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$InCl_3/SiO_2$-catalyzed α-amination of 1,3-dicarbonyl compounds under microwave irradiation

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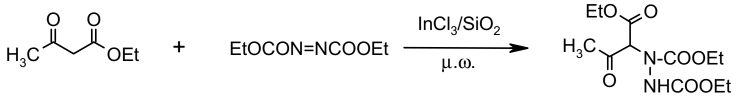
Abstract—A variety of 1,3-dicarbonyl compounds undergo smooth α-amination with diethyl azodicarboxylate (DEAD) on the surface of silica gel impregnated with indium trichloride under microwave irradiation and solvent-free conditions. Improved yields and enhanced reaction rates were observed.

The electrophilic α-amination of carbonyl compounds is a valuable synthetic route for the preparation of natural/unnatural α-amino acids and α-amino alcohols.[1] Aminating agents such as azidocarboxylates, trisyl azide and nitroso compounds or oxaziridines are typically used as the electrophilic nitrogen source.[2] The addition of β-keto esters to azodicarboxylates is one of the preferred methods for electrophilic amination.[3,4] The use of solid inorganic supports as reaction media in organic synthesis is increasingly widespread due to the improved efficiency of many surface-bound reagents.[5] Microwave irradiation has become a powerful synthetic tool for the rapid synthesis of a variety of organic compounds, because of its simplicity in operation, mild reaction conditions and improved yields.[6,7] In this letter, we wish to describe our results on the microwave-accelerated synthesis of α-hydrazino ketones using a solid supported reagent system, $InCl_3$–SiO_2. Thus treatment of ethyl acetoacetate **1** with diethyl azodicarboxylate **2** (DEAD) in the presence of indium trichloride dispersed onto the surface of silica gel using microwave irradiation under solvent-free conditions afforded the corresponding β-keto-α-hydrazino ester **3a** in 90% yield (Scheme 1).

Both acyclic and cyclic β-ketoesters reacted smoothly with diethyl azodicarboxylate under similar conditions to afford the respective α-aminated esters (Table 1, entries **b**–**e**). This direct α-amination of β-ketoesters with DEAD gives access to β-hydroxy-α-amino acid derivatives such as oxazolidinones. Like β-ketoesters, 1,3-diketones such as acetyl acetone, 1,3-cyclohexanedione and 5,5-dimethyl-1,3-cyclohexanedione (dimedone) underwent smooth addition to DEAD to produce the corresponding α-hydrazino ketones in high yields (Table 1, entries **f**–**h**).

In all the cases, the α-amination proceeded efficiently under microwave irradiation and solvent-free conditions. Microwave irradiation was carried out using a BPL, BMO-800T domestic microwave oven operated at 2450 MHz (450 W). The reaction temperature was controlled using a pulsed irradiation technique (1 min with



1 **2** **3a**

Scheme 1.

Keywords: α-Amination; Azocarboxylate; Microwave; α-Hydrazino ketones.

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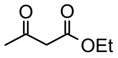
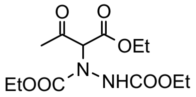
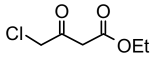
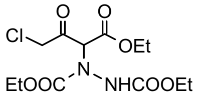
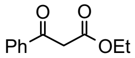
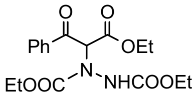
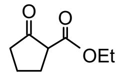
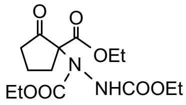
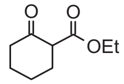
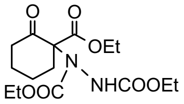
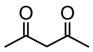
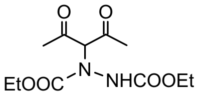
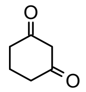
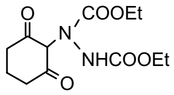
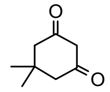
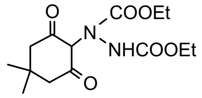
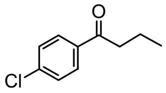
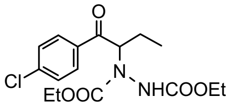
Table 1. $InCl_3/SiO_2$-catalyzed addition of 1,3-dicarbonyl compounds to diethyl azodicarboxylate

Entry	Substrate (**1**)	Product (**3**)[a]	Microwave radiation[b]		Conventional heating[c]	
			Time (min)	Yield (%)	Time (h)	Yield (%)
a[4]			4	90	8	81
b			6	87	7	79
c			5	92	6	87
d			6	90	7	85
e			4	86	6	81
f[4]			5	90	6	82
g			5	85	8	75
h			6	87	7	78
i			5	85	8	80

[a] All products were characterized by ^{1}H NMR, IR and mass spectroscopy.

[b] Pulsed irradiation (1 min with 20 s intervals).

[c] Refluxed in toluene.

20 s intervals). The temperature was measured after each pulse. The lowest observed temperature was 80 °C after irradiation for 1 min at 450 W and the highest temperature was 115 °C after irradiation for 3 min at the same power. The same reaction, under thermal conditions, at 120 °C took 6–8 h to afford yields comparable with those obtained using microwave irradiation. All the products were characterized by ^{1}H NMR, IR and mass spectroscopic data. In the absence of indium trichloride, the α-amination did not proceed on the surface of silica gel alone. Furthermore, indium trichloride alone was also found to be ineffective. The scope and generality of this process is illustrated with respect to various diketones and β-ketoesters; the results are presented in Table 1.[8]

In summary, we have described a convenient and rapid method for the synthesis of α-hydrazino ketones from 1,3-diketones and diethyl azodicarboxylate using the solid supported reagent system $InCl_3–SiO_2$ under microwave irradiation.

Acknowledgements

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8. (a) *Microwave irradiation*: 1,3-Dicarbonyl compound (1.0 mmol), diethyl azodicarboxylate (1.2 mmol) and $InCl_3/SiO_2$ (3 wt equiv of 1,3-dicarbonyl compound)[9] were admixed in an Erlenmeyer flask and subjected to microwave irradiation using a BPL, BMO-800T domestic oven operated at 450 W for the appropriate time (see Table 1). On completion, the reaction mixture was filtered and washed with dichloromethane (2×10 mL). Removal of the solvent under reduced pressure followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane 1:9) afforded the pure α-hydrazino ketone. (b) *Conventional method*: A mixture of 1,3-dicarbonyl compound (1.0 mmol), diethyl azodicaboxylate (1.2 mmol) and $InCl_3$ (30 mol%) in toluene (10 mL) was stirred at reflux for the appropriate time (see Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were dried over anhydrous Na_2SO_4 and purified by column chromatography to afford the pure α-hydrazino ketone. Spectral data for selected compounds: **3a**:[4] Solid, mp 84 °C [Ref. 4 (80–81 °C)], IR (KBr): ν 3392, 2992, 2376, 1728, 1496, 1376, 1240, 1064, 784 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25–1.45 (m, $J = 7.01$ Hz, 9H), 2.25 (s, 3H), 4.13–4.36 (m, $J = 7.01$ Hz, 6H), 6.75 (s, 1H), 12.10 (br s, 1H, NH). ^{13}C NMR (proton decoupled ^{13}C in $CDCl_3$; 75 MHz): δ 13.8, 13.9, 14.3, 22.7, 61.2, 61.6, 63.1, 107.5, 154.7, 155.9, 169.6, 194.6. EIMS: *m*/*z*: 304 [M$^+$], 262, 232, 190, 158, 144, 117, 90. [Calcd for $C_{12}H_{20}N_2O_7$ (304.3024): C, 47.37; H, 6.62; N, 9.21. Found: C, 47.40; H, 6.60; N, 9.23%.] Compound **3b**: Solid, mp 89 °C, IR (KBr): ν 3280, 3008, 2952, 2384, 1752, 1712, 1664, 1504, 1320, 1216, 1064, 768 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20–1.40 (m, $J = 6.79$, 7.55 Hz, 9H), 4.10–4.40 (m, $J = 4.53$, 6.79, 7.55 Hz, 8H), 6.70 (s, 1H), 12.0 (br s, 1H, NH). ^{13}C NMR (proton decoupled ^{13}C in $CDCl_3$; 75 MHz): δ 13.9, 14.1, 14.3, 38.8, 61.9, 62.2, 63.5, 108.0, 156.0, 169.2, 170.8, 197.1. EIMS: *m*/*z*: 338 [M$^+$], 266, 218, 190, 144, 115, 90. [Calcd for $C_{12}H_{19}ClN_2O_7$ (338.7474): C, 42.55; H, 5.65; N, 8.27. Found: C, 42.60; H, 5.63; N, 8.29%.] Compound **3f**:[4] Solid, mp 123 °C [Ref. 4 (114–116 °C)], IR (KBr): ν 3264, 2992, 2864, 1760, 1696, 1600, 1520, 1312, 1056, 800 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23–1.45 (t, $J = 7.01$ Hz, 6H), 2.10–2.28 (s, 6H), 4.12–4.32 (m, $J = 7.01$ Hz, 4H), 6.85 (s, 1H), 7.30 (br s, 1H, NH). ^{13}C NMR (proton decoupled ^{13}C in $CDCl_3$; 75 MHz): δ 14.3, 14.4, 22.0, 62.2, 63.4, 117.9, 155.8, 156.3, 191.9. EIMS: *m*/*z*: 274 [M$^+$], 233, 202, 113, 90, 43. [Calcd for $C_{11}H_{18}N_2O_6$ (274.2759): C, 48.17; H, 6.62; N, 10.21. Found: C, 48.15; H, 6.62; N, 10.23%].
9. The catalyst ($InCl_3/SiO_2$) was prepared by adding silica gel (1 g, Aldrich, 230–400 mesh) to a stirred solution of $InCl_3$ (0.3 mmol) in dichloromethane (5 mL) followed by evaporation of the solvent in vacuo.