Reversed Chemoselectivity in Titanium-induced Coupling Reactions: Syntheses of Salvadoricine and Diazepam

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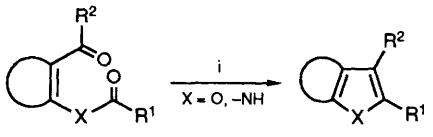
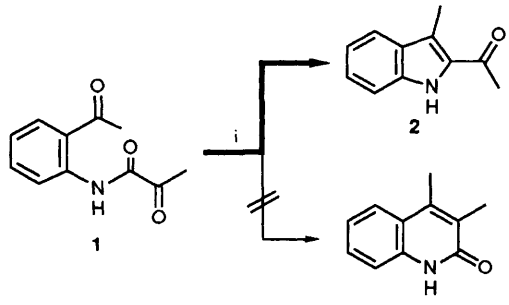
Titanium/graphite-promoted indole formation is favoured over inter- as well as intra-molecular McMurry coupling as evidenced by chemoselective syntheses of compounds **2** and **5–7**.

The titanium-induced coupling of carbonyl compounds to alkenes (McMurry reaction),[1] which is particularly well suited for the preparation of carbocycles of all ring sizes, has recently been extended to the formation of heterocycles.[2] Thus, acylamidocarbonyl compounds on treatment with titanium on graphite[3] as the reagent of choice are smoothly cyclized to indole derivatives (Scheme 1) in good to excellent yields,[2] although amides were hitherto considered to be essentially inert towards low-valent titanium.[1] This procedure turned out to be compatible with a variety of reducible functional groups and was equally suited to the formation of strained products.[2b] We now report the striking chemoselectivity of this indole formation exhibiting a complete reversal of the known bias of different carbonyl groups towards reductive coupling reactions.

This unprecedented behaviour became evident in the synthesis of salvadoricine **2** (Scheme 2), a simple indole



Scheme 1 *Reagents and conditions*: i, Ti/graphite, THF or DME, reflux, ref. 2



Scheme 2 *Reagents and conditions*: i, Ti/graphite, DME, reflux, Ar, 0.5 h, 60%

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isolated from *Salvadora persica* and used in Pakistan as a drug ('peelu').[4] Treatment of a 0.05 mol dm^{-3} solution of diketo-amide **1**, readily prepared from 2-aminoacetophenone and pyruvic acid chloride under standard conditions (CH_2Cl_2–pyridine, 2 h, 85%), with freshly prepared titanium on graphite (4 equiv.)[3] in anhydrous 1,2-dimethoxyethane (DME) resulted in its clean conversion to the desired product **2**, isolated in 60% yield by filtration of the reaction mixture and recrystallisation [light petroleum (35–60 °C)] of the crude product.‡ Several aspects of this transformation are worth mentioning

(*i*) The observation, that a keto–amide coupling completely overcomes both inter- as well as intra-molecular diketone coupling, contrasts with all previous experiences with low-valent titanium-induced reactions.[1]

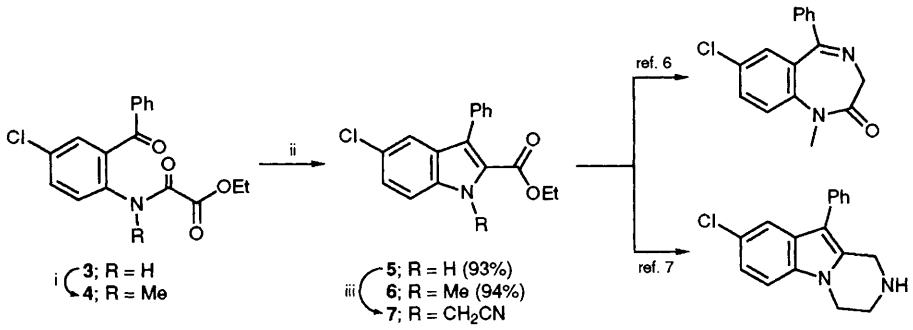
(*ii*) This pathway is even more surprising since the regular intramolecular McMurry reaction would lead to the well known 3,4-dimethyl-2(1*H*)-quinolone (*cf.* Scheme 2).

(*iii*) High-dilution techniques are not mandatory to favour the indole formation.[2]

(*iv*) Owing to the short reaction times the remaining ketone function in **2** perfectly resists subsequent intermolecular coupling although an excess of the highly reactive titanium has been employed.

In accordance with this result, the trifunctional substrates **3** and **4**, obtained from commercially available 5-chloro-2-amino-

‡ *Selected data* for Compound **2**: m.p. 147–149 °C (lit.[4a]: 143–144 °C; lit.[4b]: 149 °C; lit.[4c]: 146–147 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.98 (1H, bs), 7.71 (1H, d), 7.28–7.37 (2H, m), 7.16 (1H, ddd), 2.67 (3H, s), 2.65 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.59, 136.34, 132.98, 129.25, 126.76, 121.52, 120.36, 112.08, 29.20, 11.31. Compound **5**: m.p. 178–80 °C (lit.[6]: 178–180 °C); ^{1}H NMR [300 MHz, $(CD_3)_2SO$]: δ 12.20 (1H, bs), 7.34–7.61 (8H, m), 4.28 (2H, q), 1.21 (3H, t): ^{13}C NMR [75 MHz, $(CD_3)_2SO$]: 161.23, 134.80, 133.18, 130.55, 128.07, 127.29, 125.39, 124.49, 122.08, 119.65, 114.68, 60.69, 14.11. Compound **6**: m.p. 84–86 °C (lit.[6]: 80–84, 88–89 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (1H, s), 7.34–7.52 (5H, m); 7.32 (2H, s), 4.24 (2H, q), 4.06 (3H, s), 1.11 (3H, t); ^{13}C NMR (75 MHz, $CDCl_3$): 162.42, 136.83, 134.30, 130.49, 128.00, 127.67, 127.22, 126.60, 125.73, 123.88, 120.78, 111.37, 60.80, 32.18, 13.79. Compound **7**: m.p. 113–115 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (1H, s), 7.38–7.50 (7H, m), 5.62 (2H, s), 4.21 (2H, q), 1.05 (3H, t); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.22, 136.30, 133.33, 130.55, 128.87, 128.37, 128.22, 127.77, 127.51, 124.56, 121.96, 114.99, 110.88, 61.54, 33.21, 13.80.



Scheme 3 *Reagents and conditions*: i, NaH, MeI, THF, 61%; ii, Ti/graphite, DME, reflux, Ar, 1 h (**3** → **5**: 93%, **4** → **6**: 94%); iii, NaH, $ClCH_2CN$ (4 equiv.), DMF, room temp., 80%

benzophenone and ethyl oxalyl chloride, formed indoles **5** and **6** in 93 and 94% isolated yield, respectively (Scheme 3).‡ No inconveniences due to the adjacent ester group were encountered, although titanium-induced cyclization of oxoalkanoates are well established in the literature.[3,5] While indole **6** is a known starting material for the synthesis of diazepam,[6] alkylation of the nitrogen atom in compound **5** with chloroacetonitrile [NaH, dimethylformamide (DMF)] afforded indole **7** being structurally related to precursors for serotonin and histamine antagonists.[7] Further studies on this new indole synthesis are in progress.

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