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One pot synthesis of unsaturated enaminoketoesters or of pyridines in the tin(IV) chloride-promoted reactions of β-ketoesters with α,β-unsaturated nitriles

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Abstract—Tin(IV) chloride selectively promotes the nucleophilic attack of methyl acetoacetate to the cyano instead of the olefinic carbon atom of α,β-unsaturated nitriles to give enaminoketoesters. In the presence of an excess of ketoester a second C–C bond formation occurs followed by cyclisation affording substituted pyridines in a selective cascade sequence.

1. Introduction

α,β-Unsaturated nitriles generally react with nucleophiles to give addition compounds derived from nucleophilic attack on the C–C double bond in a Michael reaction.[1] In particular the reaction of β-ketoesters with α,β-unsaturated nitriles is carried out in the presence of alcoholate,[2–4] or of other bases,[5–7] to afford mono or bis adducts. More recently the same reaction was shown to be efficiently catalysed by an iridium(II) hydride complex.[8]

Taking into account the specific activation of the cyano group discovered by us in the metal promoted reaction of nitriles with β-dicarbonyl compounds,[9,10] we investigated the reactivity of methyl acetoacetate (**1**) with the α,β-unsaturated nitriles acrylonitrile (**2a**), methacrylonitrile (**2b**) and crotononitrile (**2c**) in the presence of metal acetoacetonates or of $SnCl_4$.

2. Results and discussion

No reaction was observed using catalytic amounts (1–5 mol%) of acetylacetonates of Ni(II), Co(II), Zn(II) or Cu(II) (1,2-dichloroethane (DCE) at rt for 7 days or at reflux for 24 h), whereas stoichiometric $SnCl_4$ effectively promotes C–C bond formation. The nature of the final products depends on the experimental conditions. Using an excess of nitrile over ketoester (molar ratio **1/2**/$SnCl_4$=1/3/1.5) compounds **3a–c** are obtained at rt in good yield. When the ratio is reversed (excess of ketoester, **1/2**/$SnCl_4$= 2.4/1/2), tin(IV) promotion gives at higher temperatures pyridine derivatives of the type **4** and **5** (Scheme 1).

The results obtained demonstrate that the reactions of ketoester **1** with α,β-unsaturated nitriles **2a–c**, carried out in the presence of stoichiometric amounts of $SnCl_4$ afford compounds **3a–c** derived from a C–C bond formation between the methylene and the cyano carbon atoms (instead of the expected olefinic carbon).

The ^1H NMR spectra of these compounds in $CDCl_3$ show two absorptions at ca. 5.6 and 11.0 ppm attributable to the two NH_2 hydrogens while the ^{13}C NMR spectra show absorptions at ca. 197 ppm attributable to the acetyl carbonyl group. These data indicate a strong hydrogen bond between one of the hydrogen of the NH_2 group (at ca. 11.0 ppm) and the acetyl group suggesting the *E* configuration for compounds **3a–c** as depicted in Scheme 1.

The formation of compounds **3** can be explained by the the ability of $SnCl_4$ in coordinating both the ketoester and the cyano group so enhancing the nucleophilic character of ketoester and the electrophilic character of nitriles.[9]

When the reactions are carried out in the presence of an excess of ketoester, acrylonitrile **2a** gives the pyridine derivative **4a** (DCE, reflux, 6 h) or, under more drastic conditions (toluene, 100°C, 2.5 h), the deacetylated derivatives **5a**. No evidence for the formation of **4b** is obtained starting from methacrylonitrile **2b**; in fact, the deacylated pyridine derivative **5b** is the major product, together with a

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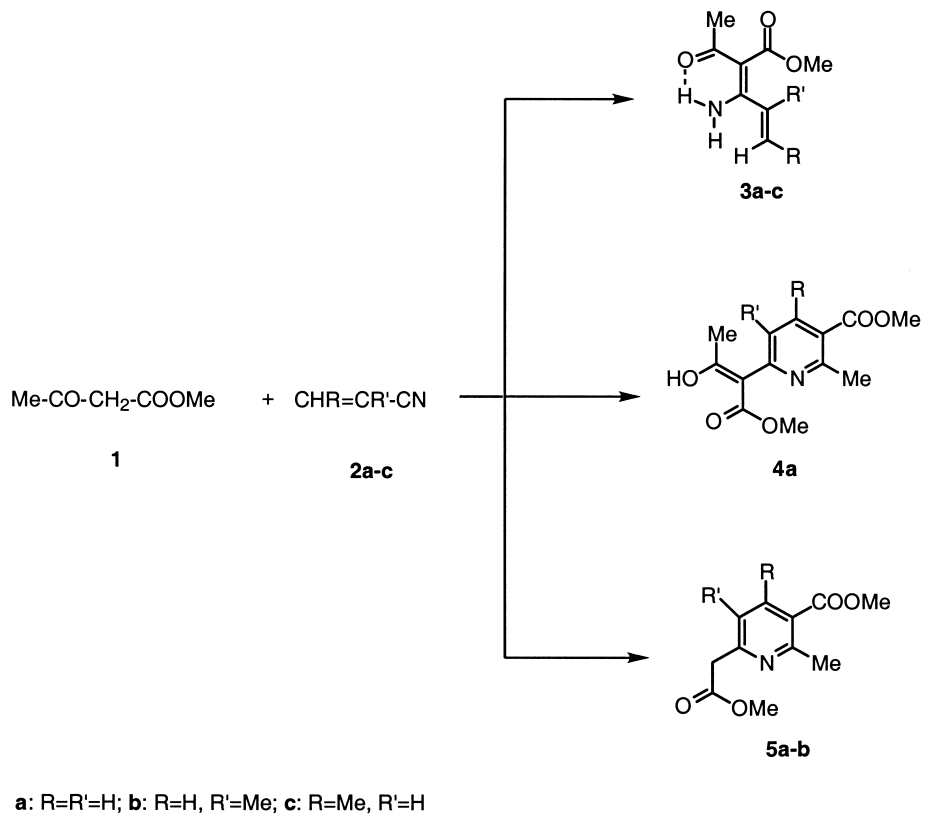
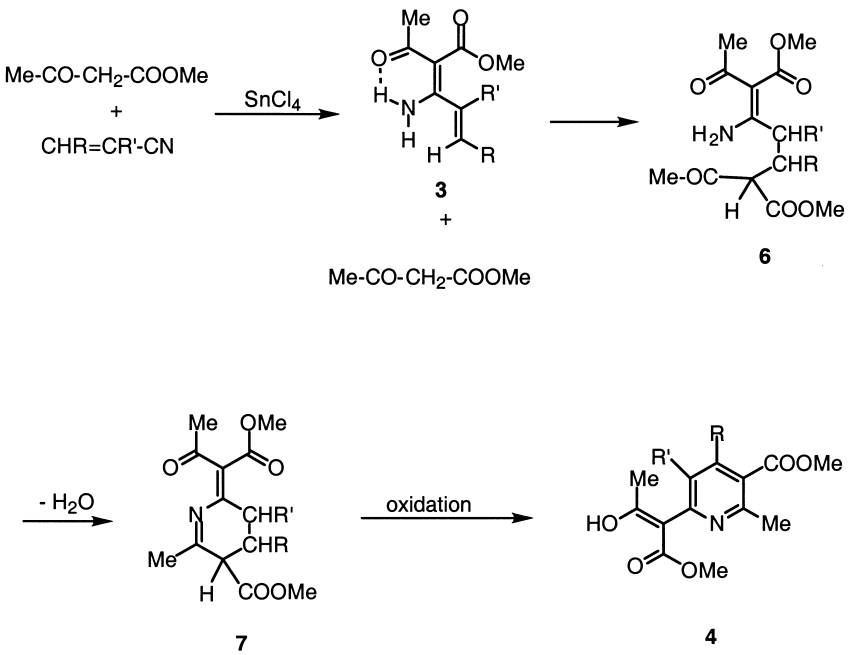


Scheme 1.

small amount of **3b**, running the reaction in DCE at reflux for 2 h. The substituted pyridines **4** or **5** are not obtained in the reaction of crotononitrile **2c**, which affords, in different experimental conditions, always the same adduct **3c**.

The formation of pyridine compounds **4** and **5** can be explained by assuming that the intermediate **3** in the presence of $SnCl_4$ undergoes a Michael type attack from the ketoester on to the delta carbon atom of the conjugated diene system to give an intermediate **6** which cyclises to the dihydropyridine **7**. The following step necessarily implies the oxidation to the pyridine **4**, which is possible in the aerobic conditions adopted (Scheme 2).

Compound **4** can be deacetylated through a retro-Claisen reaction[10] to pyridine derivative **5**. In this view, the lack of



Scheme 2.

reactivity of compound **3c** can be attributed to a more difficult Michael attack to the methyl substituted delta carbon, compared with the unsubstituted ones in **3a**,**b**.

3. Conclusions

The two main aspects of this tin(IV) promotion are: (a) the reaction pathway of α,β-unsaturated nitriles with β-ketoester **1** is modified compared to the classical base-catalysed reactions reported in the literature; the specific CN metal-activation gives in our case a non-Michael C–C bond formation and affords the enamino derivatives **3**; however, (b) the same metal centre is able to promote a Michael C–C bond formation in the presence of excess ketoester in a highly selective cascade sequence.

4. Experimental

4.1. General

Mps were determined on a 'Kofler' apparatus and are uncorrected. IR spectra were recorded on a FT-IR Perkin–Elmer Paragon 500 spectrometer. NMR spectra were recorded on a Bruker AC (200 MHz) spectrometer. Chemical shifts are given in ppm (δ) with respect to tetramethylsilane and coupling constants (J) are in hertz. Glass plates 'Merk Kieselgel 60' F 245 were used for thin layer chromatography. Silica gel 'ICN Silica 32–60, 60 Å' was used for column chromatography.

4.2. Reactions of methyl acetoacetate with acrylonitrile

4.2.1. Methyl 2-acetyl-3-amino-2,4-pentadienoate (3a). To a solution of methyl acetoacetate (0.32 mL, 3.0 mmol) and acrylonitrile (0.59 mL, 9.0 mmol) in 1,2-dichloroethane (DCE, 2 mL) was added $SnCl_4$ (0.53 mL, 4.5 mmol). The reaction mixture was stirred at rt for 45 h, diluted with ethyl acetate (20 mL) and treated with an aqueous saturated solution of Na_2CO_3 (pH ca. 8). The reaction mixture was stirred at rt for 30 min, filtered through celite, the organic layer was separated and the aqueous solution was extracted with ethyl acetate (15×3 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give an oil which slowly crystallizes to yellow crystals, mp 33–35°C, 0.410 g (yield 81%). IR (KBr): 3290, 1705, 1641, 1593, 1288 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.32 (s, 3H, Me), 3.77 (s, 3H, OMe), 5.55 (d, J=11.0 Hz, 1H, CH), 5.78 (d, J=17.3 Hz, CH), 6.79 (dd, J=11.0 and 17.3 Hz, CH), 5.6 (br, 1H, NH), 11.0 (br, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 24.64, 51.29, 102.76, 120.76, 134.66, 162.38, 169.51, 197.56. Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.90; H, 6.50; N, 8.25.

4.2.2. Methyl 3-hydroxy-2-(2-methyl-3-methoxycarbonyl-6-pyridyl)-2-butenoate (4a). To a solution of $SnCl_4$ (1.17 mL, 10 mmol) in DCE (10 mL) was added a solution of methyl acetoacetate (1.29 mL, 12 mmol) and acrylonitrile (0.33 mL, 5 mmol) in DCE (3 mL). The reaction mixture was heated at reflux for 6 h, diluted with ethyl acetate (20 mL) and treated following the same procedure used for the synthesis of **3a** to give a yellow oil (1.17 g) of a crude product which was crystallized with diethyl ether: yellow crystals of compound **4**, mp 132–135°C, 620 mg (yield 47%). IR (KBr): 1724, 1606, 1560, 1264 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.42 (s, 3H, Me), 2.79 (s, 3H, Me), 3.08 (s, 3H, OMe), 3.88 (s, 3H, OMe), 7.80 (d, J=9.3 Hz, 1H, Ar), 8.10 (d, J=9.3 Hz, 1H, Ar), 14.15 (br, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 21.22, 29.35, 50.92, 52.11, 97.23, 116.19, 117.71, 139.67, 150.77, 156.30, 164.67, 169.05, 193.44. Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.90; H, 5.60; N, 5.25.

4.2.3. Methyl (2-methyl-3-methoxycarbonil-6-pyridyl)-ethanoate (5a). To a solution of methyl acetoacetate (1.29 mL, 12 mmol) and of acrylonitrile (0.33 mL, 5 mmol) in toluene (5 mL) was added $SnCl_4$ (1.17 mL, 10 mmol). The reaction mixture was heated in an oil bath at 100°C for 2 h 30 min and was treated following the same procedure used for the synthesis of **3a** to give a yellow oil, 854 mg (yield 76%). ^1H NMR ($CDCl_3$) δ: 2.82 (s, 3H, Me), 3.72 (s, 3H, OMe), 3.85 (s, 2H, CH_2), 3.91 (s, 3H, OMe), 7.21 (d, J=8.0 Hz, 1H, CH), 8.17 (d, J=8.0 Hz, CH). ^{13}C NMR ($CDCl_3$) δ: 17.26, 40.35, 51.15, 52.35, 121.15, 126.67, 136.58, 156.17, 159.11, 167.26, 168.79. Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.10; H, 5.80; N, 6.30.

4.3. Reactions of methyl acetoacetate 1 with methacrylonitrile (2b)

4.3.1. Methyl 2-acetyl-3-amino-4-methyl-2,4-pentadienoate (3b). To a solution of methyl acetoacetate (0.32 mL, 3 mmol) and methacrylonitrile (0.75 mL, 9 mmol) in DCE (2 mL) was added $SnCl_4$ (0.53 mL, 4.5 mmol). The reaction was treated following the same procedure used for the synthesis of **3a** to give colourless crystals, mp 74–76°C, 395 mg (yield 72%). ^1H NMR ($CDCl_3$) δ: 1.96 (s, 3H, Me), 2.31 (s, 3H, Me), 3.66 (s, 3H, OMe), 5.09 (m, 2H, =CH_2), 5.69 (br, 1H, NH), 10.93 (br, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 21.33, 29.78, 51.14, 101.64, 115.45, 143.59, 169.83 (2C), 197.46. Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.10; H, 7.20; N, 7.55.

4.3.2. Methyl (2,5-dimethyl-3-methoxycarbonyl-6-pyridyl)-ethanoate (5b). To a solution of methyl acetoacetate (1.29 mL, 12 mmol) and methacrylonitrile (0.42 mL, 5 mmol) in DCE (5 mL) was added $SnCl_4$ (1.17 mL, 10 mmol). The reaction mixture was heated under reflux for 2 h and was treated following the same procedure used for the synthesis of **3a** to give a pale yellow oil, which was purified by flash chromatography (eluent ethyl acetate/light petroleum 1/3). Two products were obtained: R_f 0.47, pale yellow oil (0.523 mg) which crystallizes by cooling at −20°C to give pale yellow crystals of compound **5b**: mp 68–70°C (ethyl acetate/light petroleum), 485 mg (yield 41%). IR (KBr): 1735, 1601, 1560, 1442 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.30 (s, 3H, Me), 2.77 (s, 3H, Me), 3.72 (s, 3H, OMe), 3.89 (s, 2H, CH_2), 3.90 (s, 3H, OMe), 7.99 (s, 1H, CH, Ar). ^{13}C NMR ($CDCl_3$) δ: 18.05, 24.23, 41.83, 52.08, 52.12, 123.87, 129.32, 140.15, 155.67, 156.87, 166.91, 170.38. Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.65; H, 6.30; N, 5.95. R_f 0.37: pale yellow crystals of **3b**, 84 mg (yield 9%).

4.4. Reactions with crotononitrile

4.4.1. Methyl 2-acetyl-3-amino-2,4-hexadienoate (3c). To a solution of methyl acetoacetate (0.32 mL, 3 mmol) and crotononitrile (0.49 mL, 6 mmol) in DCE (2 mL) $SnCl_4$ (0.35 mL, 3 mmol) was added. The reaction mixture was heated in an oil bath at 60°C for 2 h 30 min, diluted with AcOEt (20 mL) and treated following the same procedure used for the synthesis of **3a** to afford a yellow oil (420 mg), which was purified by column chromatograpy (florisil, eluent ethyl acetate/light petroleum: 1/3); colourless crystals of compounsd **3c**: 365 mg (yield 65%). In a similar reaction carried out in DCE at rt, following the same procedure used for the synthesis of **3a**, compound **3c** was obtained in 50% yield. IR (KBr): 3366, 1678, 1588, 1438 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.90 (d, J=6.2 Hz, 3H, Me), 2.29 (s, 3H, Me), 3.77 (s, 3H, OMe), 6.3 (dq, J=16.0 and 6.2 Hz, 1H, CH), 5.7 (br, 1H, NH), 6.50 (d, J=16.0 Hz, 1H, CH), 11.0 (br, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 19.03, 27.78, 50.55, 103.34, 121.70, 142.24, 165.60, 166.52, 196.92. Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.95; H, 7.10; N, 7.75.

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