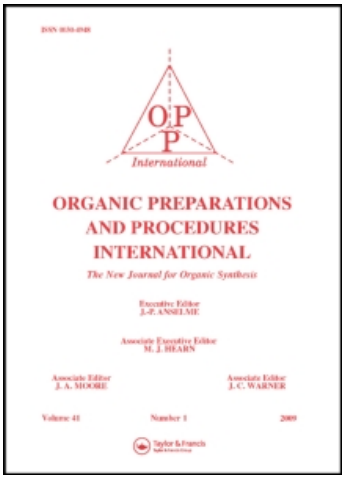

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A CONVENIENT PREPARATION OF ETHYL 3,3 DIMETHYL-3H-INDOLE-2-CARBOXYLATE

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A CONVENIENT PREPARATION OF ETHYL 3,3-DIMETHYL-3H-INDOLE-2-CARBOXYLATE

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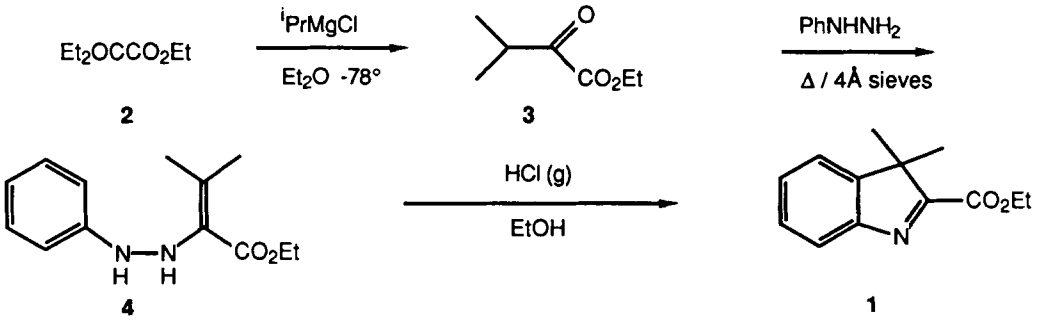
We required access to 2-alkoxycarbonyl-substituted 3H-indoles as dipole precursors for an investigation into the 1,3-dipolar cycloadditions of 3H-indolium-N-methylides.[1] However, the literature methods[2] for the preparation of ethyl 3,3-dimethyl-3H-indole-2-carboxylate (1) which center around the Japp-Klingmann modification of the Fischer indole synthesis[3] proved to be highly unsatisfactory. We now describe a convenient and high yielding route to 1 utilizing cheap, readily available reagents.

Our retrosynthetic analysis of 1 was based on a Fischer indole cyclization of hydrazone 4 derived from α-ketoester 3. The numerous routes to α-ketoesters[4] are usually multi-step procedures. A recent method reported by Singh[5] proved to be very convenient for the preparation of α-ketoester 3, by addition of a solution of isopropylmagnesium chloride to diethyl oxalate 2 in ether at -70° to afford the desired α-ketoester 3 cleanly and in excellent yield. Formation of hydrazone 4 was achieved in high yield by heating a solution of α-ketoester 3 and phenylhydrazine in benzene at reflux over 4Å molecular sieves. Fischer cyclization of the hydrazone 4 was accomplished by heat-

ing a solution of 4 in super dry ethanol saturated with hydrogen chloride at reflux to afford the 3H-indole 1 in good yield (47% overall yield from 2).



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EXPERIMENTAL SECTION

All reagents were employed as obtained from commercial sources unless otherwise stated. Diethyl ether and benzene were dried over sodium wire. Flash chromatography was carried out using E. Merck silica gel 9385 following the general procedure of Still.[6] ^1H and ^{13}C NMR were recorded on a JEOL FX90 Q spectrometer at 90 and 22.5 MHz respectively and referenced to $CDCl_3$ at 7.26 and 77.0 ppm. IR spectra were recorded on a Perkin Elmer 1420 ratio recording spectrometer as liquid films or dichloromethane solutions. Mass spectra were recorded on a KRATOS DS5 spectrometer at 70 eV ionization potential.

Ethyl α-Ketoisovalerate (3).- To a solution of diethyl oxalate 2 (29.23 g, 200 mmol) in diethyl ether (100 mL) at -70° was added isopropylmagnesium chloride (2.0 M in ether, 200 mmol) over the course of 1 hr. The mixture was stirred at 70° for an additional 0.5 hr before being immediately poured into a rapidly stirred slurry of ice (80 g), diethyl ether (100 mL) and conc. HCl (18 mL). The aqueous layer was separated and the organic layer washed successively with water (100 mL) and saturated brine (2 x 100 mL). The ethereal layer was dried ($MgSO_4$) and the solvent removed to leave the desired product as a colorless oil which was of sufficient purity for use in the next step; however it could be further purified by distillation at reduced pressure [26.24 g (91%), bp. 113°/31 mm Hg, lit.[5] 110°/30 mm Hg]. ^1H NMR: δ 1.1 (d, 6H, J =7.5Hz), 1.3 (t, 3H, J = 8Hz), 3.2 (sept, 1H, J = 7.5Hz), 4.3 (q, 2H, J = 8Hz). ^{13}C NMR: δ 14.2, 17.4, 370, 62.7, 162.5, 198.5. IR: 3000, 1740, (bs), 1480, 1400, 1380, 1285, 1190, 1100, 1055 cm^{-1}.

Ethyl α-Ketoisovalerate Phenylhydrazone (4).- A mixture of α-ketoester 3 (9.0 g, 62.5 mmol) and phenylhydrazine (10.1 g, 93.8 mmol) was heated at reflux in benzene (40 mL) over 4Å molecular sieves for 2 hrs. The cooled solution was added to water (20 mL) and extracted with diethyl ether (2 x 50 mL). The combined organic extracts were washed with water (50 mL) and saturated brine (50 mL) and dried ($MgSO_4$). Solvent removal provided a brown oil which was chromatographed (diethyl ether/pentane 1:2) to afford the title compound 4 as a yellow oil which was used directly in

the cyclization step (11.57 g, 79%). ^{1}H NMR: δ 1.22 (d, 6H, J = 9Hz), 1.35 (t, 3H, J = 8Hz), 3.05 (sept, 1H, J = 9Hz), 4.25 (q, 2H, J = 8Hz), 6.8-7.4 (m, 5H). ^{13}C NMR: δ 13, 21, 31, 60, 112.5, 121, 129, 133, 144, 153. IR: 3180 (NH), 300 cm^{-1}.

Ethyl 3,3-Dimethyl-3H-indole-2-carboxylate (1).- A solution of hydrazone 4 (5.0 g, 21.3 mmol) in "super dry" ethanol[7] (80 mL) at 0° was saturated with hydrogen chloride gas (~ 3 mins).The resulting yellow solution was heated at reflux for 10 mins. during which time the solution became orange in color and a precipitate formed. The mixture was cooled and the ethanol removed at reduced pressure. The residue was added to ether (20 mL) and 5% sodium bicarbonate added until effervescence had ceased. The organic layer was removed and the aqueous layer extracted with ether (3 x 50 mL). The combined organic extracts were washed with water (3 x 100 mL) until neutral to indicator paper (wide range pH 0-14 BDH) and then washed with saturated brine (100 mL). The organic layer was dried ($MgSO_4$) and solvent removed to leave golden crystals. Addition of pentane (30 mL) and cooling to -30° for 1 hr afforded the title compound 1 as pale cream-colored crystals. Repetition of this procedure (pentane, 10 mL) on the residue after removal of pentane afforded a further crop of product [3.12 g (67%), mp. 75.7-76.7°, lit.[3] 78-79°]. ^{1}H NMR: δ 1.45 (t, 3H, J = 8Hz), 1.55 (s, 6H), 4.45 (q, 2H, J = 8Hz), 7.4 (m, 32H), 7.8 (m, 1H). ^{13}C NMR: δ 12, 22, 53, 62, 121, 123, 127, 128, 147, 152, 161, 176. IR: 3000, 1720, 1450, 1310, 1210, 1120, 850, 760 cm^{-1}.

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7. Ethanol heated at reflux with magnesium turnings under N_2 for 24 hrs and stored over 4Å molecular sieves.

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