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

Aitor Ortega-Martínez,^{a,b} Cynthia Molina,^{a,b} Cristina Moreno-Cabrerizo,^{a,b} José M. Sansano^{*a,b} and 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.

^b Instituto de Síntesis Orgánica, Facultad de Ciencias, Universidad de Alicante 03080-Alicante, Spain. Fax: +34-965903549; Tel: +34-965903728.

* indicates the main/corresponding author.

jmsansano@ua.es, cnajera@ua.es

Received:
Accepted:
Published online:
DOI:

Abstract The monoalkylation of 3-acetyl-2-oxindoles can be performed under mild reaction conditions using alkyl halides and benzyltrimethylammonium hydroxide (Triton B) as base at room temperature in good yields. This methodology is applied to the synthesis of 1,3-dimethyl-2-oxindole. Subsequent deacylative alkylation (DaA) of the different 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 rt 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

generation of fluoroenolates¹⁰ 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

In the last years, the family of 3,3-disubstituted 2-oxindoles has received a great 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 3,3-disubstituted 2-oxindoles based on: (a) intramolecular coupling reactions such as Heck reactions,² arylations of *o*-halogenated³ and unsubstituted⁴ anilides and (b) alkylation of 3-substituted 2-oxindoles⁵ (Scheme 1). Recently, (c) Pd-catalyzed decarboxylative allylation and benzylation reactions,⁶ (d) the Meerwein-Eschenmoser Claisen rearrangement⁷ and (e) Pd-catalyzed deacylative allylation⁸ have been also 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. Detrifuoroacetylative reactions have been studied for the

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 be controlled and needs 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).

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

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-dimethylaminopyridine (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 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**.

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

The alkylation of compounds **2** was initially performed with LiOEt as base and allyl bromide affording the allylated product **3ab** in less than 5%. However, when Triton B (40% wt in MeOH) was used as base in THF, at room temperature, the corresponding allylated product **3ab** was obtained in 84% yield (Table 1, entry 2). These reaction conditions were employed for the alkylation of compounds **2** with different alkyl halides giving products **3** in good yields (Table 1). Under these reaction conditions the alkylation took place regioselectively at the 3-position of the oxindole. Only in the case of the *n*-pentyl bromide the reaction had to be carried out under reflux (Table 1, entry 6). In the case of methyl bromoacetate, the methyl ester was used in order to avoid transesterification with MeOH (Table 1, entry 7). Compounds **3** were sensitive to deacylation during the purification by flash chromatography affording the monoalkylated 2-oxindoles **4** in less than 10% (Table 1, entries 2-7).

Table 1 Monoalkylation of 3-acetyl-2-oxindoles **2**^a

Entry	2	X	R ¹	R ² Hal	3	Yield ^b (%)
1	2a ^c	H	Me	MeI	3aa	88
2	2a	H	Me	allylBr	3ab	84 ^d
3	2a	H	Me	4-bromobutylBr	3ac	54 ^e
4	2a	H	Me	3-bromopropylBr	3ad	68 ^e
5	2a	H	Me	PhCH ₂ Br	3ae	84 ^f
6	2a ^g	H	Me	<i>n</i> -C ₅ H ₁₁ Br	3af	50 ^{h,d}
7	2a	H	Me	MeO ₂ CCH ₂ Br	3ag	69 ⁱ
8	2b	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 rt overnight in a 1:1 molar ratio.

^b Isolated yield after flash chromatography.

^c 2 equiv of MeI were used on a 7.2 mmol scale.

^d 6% of deacylated compound was also obtained.

^e 4% of deacylated compound was also obtained.

^f 5% of 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% of deacylated compound was also obtained.

^j 4.6 mmol scale.

^k 0.6 mmol scale.

For the deacylative alkylation (DaA) of compounds **3** several basic conditions were tested, the best results being obtained with a 1M solution of lithium ethoxide in dry THF at rt under argon in order to avoid 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 horsifoline **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

Entry	3	R ³ Hal	Product	6	Yield (%) ^b
1	3aa	CH ₂ =CHCH ₂ Br		6aab	72
2	3aa			6aad	69
3	3aa	PhCH ₂ Br		6aae	87
4	3aa			6aah	75 ^c
5	3aa	NCCH ₂ Br		6aai	88
6	3aa	EtO ₂ CCl		6aaaj	65
7	3ae	CH ₂ =CHCH ₂ Br		6aeb	67
8	3ae	CH ₂ =CHCH ₂ Br		6aeb	58 ^d
9	3ba	CH ₂ =CHCH ₂ Br		6bab	75
10	3ba	NCCH ₂ Br		6bai	93 ^e
11	3ca	CH ₂ =CHCH ₂ Br		6cab	70

12 **3ca** NCCH₂Br

6cai 74

^a The reaction was performed on a 0.15 mmol scale at rt overnight in a 1:1 molar ratio.

^b Isolated yield after flash chromatography.

^c 1.5 equiv of cinnamyl bromide were used.

^d With Triton B as base (1 equiv).

^e 2 mmol scale.

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

Conjugate addition of compound **3aa** to electrophilic alkenes was also studied using DaA. In this case, Triton B was a better base than LiOEt giving, in THF at rt under argon, compounds **9** in good yields (Table 3). Only in the presence of oxygen the formation of 3-hydroxy-3-methyl-2-oxindole in less than 5% was observed. Acrylic systems gave the corresponding products in high yields. In the case of phenyl vinyl sulfone, a lower 51% yield was observed with formation of 13% of *O*-alkylated product (Table 3, entry 5). However, the more electrophilic 1,1-disulfone, gave exclusively product **9af** in 83% yield (Table 3, entry 6). When chalcone was used as electrophile a 1:0.7 mixture of diastereoisomers was obtained (Table 3, entry 8).

Table 3 DaA of 3-acetyl-2-oxindoles **3** with electrophilic alkenes^a

Entry	Alkenes	Product	9	Yield (%) ^b
1	CH ₂ =CHCO ₂ tBu		9aa	90
2	CH ₂ =CHCN		9ab	89
3	CH ₂ =CHCONMe ₂		9ac	86
4	CH ₂ =CHCOMe		9ad	86

^a The reaction was performed on a 0.15 mmol scale at rt overnight in a 1:1.4 molar ratio.

^b Isolated yield after flash chromatography.

^c 13% of the *O*-alkylated product was also obtained using 1 equiv of phenyl vinyl sulfone.

^d A 1:0.7 mixture of diastereomers was formed.

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 deacetylation 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 adequate for the preparation of unsymmetrical 3,3-disubstituted oxindoles, which cannot be easily prepared by other strategies.

Experimental section

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. ^1H NMR (300, 400 MHz or 500 MHz) and ^{13}C NMR (75, 101 or 126 MHz) spectra were recorded using Bruker AV300, Bruker AV400 and Bruker ADVANCE DRX500, respectively, with CDCl_3 as solvent and TMS as internal standard for ^1H NMR, and the own chloroform signal for ^{13}C NMR, and chemical shifts are given in ppm. Low-resolution electron impact (GC-EI) mass spectra were obtained at 70 eV using a Agilent 6890N Network GC system and Agilent 5973Network Mass Selective Detector. High-resolution mass spectra (GC-EI) were recorded using a QTOF Agilent 7200 instrument for the exact mass and Agilent 7890B for the GC. Analytical TLC was performed using ALUGRAM® Xtra SIL G/UV₂₅₄ silica gel plates, and the spots were determined under UV light ($\lambda=254$ nm).

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

In a round-bottom flask that contains 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 crude was dried at reduce pressure and dissolved in MeOH (80 mL). To the residue was added a solution of KOH (18 g, 321 mmol) in MeOH (120 mL) at 0 °C. After the addition, the solution was stirred at room temperature for 22 h and then the solution was introduced in a 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 x 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 compound **2a** (5.5 g) as a purple solid (88% yield): m.p. 109–110 °C

(hexane/EtOAc) (Lit.¹² m.p. 110–111 °C). The spectral data are in concordance with the literature.¹²

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

In a round-bottom flask that contains a solution of 5-methoxyisatin (3.54 g, 20 mmol) in dry DMF (40 mL) was cooled at 0 °C. Then, sodium hydride (606 mg, 24 mmol) was added in one portion and stirred for 5 min. Afterwards, iodomethane was added (1.84 mL, 30 mmol) and the reaction was stirred at 0 °C for 30 min. The mixture was poured in saturated aqueous NH_4Cl (20 mL) and extracted with dichloromethane (3 x 40 mL). The organic phase was washed with H_2O (3 x 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 at room temperature, H_2O (50 mL) was added and extracted with EtOAc (3 x 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 refluxed at 140 °C for 5 h and then evaporated under reduce pressure. The residue was dissolved in MeOH (50 mL) and then was added a solution of KOH (11 g, 196 mmol) in MeOH (70 mL) at 0 °C. The solution was stirred at room temperature for 22 h and then introduced in a 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 x 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** (2.97 g) as purple solid (68% overall yield): m.p. 83–84 °C (hexane/EtOAc) (Lit.²⁰ m.p. 83 °C). The spectral data are in concordance with the literature.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. Then, benzyl bromide (5.71 mL, 48 mmol) was added dropwise and stirred at room temperature for 19 h. The mixture was extracted with dichloromethane (3 x 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 was dissolved in DMSO (12 mL), and hydrazine hydrate (1.81 mL, 32 mmol) was added dropwise and heated at 150 °C for 5 h. The mixture was cooled at room temperature and extracted with AcOEt (2 x 100 mL), the organic phases were 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) as brown oil in 63% of yield.¹⁵ The product was dissolved in acetic anhydride (11.5 mL, 121 mmol) and DMAP (37 mg, 0.3 mmol) was added. The mixture was refluxed at 140 °C for 6 h and then cooled at rt and dried at reduce 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 room temperature for 18 h. Afterwards, the solution was introduced in a bath at 0 °C and 12 M aqueous HCl was added until pH 3. The organic solvent was evaporated at reduced pressure and to the residue was added H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The organic phases were dried over MgSO_4 , filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc) to give pure **2c** (1.15 g) as brown solid in 24% overall yield: m.p. 145–146 °C (hexane/EtOAc) (Lit.²¹ m.p. 150–151 °C). The spectral data are in concordance with the literature.

General procedure for the monoalkylation of 3-acetyl-2-oxindoles 2

To a solution of 3-acetyl-2-oxindole **2** (227 mg, 1.2 mmol) and the alkyl halide (1.2 mmol) in THF (7 mL) was added benzyltrimethylammonium hydroxide (Triton B) in MeOH (40% wt, 0.545 mL, 1.2 mmol). The reaction was stirred at room temperature overnight and then H_2O (20 mL) was added and extracted with EtOAc (3 x 20 mL) and dried over MgSO_4 . After evaporation of the solvents the residue was purified by flash chromatography (ethyl acetate/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. Data for new compounds follow.

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

Pale yellow oil, 192 mg, 84%.

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

¹³C 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): calcd. for [C₁₄H₁₅NO₂] 229.1103; found 229.1107.

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

Brown oil, 210 mg, 54%.

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

¹³C 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): calcd. for [C₂₁H₂₇NO₂] 325.2042; found 325.2044.

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

Brown solid, 186 mg, 68%, m.p. 84–86 °C (hexane/EtOAc).

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

¹³C 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): calcd. for [C₁₄H₁₃NO₂] 225.0946; found 227.0945.

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

Colorless oil, 39 mg, 50%.

¹H NMR (300 MHz): δ = 7.35 (td, J = 7.6, 1.5 Hz, 1H), 7.22–7.04 (m, 2H), 6.91 (d, J = 7.8 Hz, 1H), 3.29 (s, 3H), 2.27–2.04 (m, 2H), 2.00 (s, 3H), 1.23–1.14 (m, 5H), 0.83–0.72 (m, 4H).

¹³C 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): calcd. for [C₁₆H₂₁NO₂] 259.1572; found 259.1576.

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

Purple oil, 215 mg, 69%.

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

¹³C 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): calcd. for [C₁₄H₁₅NO₄] 261.1001; found 261.1005.

General procedure for the deacylative alkylation of 3-acetyl-2-oxindoles **3** with alkyl halides

The oxindole **3** (0.15 mmol) and the alkyl halide (0.165 mmol) were dissolved under argon atmosphere in dry THF (1.5 mL). Then, a 1M solution of LiOEt (0.15 mL, 0.15 mmol) was added dropwise and the reaction mixture was stirred overnight at room temperature. After

extractive work-up and flash chromatography the 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. Data for new compounds follow.

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

Yellow oil, 21 mg, 69%.

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

¹³C RMN (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): calcd. for [C₁₃H₁₃NO] 199.0997; found 199.0996.

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

Pale yellow solid, 32 mg, 70%, m.p. 74–76 °C (hexane/EtOAc).

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

¹³C RMN (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): calcd. for [C₂₀H₂₁NO₂] 307.1572; found 307.1570.

General procedure for the deacylative alkylation of 3-acetyl-2-oxindoles **3** with electrophilic alkenes

The oxindole **3aa** (30.5 mg, 0.15 mmol) and the electrophilic alkene (0.21 mmol) were dissolved in THF (1.5 mL). Then, 3 cycles of freezing-pump-thaw was made to the reaction mixture and after filling the flask with Ar, benzyltrimethylammonium hydroxide (Triton B) in MeOH (40% wt, 0.068 mL, 0.15 mmol) was added. The reaction was stirred overnight at room temperature and an extractive work-up was performed with (10 mL x 3) of AcOEt in 10 mL of H₂O, drying the organic phases with MgSO₄, filtering and concentrating. The resulting crude product was purified by flash chromatography (ethyl acetate/hexane) providing compounds **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. Data for new compounds follow.

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

Yellow oil, 34 mg, 86%.

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

¹³C 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): calcd. for [C₁₅H₂₀N₂O₂] 260.1525; found 260.1521.

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

Pale yellow solid, 58 mg, 83%, m.p. 171–173 °C (hexane/EtOAc).

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

¹³C 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): calcd. for [C₂₄H₂₃NO₅S₂] 469.1018; found 469.1016.

Diethyl [2-(1,3-dimethyl-2-oxoindolin-3-yl)ethyl] phosphonate (9ag)

Yellow wax, 41 mg, 85%.

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

¹³C 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): calcd. for [C₁₆H₂₄NO₄P] 325.1443; found 325.1443.

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

Colorless oil, 54 mg, 97%.

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

¹³C 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): calcd. for [C₂₅H₂₃NO₂] 369.1729 found 369.1723.

Acknowledgement

We gratefully acknowledge financial support from the Spanish Ministerio de Ciencia e Innovación (MICINN) (projects CTQ2010-20387 and Consolider Ingenio 2010, CSD2007-00006), the Spanish Ministerio de Economía y Competitividad (MINECO) (projects CTQ2013-43446-P and CTQ2014-51912-REDC), the Spanish Ministerio de Economía, Industria y Competitividad, Agencia Estatal de Investigación (AEI) and Fondo Europeo de Desarrollo Regional (FEDER, EU) (projects CTQ2016-76782-P and CTQ2016-81797-REDC), the Generalitat Valenciana (PROMETEO2009/039 and PROMETEOII/ 2014/017) and the University of Alicante. A. O.-M. thanks MINECO for a predoctoral fellowship.

Electronic supplementary information (ESI) available : [Copies of ¹H and ¹³C NMR, spectra of new products].

References

- (1) For recent reviews, see: (a) Cao, Z.-Y.; Wang, Y.-H.; Zeng Y.-P.; Zhou, J. *Tetrahedron Lett.* **2014**, *55*, 2571; (b) Shen, K.; Liu X.; Feng, X. *Chem. Sci.* **2012**, *3*, 327; (c) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104; (d) Dalpozzo, R.; Bartoli G.; Bencivenni, G. *Chem. Soc. Rev.* **2012**, *41*, 7247; (e) Zhou, F.; Liu Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381; (f) Galliford C. V.; Scheidt K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 8748.
 - (2) (a) Ashimori, A.; Matsuura, T.; Overman L. E.; Poon, D. J. *J. Org. Chem.* **1993**, *58*, 6949; (b) Matsuura, T.; Overman L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500.
 - (3) (a) Shaughnessy, K. H.; Hamann B. C.; Hartwig, J. F. *J. Org. Chem.*, **1998**, *63*, 6546; (b) Kundig, E. P.; Seidel, T. M.; Jia Y.-X.; Bernardinelli, G. *Angew. Chem. Int. Ed.* **2007**, *46*, 8484; (c) Marsden, S. P.; Watsonand, E. L.; Raw, S. A. *Org. Lett.* **2008**, *10*, 2905; (d) Altman, R. A.; Hyde, A. M.; Huang X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 9613; (e) Ruck, T. R.; Huffman, M. A.; Kim, M. M.; Shevlin, M.; Kandur, W. V.; Davies, I. W. *Angew. Chem. Int. Ed.* **2008**, *47*, 4711.
 - (4) (a) Jia Y.-X.; Kundig, E. P. *Angew. Chem. Int. Ed.* **2009**, *48*, 1636; (b) Perry A.; Taylor, R. J. K. *Chem. Commun.* **2009**, 3249; (c) Ghosh, S.; De, S.; Kakde, B. N.; Bhunia, S.; Adhikary A.; Bisai, A. *Org. Lett.* **2012**, *14*, 5864.
 - (5) (a) Tian, X.; Jiang, K.; Peng, J.; Du W.; Chen, Y.-C. *Org. Lett.* **2008**, *10*, 3583; (b) He, R.; Ding C.; Maruoka, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 4559; (c) Cheng, L.; Liu, L.; Jia, H.; Wang D.; Chen, Y.-J. *J. Org. Chem.* **2009**, *74*, 4650; (d) Wu, X.; Liu, Q.; Liu, Y.; Wang, Q.; Zhang, Y.; Chen, J.; Cao W.; Zhao, G. *Adv. Synth. Catal.* **2013**, *355*, 2701; (e) Wei, Y.; Wen, S.; Liu, Z.; Wu, X.; Zheng B.; Ye, J. *Org. Lett.* **2015**, *17*, 2732; (f) Mechler M.; Peters, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 10303; (g) Müller J. M.; Stark, C. B. W. *Angew. Chem. Int. Ed.* **2016**, *55*, 4798; (h) Ohmatsu, K.; Kikoyama M.; Ooi, T. *J. Am. Chem. Soc.* **2011**, *133*, 1307; (i) Zhu Q.; Lu, Y. *Angew. Chem. Int. Ed.*, **2010**, *49*, 7753; (j) Peng, J.; Huang, X.; Cui H.-L.; Chen, Y.-C. *Org. Lett.* **2010**, *12*, 4260; (k) Bui, T.; Syed S.; Barbas, III, C. F. *J. Am. Chem. Soc.* **2009**, *131*, 8758; (l) Jiang, K.; Peng, J.; Cui H.-L.; Chen, Y.-C. *Chem. Commun.* **2009**, 3955; (m) Li, X.; Xi, Z.-G.; Luo S.; Cheng, J.-P. *Org. Biomol. Chem.* **2010**, *8*, 77; (n) Wang, L.-L.; Peng, L.; Bai, J.-F.; Huang, Q.-C.; Xu X.-Y.; Wang, L.-X. *Chem. Commun.* **2010**, *46*, 8064; (o) Trost B. M.; Czabaniuk, L. C. *J. Am. Chem. Soc.* **2010**, *132*, 15534; (p) Trost B. M.; Frederiksen, M. U. *Angew. Chem. Int. Ed.* **2005**, *44*, 308.
 - (6) For a recent review, see: Weaver, J. D.; Recio, III, A.; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846.
 - (7) Linton, E. C.; Kozłowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 16162.
 - (8) Kumar, N.; Das, M. K.; Ghosh, S.; and Bisai, A. *Chem. Commun.* **2017**, *53*, 2170.
 - (9) (a) Grenning A. J.; Tunge, J. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 1688; (b) Grenning A. J.; Tunge, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 14785.
 - (10) For a review, see: Mei, H.; Xie, C.; Aceña, J. L.; Soloshonok, V. A.; Röschenthaler, G.-V.; Han, J. *Eur. J. Org. Chem.* **2015**, 6401.
 - (11) Xie, C.; Zhang, L.; Sha, W.; Soloshonok, V. A.; Han, J.; Pan, Y. *Org. Lett.* **2016**, *18*, 3270.
- A very similar reaction principle was employed but using harsher conditions: Reisch J.; Muller M.; Labitzke H. *Arch. Pharm.* **1984**, *317*, 639.
- (12) Jha, M.; Chou, T.-Y.; Blunt, B. *Tetrahedron Lett.* **2011**, *67*, 982.
 - (13) Zhang, Q. B.; Jia, W. L.; Ban, Y. L.; Zheng, Y.; Liu Q.; Wu, L. Z. *Chem. Eur. J.* **2016**, *22*, 2595.
 - (14) Shelke A. M.; Suryavanshi, G. *Org. Biomol. Chem.* **2015**, *13*, 8669.
 - (15) Sampson, P. B.; Liu, Y.; Patel, N. K.; Feher, M.; Forrest, B.; Li, S.; Edwards, L.; Laufer, R.; Lang, Y.; Ban, F.; Awrey, D. E.; Mao, G.; Plotnikova, O.; Leung, G.; Hodgson, R.; Mason, J.; Wei, X.; Kiarash, R.; Green, E.; Qiu, W.; Chirgadze, N. Y.; Mak, T. W.; Pan G.; Pauls, H. W. *J. Med. Chem.* **2015**, *58*, 147.
 - (16) Trost B. M.; Brennan, M. K. *Org. Lett.* **2006**, *8*, 2027.
 - (17) Trost B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590.
 - (18) Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043.
 - (19) Pinto, A.; Jia, Y.; Neuville L.; Zhu, J. *Chem. Eur. J.* **2007**, *13*, 961.
 - (20) Xia, X. D.; Lu, L. Q.; Liu, W. Q.; Chen, D. Z.; Zheng, Y. H.; Wu, L. Z.; Xiao, W. J. *Chem. Eur. J.* **2016**, *22*, 8432.
 - (21) Hugel, H. M.; Greenwood R. J.; Mackayb, M. F. *Aust. J. Chem.* **1992**, *45*, 1953.
 - (22) Ju, X.; Liang, Y.; Jia, P.; Li, W.; Yu, W. *Org. Biomol. Chem.* **2012**, *10*, 498.
 - (23) Kikue, N.; Takahashi T.; Nishino, H. *Heterocycles* **2015**, *90*, 540.
 - (24) Zhou, Y.; Zhao, Y.; Dai, X.; Liu, J.; Li L.; Zhang, H. *Org. Biomol. Chem.* **2011**, *9*, 4091.
 - (25) Zhou, B.; Hou, W.; Yang, Y.; Feng H.; Li, Y. *Org. Lett.* **2014**, *16*, 1322.
 - (26) Trost B. M.; Zhang, Y. *Chem. Eur. J.* **2011**, *17*, 2916.
 - (27) Yasui, Y.; Kamisaki, H.; Takemoto, Y. *Org. Lett.* **2008**, *10*, 3303.
 - (28) Wang, S.; Huang, X.; Li, B.; Ge, Z.; Wang X.; Li, R. *Tetrahedron Lett.* **2015**, *71*, 1869.
 - (29) Zhao, Y.; Sharma, N.; Sharma, U. K.; Li, Z.; Song, G.; Van der Eycken, E. *V. Chem. Eur. J.* **2016**, *22*, 5878.
 - (30) Liu, F. and; Li, P. *J. Org. Chem.* **2016**, *81*, 6972.