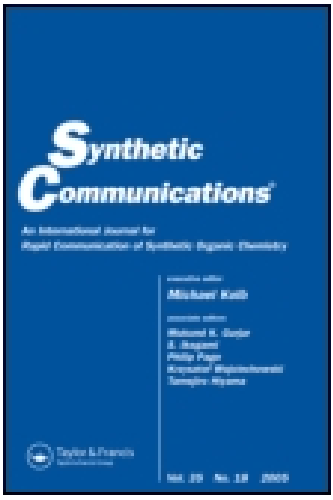

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New Approach for the Synthesis of N-Indolyl Ketones and Aldehydes

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New Approach for the Synthesis of *N*-Indolyl Ketones and Aldehydes

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Abstract: A new approach for the synthesis of *N*-indolyl ketones and aldehydes was developed. In the reaction of *N*-indolyl carboxylic acids with alkyl lithium, an interesting phenomenon appeared when using THF as solvent instead of ethyl ether.

Keywords: Alkyl lithium, *N*-indolyl aldehyde, *N*-indolyl ketone, solvent effect

INTRODUCTION

In our recent studies of anticancer agents, we have found some interesting indole α-methylene-γ-butyrolactone compounds, prepared from the intermediates indolyl aldehydes or ketones (such as compound **1**), which can significantly inhibit AKT-mTOR signaling pathway kinases. Furthermore, the indole ring system found in a wide range of naturally occurring compounds has attracted great interest for its biological activities.[1,2] So, those

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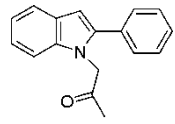
intermediates could be a useful component in the organic synthesis. Here we report a novel method for the synthesis of this type of compound.



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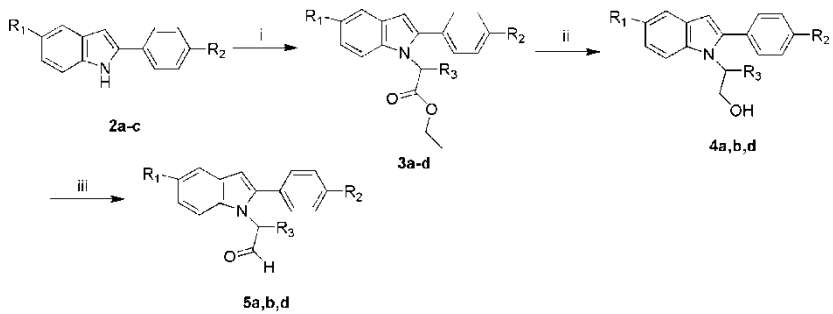
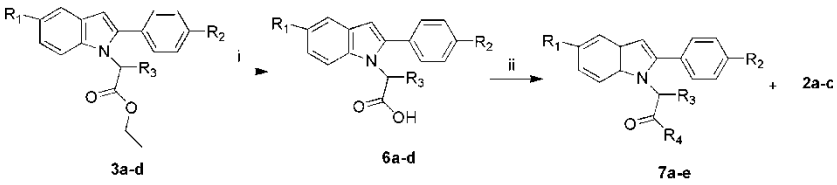
For the synthesis of **1**, we first tried to treat indole with sodium hydride in dry DMF followed by addition of α-bromoacetone but failed. Then, we tried to protect the carbonyl group with ketal, but the cleavage of ketal encountered many difficulties. Many methods appearing in References 3 to 5 have been tested, but no desired product could be obtained. Gianluca Araldi et al. reported a method of synthesis of carbonyl indole by the reaction of indole with propylene oxide followed by oxidization via the Moffat reaction.[6] But in our studies, we found that the alkylation of the indole system occurs not only at 1-position, but also at 3-position. Furthermore, the 1-alkyl product, 3-alkyl product, and the 1,3-dialkyl product are very close to each other on the silica-gel plate and it's difficult to separate them. Besides, the yield is low for the 2-phenyl indole. Also, only a few types of *N*-carbonyl indoles could be obtained by this method.

Finally, we used ethyl α-bromoacetate as the alkylation agent (Scheme 1). The obtained indole derivatives **3** could be reduced with $LiAlH_4$ to alcohol, which was subsequently oxidized to corresponding aldehydes just as Gianluca Araldi et al. reported. **3** could also be hydrolyzed to their corresponding carboxylic acids **6** and treated with alkyl lithium; thus, the ketones were obtained with little indoles **2** (Scheme 2). In view of the availability of many kinds of α-bromocarboxylic esters and alkyl lithium, we can get many more kinds of carbonyl indoles.

Interestingly, we found when indole carboxylic acids **6** were treated with alkyl lithium in dry Et_2O, the products **7** were obtained readily. But when the



Scheme 1. i: $BrR_3CHCOOEt$, NaH, DMF; ii: $LiAlH_4$, THF; and iii: DCC, Py, TFA, DMSO, benzene.



Scheme 2. i: NaOH, EtOH and ii: R_4Li, Et_2O.

reaction was carried out in dry THF, the corresponding indoles **2** were obtained and no ketones were produced (Scheme 3).

EXPERIMENTAL

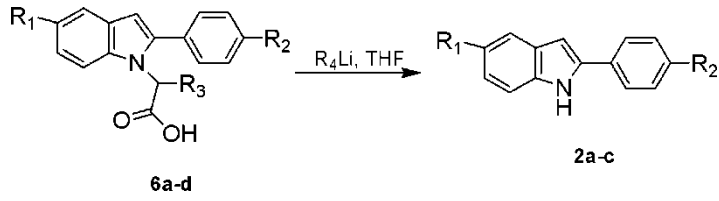
Melting points were determined using a Büchi 510 apparatus and are uncorrected. IR spectra were measured with a Perkin-Elmer 983 grating IR spectrophotometer in KBr pellets. ^{1}H NMR (400.13-MHz) spectra were recorded on a Brucker-400 NMR spectrometer with TMS as internal standard. The mass spectra were determined using Finnigan MAT 95, EI: 70 eV. Microanalyses were carried out on a Leco CHN-2000 elemental analyzer. Starting indoles **2** were prepared according to the literature procedure.[7]

2-(2-Phenyl-1*H*-indol-1-yl)ethanol (4a)

A solution of 2-phenyl-1*H*-indole (470 mg, 2.4 mmol) **2a** in dry DMF (3 mL) was added dropwise to a stirred suspension of sodium hydride (144 mg, 3.6 mmol) in dry DMF (2 mL) under N_2 at 0°C. After 20 min, ethyl α-bromoacetate (600 mg, 3.6 mmol) in dry DMF (2 mL) was added dropwise and the mixture was stirred at room temperature for 8 h. The resulting mixture was then poured into ice water (10 mL) and extracted with ethyl acetate (3×10 mL). The obtained organic phase was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue was purified by column chromatography (1/40 EtOAc/petroleum) to produce 350 mg of ethyl 2-(2-phenyl-1*H*- indol-1-yl)acetate as a pale yellow oil.

Table 1. Substituent groups of compounds in Schemes 1–3

Compound	R_1	R_2	R_3	R_4
a	H	H	H	CH_3
b	OCH_3	H	H	CH_3
c	H	OCH_3	H	CH_3
d	H	H	CH_3	CH_3
e	H	H	H	n-Bu



6a-d 2a-c

Scheme 3.

The indole ester **3a** (165 mg, 0.6 mmol) was added to a solution of $LiAlH_4$ (0.19 g, 1.8 mmol) in Et_2O (5 mL) and the mixture was stirred at rt for 3 h. Then, the reaction was quenched with ice water (10 mL) and acidified with 1 mL of hydrochloric acid (2.5 mol/L), followed by extraction with EtOAc (2 × 10 mL). Evaporation of the dried organic phase gave an oil, which was purified by silica-gel chromatography (1/4 EtOAc/petroleum) to give **4a** (130 mg, 47.8%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.54–7.14 (m, 9H, ArH), 6.56 (s, 1H, H-3), 4.34 (t, $J = 6.0$ Hz, 2H, NCH_2), 3.85 (t, $J = 6.0$ Hz, 2H, CH_2O). Compounds **4b** and **4d** were prepared using the same method.

2-(5-Methoxy-2-phenyl-1*H*-indol-1-yl)ethanol (4b)

Yield 44.8%, pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.53–6.88 (m, 8H, ArH), 6.48 (s, 1H, H-3), 4.29 (t, $J = 6.0$ Hz, 2H, CH_2), 3.87 (s, 3H, OCH_3), 3.82 (t, $J = 6.0$ Hz, 2H, CH_2).

2-(2-Phenyl-1*H*-indol-1-yl)propanol (4d)

Yield 35.1%, pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.67–7.13 (m, 9H, ArH), 6.52 (s, 1H, H-3), 4.71–4.64 (m, 1H, CH), 4.33–3.76 (m, 2H, CH_2), 1.58–1.51 (dd, $J = 2.0$, 9.6 Hz, 3H, CH_3).

2-(2-Phenyl-1*H*-indol-1-yl)acetaldehyde (5a)

2-(2-Phenyl-1*H*-indol-1-yl)ethanol (130 mg, 0.55 mmol) in anhydrous dimethylsulfoxide (4 mL) and *N, N′*- dicyclohexylcarbodiimide (339 mg, 1.65 mmol) were added to a solution of pyridine (43 mg, 0.55 mmol) and trifluoroacetic acid (31 mg, 0.27 mmol) in benzene (10 mL). After stirring at 25°C for 30 h, diethylether (3 mL) was added followed by a solution of oxalic acid (276 mg, 2.19 mmol) in methanol (3 mL). After the gas had stopped evoluting, water (10 mL) was added and the produced 1,3-dicyclohexylurea (DCU) was removed by filtration. The organic phase was then washed with 5% aqueous $NaHCO_3$ (2 × 10 mL) and water (10 mL), dried over anhydrous Na_2SO_4, and

evaporated to dryness. The residue was purified by column chromatography (SiO_2, 1/5 EtOAc/petroleum) to give 90 mg (69.8%) of white solid **5a**. It can be recrystallized from ethanol. Mp 106–107°C. IR (KBr) 1726 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.69 (s, 1H, CHO), 7.70–7.18 (m, 9H, ArH), 6.67 (s, 1H, H-3), 4.85 (s, 2H, CH_2); MS: m/z 235 (M^+), 206 (indole-CH_2^+); HRMS: m/z calcd. for $C_{16}H_{13}NO$ 235.0997 (M); found 235.1001. Anal. calcd. for $C_{16}H_{13}NO.0.1C_2H_5OH$: C, 81.11; H, 5.71; N, 5.84; found: C, 81.06; H, 5.61; N, 5.81. Compounds **5b** and **5d** were prepared using the same method.

2-(5-Methoxy-2-phenyl-1*H*-indol-1-yl)acetaldehyde (5b)

Yield 61.7%, pale solid, Mp 117–119°C. IR (KBr) 1724 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.66 (s, 1H, CHO), 7.48–6.90 (m, 8H, ArH), 6.60 (s, 1H, H-3), 4.81 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3). MS: m/z 265 (M^+), 236 (indole-CH_2^+); HRMS: m/z calcd. for $C_{17}H_{15}NO_2$ 265.1103 (M); found 265.1090. Anal. calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28; found: C, 76.88; H, 5.97; N, 5.14.

2-(2-Phenyl-1*H*-indol-1-yl)propionaldehyde (5d)

Yield 72.1%, white solid, Mp 80–82°C. IR (KBr) 1734 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.77 (s, 1H, CHO), 7.70–7.15 (m, 8H, ArH), 6.65 (s, 1H, H-3), 4.98–4.90 (q, $J = 9.6$ Hz, 1H, CH), 1.69 (d, $J = 9.6$ Hz, 3H, CH_3); MS: m/z 249 (M^+), 220 (indole-$CHCH_3^+$); HRMS: m/z calcd. for $C_{17}H_{15}NO$ 249.1154 (M); found 249.1169. Anal. calcd. for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62; found: C, 81.61; H, 5.98; N, 5.60.

2-(2-Phenyl-1*H*-indol-1-yl)acetic acid (6a)

The ester **3a** (165 mg) was dissolved in EtOH (4 mL) and 1 mL of NaOH solution (3 mol/L) was added. The solution was heated at 80°C for 30 min. After cooling to room temperature, 10 ml of water was added and the mixture was washed with CH_2Cl_2 (2 × 10 mL). Then, the water phase was acidified with dilute hydrochloride solution. Product **6a** (140 mg, 48.6%) was obtained after filtration and drying as a white solid. Mp 172–174°C (lit.[8] 181°C). ^1H NMR (acetone-d_6): δ 7.67–7.17 (m, 9H, ArH), 6.62 (s, 1H, H-3), 4.86 (s, 2H, CH_2). Compounds **6b**–**d** were prepared using the same method.

2-(5-Methoxy-2-phenyl-1*H*-indol-1-yl)acetic acid (6b)

Yield 41.6%, white solid, mp 173–175°C. ^1H NMR (acetone-d_6): δ 7.48–6.77 (m, 8H, ArH), 6.45 (s, 1H, H-3), 4.81 (s, 2H, CH_2), 3.75 (s, 3H, CH_3).

2-(2-(4-Methoxyphenyl)-1*H*-indol-1-yl)acetic acid (6c)

Yield 49.6%, white solid, Mp 166–168°C. ^{1}H NMR (acetone-d_6): δ 7.58–7.05 (m, 8H, ArH), 6.50 (s, 1H, H-3), 4.88 (s, 2H, CH_2) 3.86 (s, 3H, CH_3).

2-(2-Phenyl-1*H*-indol-1-yl)propionic acid (6d)

Yield 38.0%, white solid, Mp 177–179°C (lit.[8] 250°C). ^{1}H NMR (acetone-d_6): δ 7.60–7.05 (m, 9H, ArH), 6.51 (s, 1H, H-3), 5.25–5.20 (q, $J = 7.2$ Hz, 1H, CH), 1.63 (d, $J = 7.2$ Hz, 3H, CH_3).

1-(2-Phenyl-1*H*-indol-1-yl)propan-2-one (7a)

Under nitrogen, 0.5 mL of methyl lithium (1.6 mol/L in ether) was added dropwise to a solution of compound **6a** (100 mg, 0.40 mmol) in 5 mL of dry Et_2O cooled with ice salt. After stirring at room temperature for 2 h, 5 mL of water was added and acidified with 1 mL of hydrochloric acid (3 mol/L). Then extracted the mixture with EtOAc (2 × 20 mL) and the combined organic phase was washed with water. Evaporation of the dried organic phase gave an oil that was purified by silica-gel chromatography (1/25 EtOAc/petroleum) to give 60 mg (60.6%) of white solid. The product can be recrystallized from ethanol. Mp 116–118°C. IR (KBr) 1732 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.67–7.14 (m, 9H, ArH), 6.65 (s, 1H, H-3), 4.84 (s, 2H, CH_2), 1.96 (s, 3H, CH_3); MS: m/z 249 (M^+), 206 (indole-CH_2^+); HRMS: m/z calcd. for $C_{17}H_{15}NO$ 249.1154 (M); found 249.1154. Anal. calcd. for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62; found: C, 81.78; H, 5.98; N, 5.61. Compounds **7b**–**e** were prepared using the same method.

1-(5-Methoxy-2-phenyl-1*H*-indol-1-yl)propan-2-one (7b)

Yield 58.0%, white solid, Mp 126–128°C. IR (KBr) 1720 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.46–6.89 (m, 8H, ArH), 6.58 (s, 1H, H-3), 4.80 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3), 1.93 (s, 3H, CH_3); MS: m/z 279 (M^+), 236 (indole-CH_2^+); HRMS: m/z calcd. for $C_{18}H_{17}NO_2$ 279.1259 (M); found 279.1240. Anal. calcd. for $C_{18}H_{17}NO_2 \cdot 0.1C_2H_5OH$: C, 76.99; H, 6.25; N, 4.93; found: C, 76.98; H, 6.18; N, 4.94.

1-(2-(4-Methoxyphenyl)-1*H*-indol-1-yl)propan-2-one (7c)

Yield 58.6%, white solid, Mp 108–109°C. IR (KBr) 1716 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.66–6.98 (m, 8H, ArH), 6.58 (s, 1H, H-3), 4.80 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3), 1.95 (s, 3H, CH_3); MS: m/z 279 (M^+), 236 (indole-CH_2^+);

HRMS: m/z calcd. for $C_{18}H_{17}NO_2$ 279.1259 (M); found 279.1271. Anal. calcd. for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01; found: C, 77.21; H, 6.26; N, 5.01.

3-(2-Phenyl-1*H*-indol-1-yl)butan-2-one (7d)

Yield 61.2%, pale yellow solid, Mp 65–67°C. IR (KBr) 1720 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.68–7.14 (m, 8H, ArH), 6.64 (s, 1H, H-3), 4.92–4.85 (q, $J = 9.2$ Hz, 1H, CH), 1.74 (d, $J = 9.2$ Hz, 3H, $CHC\underline{H}_3$), 1.70 (s, 3H, $COCH_3$); MS: m/z 263 (M^+), 220 (indole-$CHCH_3^+$); HRMS: m/z calcd. for $C_{18}H_{17}NO$ 263.1310 (M); found 263.1305. Anal. calcd. for $C_{18}H_{17}NO \cdot 0.1C_2H_5OH$: C, 81.58; H, 6.62; N, 5.23; found: C, 81.70; H, 6.52; N, 5.22.

1-(2-Phenyl-1*H*-indol-1-yl)hexan-2-one (7e)

Yield 51.8%, white solid, Mp 83–84°C. IR (KBr) 1716 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.68–7.12 (m, 9H, ArH), 6.64 (s, 1H, H-3), 4.84 (s, 2H, NCH_2), 2.21 (t, $J = 7.2$ Hz, 2H, $COC\underline{H}_2CH_2$), 1.58–1.43 (m, 2H, $COCH_2C\underline{H}_2$), 1.24–1.15 (m, 2H, $C\underline{H}_2CH_3$), 0.81 (t, $J = 7.2$ Hz, 3H, CH_3); MS: m/z 291 (M^+), 206 (indole-CH_2^+); HRMS: m/z calcd. for $C_{20}H_{21}NO$ 291.1623 (M); found 291.1625. Anal. calcd. for $C_{20}H_{21}NO \cdot 0.1C_2H_5OH$: C, 81.97; H, 7.36; N, 4.74; found: C, 82.01; H, 7.35; N, 4.70.

General Procedure for the Reaction in Scheme 3

Methyl lithium (0.5 mL, 1.6 mol/L in ether) was added to a solution of compound **6** (0.4 mmol) in 5 mL of dry THF cooled to 0°C under nitrogen atmosphere. After stirring at room temperature for several hours, the reaction was quenched with water (5 mL) and acidified with 1 mL of hydrochloric acid (3 mol/L). THF was evaporated in vacuum and the residue was extracted with Et_2O (2 × 10 mL). The combined organic phase was washed with water and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the column chromatography of the residue over silica gel (EtOAc/petroleum) gave the corresponding indoles **2**.

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