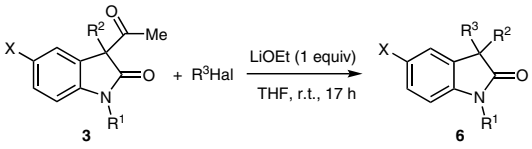
Entry	2	X	R^1	R^2Hal	3	Yield (%)[b]
1	**2a**[c]	H	Me	MeI	**3aa**	88
2	**2a**	H	Me		**3ab**	84[d]
3	**2a**	H	Me		**3ac**	54[e]
4	**2a**	H	Me		**3ad**	68[e]
5	**2a**	H	Me	$PhCH_2Br$	**3ae**	84[f]
6	**2a**[g]	H	Me	n-$C_5H_{11}Br$	**3af**	50[h,d]
7	**2a**	H	Me	MeO_2CCH_2Br	**3ag**	69[i]
8	**2b**[j]	OMe	Me	MeI	**3ba**	85
9	**2c**[k]	OMe	Bn	MeI	**3ca**	92

[a] The reaction was performed on a 1.2 mmol scale at r.t. overnight in a **2**/R^2Hal molar ratio of 1:1.
[b] Isolated yield after flash chromatography.
[c] MeI (2 equiv) was used on a 7.2 mmol scale.
[d] 6% deacylated compound was also obtained.
[e] 4% deacylated compound was also obtained.
[f] 5% deacylated compound was also obtained and the reaction was scaled up to 1.8 mmol.
[g] 0.3 mmol scale.
[h] Under reflux.
[i] 10% deacylated compound was also obtained.
[j] 4.6 mmol scale.
[k] 0.6 mmol scale.

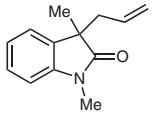
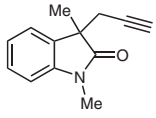
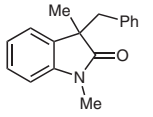
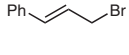
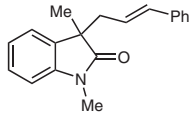
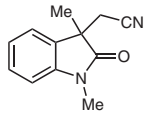
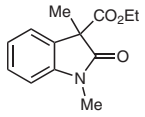
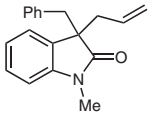
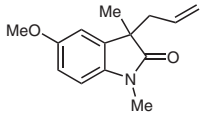
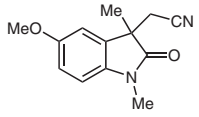
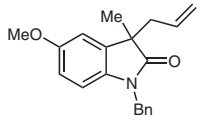
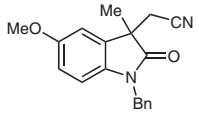
For the deacylative alkylation (DaA) of **3**, several basic conditions were tested, the best results were obtained with a 1 M solution of lithium ethoxide in anhydrous THF at room temperature under argon was used, which avoided the formation of deacylated compounds **4**. Under these reaction conditions, the preparation of 3,3-dialkylated compounds **6** could be successfully performed (Table 2). In the case of the allylation of compound **3ae** using Triton B instead of LiOEt, a lower yield was obtained for product **6afb** (Table 2, compare entries 7 and 8). This reaction took place by attack of the base to the acetyl group, forming the corresponding lithium enolate, which underwent regioselective alkylation at the 3-position.

Compounds **6bab** and **6cab**, derived from *N*-methyl- and *N*-benzyl-5-methoxy-2-oxindoles **1b** and **1c**, respectively, are precursors of the racemic natural alkaloid horsfiline **7**[16] and also of esermethole **8a**,[17] which is an intermediate for the synthesis of acetylcholinesterase inhibitors physostigmine **8b** and phenserine **8c**[18] (Figure 1). Derivatives **6bai** and **6cai** are also precursors of esermethole **8a** and physostigmine **8b** through a shorter synthetic pathway than **6bab** or **6cab**.[19]

Table 2 DaA of 3-Acetyl-2-oxindoles **3** with Alkyl Halides[a]

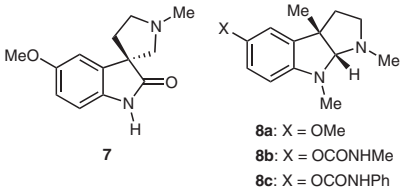


3 **6**

Entry	3	R^3Hal	Product	6	Yield (%)[b]
1	**3aa**	CH_2=$CHCH_2Br$		**6aab**	72
2	**3aa**			**6aad**	69
3	**3aa**	$PhCH_2Br$		**6aae**	87
4	**3aa**			**6aah**	75[c]
5	**3aa**	$NCCH_2Br$		**6aai**	88
6	**3aa**	EtO_2CCl		**6aaj**	65
7	**3ae**	CH_2=$CHCH_2Br$		**6aeb**	67
8	**3ae**	CH_2=$CHCH_2Br$		**6aeb**	58[d]
9	**3ba**	CH_2=$CHCH_2Br$		**6bab**	75
10	**3ba**	$NCCH_2Br$		**6bai**	93[e]
11	**3ca**	CH_2=$CHCH_2Br$		**6cab**	70
12	**3ca**	$NCCH_2Br$		**6cai**	74

[a] The reaction was performed on a 0.15 mmol scale at r.t. overnight in a **3**/R^3Hal molar ratio of 1:1.
[b] Isolated yield after flash chromatography.
[c] Cinnamyl bromide (1.5 equiv) was used.
[d] With Triton B as base (1 equiv).
[e] 2 mmol scale.

Conjugate addition of **3aa** to electrophilic alkenes was also studied using DaA. In this case, Triton B was a better base than LiOEt, giving, in THF at room temperature under argon, **9** in good yields (Table 3). Only in the absence of oxygen was not the formation of 3-hydroxy-3-methyl-2-oxindole observed (less than 5%). Acrylic systems gave the corresponding products in high yields. In the case of phenyl vinyl sulfone, a lower yield (51%) was observed with



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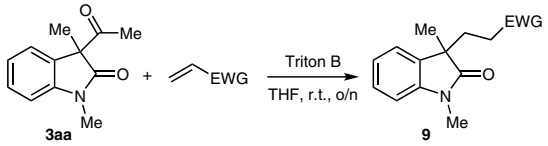
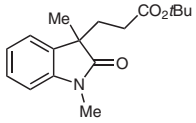
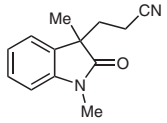
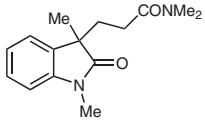
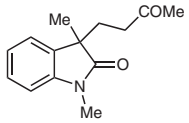
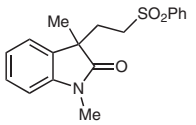
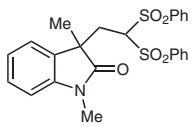
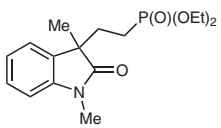
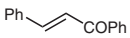
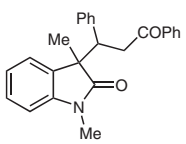
8a: X = OMe
8b: X = OCONHMe
8c: X = OCONHPh

Figure 1 Natural alkaloids whose synthetic intermediates can be accessed by using this methodology

Table 3 DaA of 3-Acetyl-2-oxindoles **3** with Electrophilic Alkenes[a]



Entry	Alkenes	Product	9	Yield (%)[b]
1	CH_2=$CHCO_2tBu$		**9aa**	90
2	CH_2=CHCN		**9ab**	89
3	CH_2=$CHCONMe_2$		**9ac**	86
4	CH_2=CHCOMe		**9ad**	86
5	CH_2=$CHSO_2Ph$		**9ae**	51[c]
6	CH_2=$C(SO_2Ph)_2$		**9af**	83
7	CH_2=$CHP(O)(OEt)_2$		**9ag**	85
8			**9ah**	97[d]

[a] The reaction was performed on a 0.15 mmol scale at r.t. overnight in a 1:1.4 molar ratio.
[b] Isolated yield after flash chromatography.
[c] The O-alkylated product (13%) was also obtained using phenyl vinyl sulfone (1 equiv).
[d] A 1:0.7 mixture of diastereomers was formed.

formation of 13% of *O*-alkylated product (entry 5). However, the more electrophilic 1,1-disulfone, gave product **9af** exclusively in 83% yield (entry 6). When chalcone was used as electrophile, a 1:0.7 mixture of diastereoisomers was obtained (entry 8).

It can be concluded that the acetylation of 2-oxindoles allows their monoalkylation under mild conditions using Triton B as base. By subsequent deacetylation it is possible to prepare the corresponding 3-alkylated 2-oxindoles. The 3-substituted 3-acetyl-2-oxindoles can undergo deacylative alkylation with alkyl halides in the presence of LiOEt or with electrophilic alkenes by means of Triton B, affording the corresponding 3,3-disubstituted 2-oxindoles under very mild reaction conditions. This methodology is suitable for the preparation of unsymmetrical 3,3-disubstituted oxindoles, which cannot be easily prepared by other strategies.

Melting points were determined with a Marienfeld melting-point meter (MPM-H2) apparatus and are uncorrected. For flash chromatography, silica gel 60 (40–60 μm) was employed. ^{1}H NMR (300, 400 MHz or 500 MHz) and ^{13}C NMR (75, 101 or 126 MHz) spectra were recorded with Bruker AV300, Bruker AV400, and Bruker ADVANCE DRX500, respectively, with $CDCl_3$ as solvent and TMS as internal standard for ^{1}H NMR spectra, and the chloroform signal for ^{13}C NMR spectra; chemical shifts are given in ppm. Low-resolution electron impact (GC-EI) mass spectra were obtained at 70 eV with an Agilent 6890N Network GC system and an Agilent 5973Network Mass Selective Detector. High-resolution mass spectra (GC-EI) were recorded with a QTOF Agilent 7200 instrument for the exact mass and Agilent 7890B for the GC. Analytical TLC was performed using ALUGRAM® Xtra SIL G/UV_{254} silica gel plates, and the spots were detected under UV light (λ=254 nm).

Synthesis of 1-(2-Hydroxy-1-methyl-1*H*-indol-3-yl)ethanone (2a)

To a round-bottom flask containing a solution of *N*-methyl-2-oxindole (4.85 g, 33 mmol) in acetic anhydride (36 mL, 381 mmol), DMAP (118 mg, 0.96 mmol) was added. The mixture was heated at 140 °C for 5 h. The mixture was evaporated under reduced pressure, the crude residue was dissolved in MeOH (80 mL) and a solution of KOH (18 g, 321 mmol) in MeOH (120 mL) at 0 °C was added. The solution was stirred at r.t. for 22 h then cooled in an ice-bath at 0 °C and 12 M aqueous HCl was added until pH 3. At this point, H_2O (140 mL) was added and the solution was extracted with EtOAc (3 × 140 mL). The organic phases were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc) to give pure **2a**.

Yield: 5.5 g (88%); purple solid; mp 109–110 °C (hexane/EtOAc) (Lit.[12] 110–111 °C).

The spectral data are consistent with reported data.[12]

Synthesis of 1-(2-Hydroxy-1-methyl-5-methoxy-1*H*-indol-3-yl)ethanone (2b)

A round-bottom flask containing a solution of 5-methoxyisatin (3.54 g, 20 mmol) in anhydrous DMF (40 mL) was cooled to 0 °C, then sodium hydride (606 mg, 24 mmol) was added in one portion and the mixture was stirred for 5 min. Iodomethane was added (1.84 mL, 30

mmol) and the mixture was stirred at 0 °C for 30 min. The mixture was poured in saturated aqueous NH_4Cl (20 mL) and extracted with dichloromethane (3 × 40 mL). The organic phase was washed with H_2O (3 × 15 mL) and brine (20 mL), dried over $MgSO_4$, and evaporated under vacuum. The dark-red solid was dissolved in hydrazine monohydrate (12 mL, 247 mmol) and heated at 130 °C for 3 h. After cooling the solution to r.t., H_2O (50 mL) was added and the mixture was extracted with EtOAc (3 × 50 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), and dried over $MgSO_4$, filtered and concentrated.[13] To the resulting residue, acetic anhydride (22.5 mL, 238 mmol) was added. Then, DMAP (73.3 mg, 0.6 mmol) was added and the mixture was heated at reflux (140 °C) for 5 h and then evaporated under reduced pressure. The residue was dissolved in MeOH (50 mL), then a solution of KOH (11 g, 196 mmol) in MeOH (70 mL) at 0 °C was added. The solution was stirred at r.t. for 22 h and then cooled in an ice-bath at 0 °C. A solution of 12 M aqueous HCl was added until pH 3. The organic solvent was evaporated and the residue was extracted with EtOAc (3 × 100 mL), washed with H_2O (100 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc) to give pure **2b**.

Overall yield: 2.97 g (68%); purple solid; mp 83–84 °C (hexane/EtOAc) (Lit.[20] 83 °C).

The spectral data are consistent with reported data.[20]

Synthesis of 1-(1-Benzyl-2-hydroxy-5-methoxy-1*H*-indol-3-yl)ethanone (2c)

A mixture of 5-methoxyisatin (2.84 g, 16 mmol) and K_2CO_3 (5.53 g, 40 mmol) was dissolved in anhydrous DMF (12 mL) under Ar. Benzyl bromide (5.71 mL, 48 mmol) was added dropwise and the mixture was stirred at r.t. for 19 h. The mixture was extracted with dichloromethane (3 × 20 mL) and the organic phase was washed with H_2O (20 mL) and brine (20 mL), dried with $MgSO_4$, filtered, and concentrated to obtain a red solid.[14] The crude material was dissolved in DMSO (12 mL), hydrazine hydrate (1.81 mL, 32 mmol) was added dropwise and the mixture was heated at 150 °C for 5 h. The mixture was cooled to r.t., extracted with EtOAc (2 × 100 mL), and the organic phase was washed with H_2O (100 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc) to give pure 1-benzyl-5-methoxy-2-oxindole (2.55 g, 63%) as a brown oil.[15]

The above product was dissolved in acetic anhydride (11.5 mL, 121 mmol) and DMAP (37 mg, 0.3 mmol) was added. The mixture was heated at reflux (140 °C) for 6 h and then cooled to r.t. and evaporated under reduced pressure. The residue was dissolved in MeOH (40 mL) cooled at 0 °C and then a solution of KOH (8.5 g, 151 mmol) in MeOH (60 mL) was added. The solution was stirred at r.t. for 18 h then the solution was cooled in an ice-bath at 0 °C and 12 M aqueous HCl was added until pH 3. The organic solvent was evaporated under reduced pressure, H_2O (50 mL) was added and the mixture was extracted with EtOAc (3 × 50 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc) to give pure **2c**.

Overall yield: 1.15 g (24%); brown solid; mp 145–146 °C (hexane/EtOAc) (Lit.[21] 150–151 °C).

The spectral data are consistent with reported data.

Monoalkylation of 3-Acetyl-2-oxindoles 2; General Procedure

To a solution of 3-acetyl-2-oxindole **2** (227 mg, 1.2 mmol) and alkyl halide (1.2 mmol) in THF (7 mL) was added benzyltrimethylammonium hydroxide (Triton B) in MeOH (40wt%, 0.545 mL, 1.2 mmol). The reaction was stirred at r.t. overnight, H_2O (20 mL) was added, the mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were evaporated and dried over $MgSO_4$. After evaporation of the solvents the residue was purified by flash chromatography (EtOAc/hexane) to afford the corresponding product **3** (see, Table 1).

Compounds **3aa** (1.36 g, 88%),[22] **3ae** (341 mg, 84%),[22] **3ba** (899 mg, 85%),[23] and **3ca** (171 mg, 92%),[22] are known.

3-Acetyl-3-allyl-1-methylindolin-2-one (3ab)

Yield: 192 mg (84%); pale-yellow oil.

^{1}H NMR (300 MHz): δ = 7.36 (td, *J* = 7.7, 1.4 Hz, 1 H), 7.18 (dd, *J* = 7.4, 1.0 Hz, 1 H), 7.10 (td, *J* = 7.5, 1.0 Hz, 1 H), 6.90 (d, *J* = 7.8 Hz, 1 H), 5.30 (dddd, *J* = 16.8, 10.0, 7.8, 6.7 Hz, 1 H), 5.00 (m, 1 H), 4.88 (m, 1 H), 3.28 (s, 3 H), 2.91 (m, 2 H), 1.99 (s, 3 H).

^{13}C NMR (101 MHz): δ = 200.7, 174.5, 144.3, 131.5, 129.3, 127.0, 124.2, 123.3, 119.5, 108.6, 66.4, 37.5, 26.6.

LRMS (EI): *m*/*z* = 229 (9) [M]$^+$, 188 (13), 187 (100), 186 (22), 172 (12), 160 (22), 158 (14), 144 (10), 143 (10).

HRMS (EI): *m*/*z* calcd. for $C_{14}H_{15}NO_2$: 229.1103; found: 229.1107.

(*E*)-3-Acetyl-3-(3,7-dimethylocta-2,6-dien-1-yl)-1-methylindolin-2-one (3ac)

Yield: 210 mg (54%); brown oil.

^{1}H NMR (300 MHz): δ = 7.34 (td, *J* = 7.7, 1.3 Hz, 1 H), 7.19 (dd, *J* = 7.5, 1.2 Hz, 1 H), 7.07 (td, *J* = 7.5, 1.0 Hz, 1 H), 6.88 (d, *J* = 7.8 Hz, 1 H), 4.89 (m, 1 H), 4.73–4.60 (m, 1 H), 3.26 (s, 3 H), 2.89 (m, 2 H), 2.01 (s, 3 H), 1.80 (m, 4 H), 1.62 (s, 3 H), 1.51 (s, 3 H), 1.49 (s, 3 H).

^{13}C NMR (101 MHz): δ = 201.4, 175.0, 144.3, 139.9, 131.4, 129.2, 127.6, 124.3, 124.1, 123.1, 116.7, 108.3, 66.6, 39.9, 32.2, 26.8, 26.8, 26.6, 25.8, 17.7, 16.5.

LRMS (EI): *m*/*z* = 325 (8) [M]$^+$, 214 (14), 198 (12), 190 (15), 189 (100), 171 (10), 160 (36), 159 (35), 69 (24).

HRMS (EI): *m*/*z* calcd. for $C_{21}H_{27}NO_2$: 325.2042; found: 325.2044.

3-Acetyl-1-methyl-3-(prop-2-yn-1-yl)indolin-2-one (3ad)

Yield: 186 mg (68%); brown solid; mp 84–86 °C (hexane/EtOAc).

^{1}H NMR (300 MHz): δ = 7.41 (td, *J* = 7.7, 1.3 Hz, 1 H), 7.24 (dd, *J* = 7.4, 0.9 Hz, 1 H), 7.13 (td, *J* = 7.5, 0.9 Hz, 1 H), 6.95 (d, *J* = 7.8 Hz, 1 H), 3.32 (s, 3 H), 3.13 (dd, *J* = 16.8, 2.7 Hz, 1 H), 2.93 (dd, *J* = 16.9, 2.6 Hz, 1 H), 1.97 (s, 3 H), 1.76 (t, *J* = 2.6 Hz, 1 H).

^{13}C NMR (101 MHz): δ = 199.5, 173.6, 144.7, 129.8, 126.7, 124.0, 123.5, 108.7, 78.6, 70.5, 65.1, 26.8, 26.3, 23.0.

LRMS (EI): *m*/*z* = 227 (8) [M]$^+$, 186 (13), 185 (100), 184 (60), 157 (12), 156 (14), 128 (13).

HRMS (EI): *m*/*z* calcd. for $C_{14}H_{13}NO_2$: 225.0946; found: 227.0945.

3-Acetyl-1-methyl-3-pentylindolin-2-one (3af)

Yield: 39 mg (50%); colorless oil.

^{1}H NMR (300 MHz): δ = 7.35 (td, *J* = 7.6, 1.5 Hz, 1 H), 7.22–7.04 (m, 2 H), 6.91 (d, *J* = 7.8 Hz, 1 H), 3.29 (s, 3 H), 2.27–2.04 (m, 2 H), 2.00 (s, 3 H), 1.23–1.14 (m, 5 H), 0.83–072 (m, 4 H).

^{13}C NMR (101 MHz): δ = 201.5, 175.3, 144.3, 129.1, 127.7, 124.0, 123.3, 108.5, 66.9, 33.4, 31.9, 26.6, 26.6, 23.4, 22.4, 14.0.

LRMS (EI): *m*/*z* = 259 (7) [M]$^+$, 218 (10), 217 (64), 161 (12), 160 (100), 147 (10).

HRMS (EI): *m*/*z* calcd. for $C_{16}H_{21}NO_2$: 259.1572; found: 259.1576.

Methyl 2-(3-Acetyl-1-methyl-2-oxoindolin-3-yl)acetate (3ag)

Yield: 215 mg (69%); purple oil.

^{1}H NMR (300 MHz): δ = 7.38 (td, *J* = 7.7, 1.3 Hz, 1 H), 7.20 (d, *J* = 7.3 Hz, 1 H), 7.08 (td, *J* = 7.5, 1.0 Hz, 1 H), 6.95 (d, *J* = 7.8 Hz, 1 H), 3.50 (s, 3 H), 3.34 (s, 3 H), 3.40–3.19 (m, 2 H), 1.93 (s, 3 H).

^{13}C NMR (101 MHz): δ = 199.2, 174.3, 170.3, 145.0, 129.7, 126.9, 123.8, 123.3, 108.8, 63.5, 51.9, 37.2, 27.0, 25.7.

LRMS (EI): *m*/*z* = 261 (2) [M]$^+$, 219 (50), 160 (31), 159 (100), 130 (21).

HRMS (EI): *m*/*z* calcd. for $C_{14}H_{15}NO_4$: 261.1001; found: 261.1005.

Deacylative Alkylation of 3-Acetyl-2-oxindoles 3 with Alkyl Halides; General Procedure

Oxindole **3** (0.15 mmol) and alkyl halide (0.165 mmol) were dissolved under an argon atmosphere in anhydrous THF (1.5 mL). A 1 M solution of LiOEt (0.15 mL, 0.15 mmol) was added dropwise and the reaction mixture was stirred at r.t. overnight. After extractive work-up and flash chromatography, pure 3,3-dialkylated 2-oxindole **6** was obtained (see, Table 2).

Compounds **6aab** (22 mg, 72%),[24] **6aae** (33 mg, 87%),[25] **6aah** (31 mg, 75%),[25] **6aai** (27 mg, 88%),[19] **6aaj** (23 mg, 65%),[22] **6aeb** (28 mg, 67%),[26] **6bab** (26 mg, 75%),[26] **6bai** (429 mg, 93%),[19] and **6cai** (34 mg, 74%)[27] are known.

3-Propargyl-1,3-dimethylindolin-2-one (6aad)

Yield: 21 mg (69%); yellow oil.

^{1}H NMR (400 MHz): δ = 7.46–7.43 (m, 1 H), 7.30 (td, *J* = 7.7, 1.2 Hz, 1 H), 7.09 (td, *J* = 7.6, 1.0 Hz, 1 H), 6.86 (d, *J* = 7.8 Hz, 1 H), 3.23 (s, 3 H), 2.70 (dd, *J* = 16.5, 2.7 Hz, 1 H), 2.49 (dd, *J* = 16.6, 2.7 Hz, 1 H), 1.96 (t, *J* = 2.7 Hz, 1 H), 1.46 (s, 3 H).

^{13}C NMR (101 MHz): δ = 179.5, 143.1, 133.1, 128.3, 123.3, 122.7, 108.1, 79.8, 70.8, 46.7, 27.8, 26.4, 21.9.

LRMS (EI): *m*/*z* = 199 (28) [M]$^+$, 161 (11), 160 (100), 132 (9), 130 (8), 117 (10).

HRMS (EI): *m*/*z* calcd. for $C_{13}H_{13}NO$: 199.0997; found: 199.0996.

3-Allyl-1-benzyl-5-methoxy-3-methylindolin-2-one (6cab)

Yield: 32 mg (70%); pale-yellow solid; mp 74–76 °C (hexane/EtOAc).

^{1}H NMR (300 MHz): δ = 7.33–7.20 (m, 5 H), 6.82 (d, *J* = 2.5 Hz, 1 H), 6.65 (dd, *J* = 8.5, 2.5 Hz, 1 H), 6.57 (d, *J* = 8.4 Hz, 1 H), 5.48 (dddd, *J* = 16.9, 10.0, 7.9, 6.7 Hz, 1 H), 5.08–4.93 (m, 3 H), 4.77 (d, *J* = 15.7 Hz, 1 H), 3.75 (s, 3 H), 2.62 (dd, *J* = 13.5, 7.9 Hz, 1 H), 2.54 (dd, *J* = 13.5, 6.7 Hz, 1 H), 1.42 (s, 3 H).

^{13}C NMR (75 MHz): δ = 180.0, 156.0, 136.2, 135.8, 135.1, 132.8, 128.8, 127.6, 127.4, 119.0, 111.7, 110.8, 109.4, 55.9, 48.9, 43.8, 42.6, 23.4.

LRMS (EI): *m*/*z* = 308 (13), 307 (58) [M]$^+$, 267 (20), 266 (100), 91 (67).

HRMS (EI): *m*/*z* calcd. for $C_{20}H_{21}NO_2$: 307.1572; found: 307.1570.

Deacylative Alkylation of 3-Acetyl-2-oxindoles 3 with Electrophilic Alkenes; General Procedure

Oxindole **3aa** (30.5 mg, 0.15 mmol) and electrophilic alkene (0.21 mmol) were dissolved in THF (1.5 mL). After three cycles of freezing-pump-thaw and filling the flask with Ar, benzyltrimethylammonium hydroxide (Triton B) in MeOH (40wt%, 0.068 mL, 0.15 mmol) was added. The mixture was stirred overnight at r.t. and extractive work-up was performed with EtOAc (3 × 10 mL) and H_2O (10 mL). The organic phases were dried with $MgSO_4$, filtered and concentrated, and the resulting crude product was purified by flash chromatography (EtOAc/hexane) to give **9**.

Compounds **9aa** (39 mg, 90%),[28], **9ab** (29 mg, 89%),[29] **9ad** (30 mg, 86%),[29] and **9ae** (50 mg, 51%)[30] are known.

3-(1,3-Dimethyl-2-oxoindolin-3-yl)-*N*,*N*-dimethyl Propanamide (9ac)

Yield: 34 mg (86%); yellow oil.

^{1}H NMR (300 MHz): δ = 7.31–7.20 (m, 2 H), 7.08 (td, *J* = 7.5, 0.9 Hz, 1 H), 6.86 (d, *J* = 7.8 Hz, 1 H), 3.23 (s, 3 H), 2.84 (s, 6 H), 2.29–2.04 (m, 3 H), 1.93–1.80 (m, 1 H), 1.39 (s, 3 H).

^{13}C NMR (101 MHz): δ = 180.4, 172.4, 143.1, 133.4, 128.1, 123.0, 122.9, 108.0, 47.8, 33.3, 28.3, 26.3, 24.0.

LRMS (EI): *m*/*z* = 260 (56) [M]$^+$, 216 (17), 188 (15), 174 (62), 162 (92), 161 (93), 160 (100), 159 (11), 146 (13), 144 (12), 130 (19), 117 (12), 100 (44), 72 (16), 55 (12).

HRMS (EI): *m*/*z* calcd. for $C_{15}H_{20}N_2O_2$: 260.1525; found: 260.1521.

3-[2,2-Bis(phenylsulfonyl)ethyl]-1,3-dimethylindolin-2-one (9af)

Yield: 58 mg (83%); pale-yellow solid; mp 171–173 °C (hexane/EtOAc).

^{1}H NMR (300 MHz): δ = 8.01 (m, 2 H), 7.85–7.75 (m, 2 H), 7.75–7.43 (m, 6 H), 7.35 (td, *J* = 7.7, 1.3 Hz, 1 H), 7.30–7.20 (m, 1 H), 7.14 (td, *J* = 7.5, 1.0 Hz, 1 H), 6.88 (d, *J* = 7.8 Hz, 1 H), 4.85 (dd, *J* = 5.2, 3.4 Hz, 1 H), 3.20 (s, 3 H), 2.78 (dd, *J* = 16.4, 3.4 Hz, 1 H), 2.69 (dd, *J* = 16.4, 5.2 Hz, 1 H), 1.37 (s, 3 H).

^{13}C NMR (101 MHz): δ = 179.0, 143.5, 138.6, 136.3, 134.8, 134.3, 132.3, 130.9, 129.4, 129.1, 129.0, 128.9, 123.3, 122.7, 108.8, 79.1, 46.0, 31.2, 26.5, 23.9.

LRMS (EI): *m*/*z* = 469 (30) [M]$^+$, 161 (34), 160 (100), 158 (11), 130 (10), 77 (21).

HRMS (EI): *m*/*z* calcd. for $C_{24}H_{23}NO_5S_2$: 469.1018; found: 469.1016.

Diethyl [2-(1,3-Dimethyl-2-oxoindolin-3-yl)ethyl] Phosphonate (9ag)

Yield: 41 mg (85%); yellow wax.

^{1}H NMR (300 MHz): δ = 7.35–7.23 (m, 1 H), 7.23–7.14 (m, 1 H), 7.08 (td, *J* = 7.5, 1.0 Hz, 1 H), 6.85 (d, *J* = 7.8 Hz, 1 H), 4.13–3.93 (m, 4 H), 3.21 (s, 3 H), 2.16 (m, 1 H), 2.00 (m, 1 H), 1.38 (s, 3 H), 1.28 (m, 8 H).

^{13}C NMR (101 MHz): δ = 179.7, 143.4, 132.8, 128.3, 122.9, 122.7, 108.3, 61.8 (dd, *J* = 10.4, 6.5 Hz), 48.4, 48.2, 31.0 (d, *J* = 3.8 Hz), 26.3, 23.3, 21.6, 20.2, 16.5 (t, *J* = 5.3 Hz).

LRMS (EI): *m*/*z* = 325 (38) [M]$^+$, 281 (13), 207 (40), 188 (10), 174 (17), 165 (16), 161 (27), 160 (100), 144 (11), 138 (15), 132 (10), 130 (12), 109 (17).

HRMS (EI): *m*/*z* calcd. for $C_{16}H_{24}NO_4P$: 325.1443; found: 325.1443.

1,3-Dimethyl-3-(3-oxo-1,3-diphenylpropyl)indolin-2-one (9ah, major diasteroisomer)

Yield: 54 mg (97%); colorless oil.

^{1}H NMR (300 MHz): δ = 7.98–7.87 (m, 2 H), 7.52 (m, 1 H), 7.48–7.35 (m, 2 H), 7.17 (m, 2 H), 7.07–6.97 (m, 6 H), 6.59 (d, *J* = 7.7 Hz, 1 H), 3.97 (dd, *J* = 8.1, 5.8 Hz, 1 H), 3.69–3.63 (m, 2 H), 3.05 (s, 3 H), 1.43 (s, 3 H).

^{13}C NMR (101 MHz): δ = 198.9, 179.9, 142.9, 139.5, 137.2, 133.3, 133.1, 129.0, 128.6, 128.3, 127.9, 127.5, 126.8, 123.8, 122.4, 107.8, 51.6, 48.1, 38.4, 26.0, 22.1.

LRMS (EI): *m*/*z* = 369 (5) [M]$^+$, 209 (17), 208 (16), 207 (25), 161 (69), 160 (13), 105 (100), 77 (27).

HRMS (EI): *m*/*z* calcd. for $C_{25}H_{23}NO_2$: 369.1729; found: 369.1723.

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Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of new products.Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590880.

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