A Facile Synthesis of Polyfunctionally Substituted Pyridines from Ethoxycarbonylmalonaldehyde

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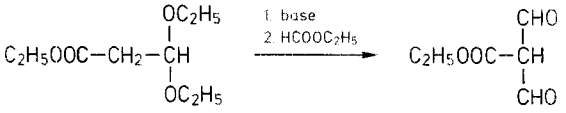
A facile access to 2,3-disubstituted-5-ethoxycarbonylpyridines (50–66% yields), derivatives of biologically and medicinally important nicotinic acid, is explored. The method involves the reaction of ethoxycarbonylmalonaldehyde with tosyl chloride and then with β-amino-α,β-unsaturated esters, ketones, or nitriles in the presence of pyridine.

Ethoxycarbonylmalonaldehyde (**1**), prepared by the condensation of ethyl 3,3-diethoxypropanoate (**2b**) with ethyl formate in the presence of base[1], is a versatile reagent; its utility in the synthesis of heterocycles[2,3] and phenolic compounds[4,5] has received some interest. Its practical use in organic synthesis, however, has virtually been limited due in part to unavailability of the starting ethyl 3,3-diethoxypropanoate **2b**.



2b **1**

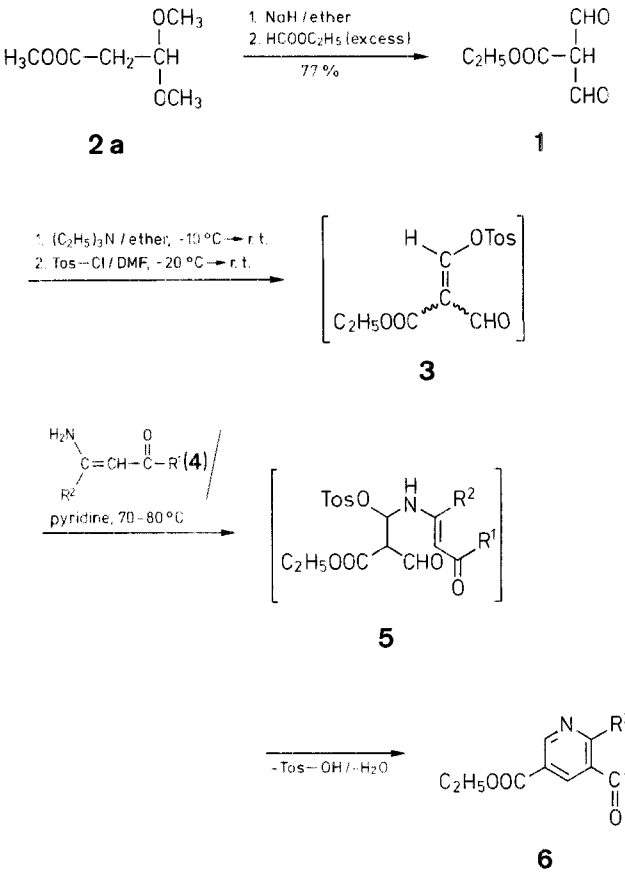
We have recently developed a facile access to methyl 3,3-dimethoxypropanoate (**2a**) from methyl acrylate via electrooxidative methoxylation[6]. As an extended use of the acetal **2a**, we report here a simple procedure for the preparation of polyfunctionalized pyridines (**6**)[7,8,9] by the reaction of compound **1** with derivatives of β-amino-α,β-unsaturated carbonyl compounds (**4**), i.e., with a 3-amino-2-alkenoic ester, with 2-amino-1-alkenyl ketones, and with a 3-amino-2-alkenenitrile.

To our knowledge, condensations of activated malonaldehydes with enamines have hitherto only been attempted with nitromalonaldehyde, giving 3-nitropyridines[10,11]. This method of nitropyridine synthesis has some drawbacks in that the starting nitromalonaldehyde is prepared as the monohydrated sodium salt by reaction of mucobromic acid with sodium nitrite in only 30–41% yields[12]. With an aim to obtain derivatives of 3-alkoxycarbonylpyridines, which represent biologically and medicinally important nicotinic acid analogues[13], we chose **1** as a starting material in the present work.

By analogy with the condensation of nitromalonaldehyde with enamines[11], the sodium salt of **1**, prepared by treatment of compound **1** with 1.2 equivalents of sodium hydride, was treated successively with tosyl chloride in dimethylformamide and ethyl β-aminocrotonate (**4a**) in the presence of pyridine at 70°C. However, the desired product **6a** was produced in only 40–45% yields due to the instability of the starting material **1** to the strong base present in this medium. The yield of **6a** could be improved to 64% by treatment of **1** with tosyl chloride in the presence of triethylamine followed by amination with enamine **4a** in the presence of pyridine at 70°C. The yields of product **6a** decreased to 48% or 34% when the reaction was carried out at 50°C or 15°C, respectively. As a sulfonylating reagent, tosyl chloride (*p*-toluenesulfonyl chloride) was found to be superior to benzenesulfonyl chloride (25% yield of **6a**) and to methanesulfonyl chloride (32% yield of **6a**).

A study of the condensation of compound **1** with a variety of other enamines[14] to investigate the scope of the method revealed (Table 1) that acyclic and cyclic 2-amino-1-alkenyl ketones as well as 3-amino-2-butenenitrile can thus be converted into pyridines (**6**) in 50–66% yields. However, attempts to condense 3-amino-2-butenamide[15,16,17] with 5-ethoxycarbonyl-2-methylpyridine-3-carboxamide were unsuccessful.

The mechanism of the reaction can be rationalized as follows. The first reaction step undoubtedly is the sulfonylation of **1** to form the β-tosyloxyacrylate **3**. In the subsequent step, the intermediate **3** undergoes nucleophilic attack by the enamine **4**. Ring closure of the resultant intermediate **5** accompanied by elimination of sulfonic acid and water under the action of base produces the desired pyridine **6**.

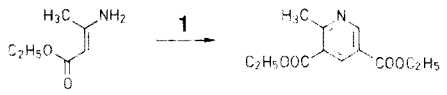
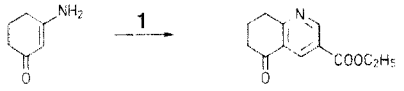
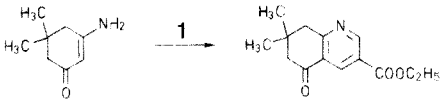
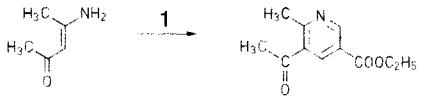
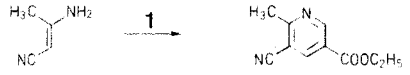


All melting points and boiling points are uncorrected. The microanalyses were performed in our laboratory.

Ethoxycarbonylmalonaldehyde (1):

To a stirred suspension of sodium hydride (144 mg, 6 mmol; freed from mineral oil by washing with dry hexane) and ethyl formate (3.7 g, 50 mmol) in dry ether (5 ml) is added a solution of methyl 3,3-dimethoxypropanoate (**2a**; 740 mg, 5 mmol) in dry ether (3 ml) at

Table 1. Pyridine Derivatives (**6**) from β-Amino-α,β-unsaturated Carbonyl Compounds (**4**) and Ethoxycarbonylmalonaldehyde (**1**)

4	6	Reaction Temp. and Time [°C], [h]	Yield[a] [%]	m.p. [°C] or b.p. [°C]/torr	Molecular Formula[b] or Lit. Data [°C]
a		70°C, 10	64	m.p. 64–65°	m.p. 60–64°[18] m.p. 64–65°[19];
b		80°, 10	58	m.p. 47–48°	$C_{12}H_{13}NO_3$ (219.2)
c		80°, 10	66	b.p. 108–109°/0.025	$C_{14}H_{17}NO_3$ (247.3)
d		70°, 10	50	b.p. 71–71°/0.013	$C_{11}H_{13}NO_3$ (207.2)
e		80°, 15	58	m.p. 56–58°	$C_{10}H_{10}N_2O_2$ (190.2)

[a] Yield of isolated product.
[b] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.29; H, ±0.29.

Table 2. Spectral Data of Compounds **6**

6	I.R.[a] ν[cm⁻¹]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int})[b] δ[ppm]	^{13}C-N.M.R. ($CDCl_3$/TMS_{int})[c] δ[ppm]
a	1720, 1600	1.40 (t, 6H, J = 7 Hz, $2CH_3$); 2.86 (s, 3H, CH_3); 4.40 (q, 4H, J = 7 Hz, $2CH_2$—O); 8.72 (d, 1H, J = 2 Hz, CH=C); 9.15 (m, 1H, CH=C)	14.3 (q); 25.0 (q); 61.6 (t); 124.0 (s); 125.5 (s); 139.2 (d); 152.4 (d); 164.0 (s); 164.7 (s); 165.8 (s)
b	1715, 1690, 1595	1.44 (t, 3H, J = 7 Hz, CH_3); 2.30 (q, 2H, J = 6 Hz, CH_2); 2.77 (t, 2H, J = 6 Hz, CH_2); 3.25 (t, 2H, J = 6 Hz, CH_2); 8.80 (d, 1H, J = 2 Hz, CH=C); 9.25 (d, 1H, J = 2 Hz, CH=C)	14.3 (q); 21.5 (t); 32.8 (t); 38.4 (t); 61.6 (t); 125.3 (s); 127.6 (s); 136.0 (d); 154.0 (d); 164.5 (s); 167.4 (s); 196.9 (s)
c	1725, 1693, 1600	1.13 (s, 6H, $2CH_3$); 1.42 (t, 3H, J = 7 Hz, CH_3); 2.59 (s, 2H, CH_2); 3.10 (s, 2H, CH_2—CO); 4.42 (q, 2H, J = 7 Hz, CH_2—O); 8.77 (d, 1H, J = 2 Hz, CH=C); 9.25 (d, 1H, J = 2 Hz, CH=C)	14.3 (q); 28.3 (q); 32.9 (s); 46.6 (t); 52.0 (t); 61.6 (t); 125.3 (s); 126.7 (s); 135.6 (d); 154.4 (d); 164.6 (s); 166.1 (s); 197.0 (s)
d	1720, 1690, 1598	1.45 (t, 3H, J = 7 Hz, CH_3); 2.66 (s, 3H, CO—CH_3); 2.69 (s, 3H, CH_3); 4.46 (q, 2H, J = 7 Hz, CH_2—O); 8.53 (d, 1H, J = 2 Hz, CH=C); 9.13 (d, 1H, J = 2 Hz, CH=C)	14.3 (q); 25.0 (q, CO—CH_3); 29.4 (q); 61.7 (t); 123.9 (s); 132.4 (s); 137.6 (d); 152.0 (d); 162.6 (s), 164.7 (s); 199.6 (s)
e	2245, 1730, 1600	1.45 (t, 3H, J = 7 Hz, CH_3); 2.84 (s, 3H, CH_3); 4.43 (q, 2H, J = 7 Hz, CH_2—O); 8.43 (d, 1H, J = 2 Hz, CH=C); 9.17 (d, 1H, J = 2 Hz, CH=C)	14.2 (q); 24.0 (q); 62.1 (t); 109.3 (s); 116.0 (s); 124.1 (s); 141.0 (d); 153.1 (d); 163.5 (s); 165.6 (s)

[a] Recorded on a JASCO IR-1 grating spectrometer.
[b] Measured at 60 MHz using a Hitachi R-24 spectrometer.
[c] Measured at 25.05 MHz using a JEOL FX-100 spectrometer.

0°C over a period of 2 h and stirring is continued for 10 h at 5°C and then overnight at room temperature. The mixture is poured into cold water (30 ml) and unchanged **2a** is removed by washing with ether. The aqueous layer is acidified to pH ~ 3 with 10% hydrogen chloride and extracted with dichloromethane (3 × 10 ml). The organic layers are washed with saturated sodium chloride, solution (10 ml), dried with sodium sulfate, and concentrated to give **1**; yield: 557 mg (77%); b.p. 115–117°C/3 torr (Ref.[1], b.p. 30–32°C/0.35 torr).

Diethyl 2-Methylpyridine-3,5-dicarboxylate (6a); Typical Procedure: To a solution of ethoxycarbonylmalonaldehyde (**1**; 144 mg, 1.0 mmol) in dry ether (1 ml) is added triethylamine (111 mg, 1.1 mmol) at −10°C and the mixture is stirred for 1 h at room temperature. Ether is then removed in vacuo and to the residue a solution of tosyl chloride (210 mg, 1.1 mmol) in dimethylformamide (2 ml) is added with stirring at −20°C. The mixture is allowed to gradually warm to room temperature and stirring is continued for an additional 3 h at room temperature. A solution of ethyl β-aminocrotonate (**4a**; 129 mg, 1.0 mmol) and pyridine (316 mg, 4.0 mmol) in dimethylformamide (1 ml) is added and the mixture is heated at 70°C for 10 h. Most of the solvent is removed under vacuum and the residue is extracted with chloroform (3 × 10 ml). The organic extract is washed with saturated sodium hydrogen carbonate solution (10 ml) and with saturated sodium chloride

solution (10 ml), and is dried with sodium sulfate. The solvent is evaporated and the residue is purified by column chromatography on silica gel using ethyl acetate/hexane (1/3) as eluent to give product **6a** as a solid; yield: 152 mg (64%); m.p. 64–65°C (Ref.[18], 60–64°C).

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