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Improved synthesis and reaction of dimethyl *a*-(bromomethyl) fumarate with primary amines

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Dimethyl α-(bromomethyl) fumarate (**2**) has been prepared in one pot by addition of bromine to dimethyl itaconate and dehydrobromination with triethylamine. The allylic bromide **2**, reacts with primary amines via two successive allylic substitutions and followed by lactamization at a high temperature (above 150°C) to give 4-methoxycarbonyl-1-N-alkyl-Δ^3-pyrrolin-2-ones (**7**) in good yields.

Ethyl α-(bromomethyl)acrylate (**1**) has been widely studied, since its first preparation by Ferris[1], because of its importance as a powerful reagent for the synthesis of biologically active species such as α-methylene-γ-butyrolactones[2,3] and γ-butyrolactames[2,4]. This is the reason why a great effort has been devoted to the development of methods for the preparation of compounds bearing an α-bromomethyl moiety[1,5]. However, only a few methods[6] were reported for the preparation of the α-bromomethylated esters analogs **2** (Scheme I).

Following the preparation process of bromomethylated substrates[7], we have previously described, we report here in a convenient large scale and one pot synthesis of dimethyl α-(bromomethyl) fumarate (**2**). Bromination of commercially available dimethyl itaconate (**3**), with bromine in boiling carbon tetrachloride, leads to the corresponding dibromide compound **4**. Addition of triethylamine to the cold mixture, induced regio- and stereoselective dehydrobromination of **3** via an elimination of β′-proton giving the unsaturated α-bromomethylated diester **2** in 73% overall yield, as shown below (Scheme II).

During the last years, reports have shown the interest of allylic bromide **2** as an intermediate, in the synthesis of β-functional α-methylene-γ-butyrolactones[8], retinoic acids[9], annelation of cyclic ketones[10], substitution reactions with enamines[11] and sulphide salts[12], oxidation with DMSO[13] and in cycloaddition reactions of the corresponding pyridinium allylides[14].

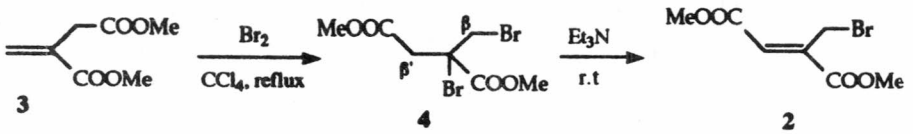
We found that bromide **2** readily reacts with primary amines, leading to 4-methoxycarbonyl-1N-alkyl-Δ^3-pyrrolin-2-ones (**7**) as white crystalline solids in high yields. The key features of our synthesis are as follows: amine (lequiv.) added to **2** in boiling bromobenzene gives a mixture of the S_N2' allylic substitution compound **5** and the desired compound **7** in moderate yields (< 20%) together with the recovered starting material. Addition of a second equivalent of amine to this mixture only provides pyrrolin-2-ones **7** in 50-90% yield (Table I).

Table 1—4-Methoxycarbonyl-1-Δ^3-pyrrolin-2-ones **7(a-g)**

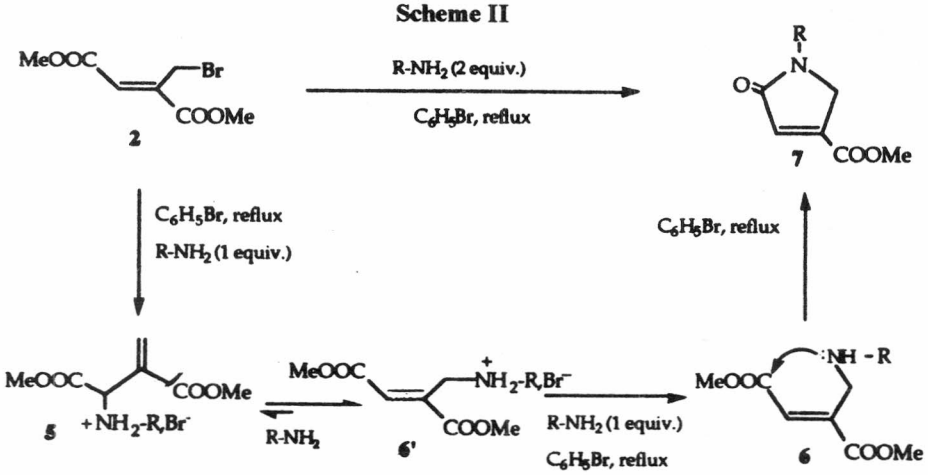
Compd	R	Yield (%)[a]	m.p. (°C)[b] (solvent)	Mol.[c] formula
7a	n Pr	66	59-60 (Hexane/PE)	$C_9H_{13}NO_3$ (183.2)
7b	*i*Pr	50	122-123 (Et_2O/PE)	$C_9H_{13}NO_3$ (183.2)
7c	*n*-C_4H_9	90	52-53 (PE)	$C_{10}H_{15}NO_3$ (197.2)
7d	C_6H_{11}	52	110-111 (Hexane)	$C_{12}H_{17}NO_3$ (223.2)
7e	$PhCH_2$	70	142-143 (Et_2O/PE)	$C_{13}H_{13}NO_3$ (231.3)
7f	*p*-$ClPhCH_2$	80	130-131 (Et_2O)/CH_2Cl_2)	$C_{13}H_{12}ClNO_3$ (265.7)
7g	EtO_2CCH_2	74	84-85 (Et_2O)	$C_{10}H_{13}NO_5$ (227.2)

a) Yield of isolated crystalline product **7(a-g)** based on **2**. b) PE: Petroleum ether (40-60°C). c) Satisfactory microanalysis obtained C ± 0.27, H ± 0.20, N ± 0.31, Cl ± 0.09.

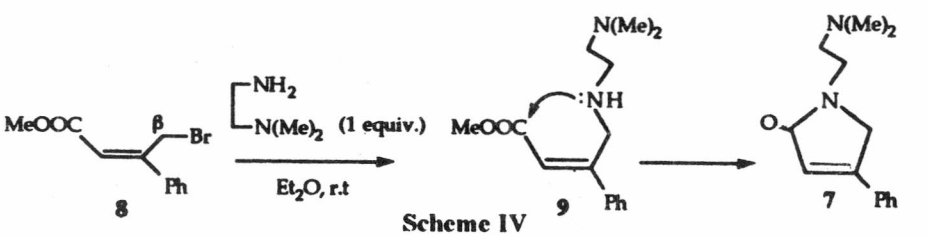
Scheme I



Scheme II



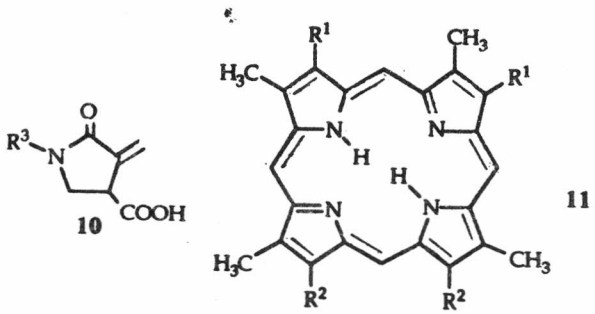
Scheme III



Scheme IV

It is clear that the reaction proceeds through a 3-step sequence two successive allylic substitutions of the primary amine, the first on the electrophilic bromide **2** giving **5** (as its hydrobromide), the second affording the isomerization product **6** which, after a 5-exo-trig[15] spontaneous cyclization process, leads to the formation of **7**. The mechanism of this reaction can be rationalized in Scheme III.

It is reasonable to explain the unusual reaction mechanism by the existence of the electron deficiency of the allylic bromide supported by the carboxylate group (Michael acceptor) on the same carbon atom, which increase the electrophilicity of the β′-carbon. Consequently, the brominated derivative **2** reacts first via a S_N2' substitution reaction, while the reported reaction of homologous methyl β-bromomethyl cinnamate homologous **8**[16] with N,N-dimethyl ethylenediamine in ether proceeds first, by a S_N2 reaction, followed by cyclization of **9** into the corresponding pyrrolin-2-one **7**[16] (Scheme IV).



In conclusion, we have developed a new simple and efficient method for preparation of dimethyl α-(bromomethyl) fumarate (**2**) which was used directly in the synthesis of β-lactams **7**. This method seems to be better then the known ones[17-19]. 4-Methoxycarbonyl-1-N-alkyl-Δ^3-pyrrolin-2-ones (**7**) are potentially useful intermediates for the synthesis of biologically active compounds like azasarkomycins **10**[20] nature or artifical biologially relevant porphirins **11**[21].

Experimental Section

Commericially dimethyl itaconate was used as received from suppliers. The progress of the reactions was monitored by TLC on silica gel plates (Fluka Kieselgel $60F_{254}$). Flash chromatography was performed on silica gel (Fluka Kieselgel, 70-230 mesh). Melting points were determined using a Büchi 510 capillary melting apparatus and were uncorrected. IR spectra are taken on Perkin-Elmer FT-IR spectrometer PARAGON 1000PC (ν_{max} in cm^{-1}) ^1H and ^{13}C NMR on Jeol C-HL 60 MHz, FX 90 MHz and Bruker 200 MHz instruments (chemical shifts in δ, ppm using TMS as internal standard) and mass spectra (MS) on a Varian Mat 112 apparatus (electron-impact ionisation: El at 70eV).

Preparation of dimethyl α-(bromomethyl) fumarate (2). To refluxing solution of dimethyl itaconate (7.9 g, 50 mmoles) in carbon tetrachloride (40 mL) was added dropwise bromine (8.32 g, 52 mmoles) in carbon tetrachloride (40 mL) at such a rate that the bromine colour gradually disappeared. The end of the bromination reaction was indicated by the persistence of a brownish colour. Triethylamine (Et_3N, 75 mmoles), 10.5 mL) was then added dropwise to the cold mixture and stirring was continued for 16 hr. After filtration of ammonium salt and removal of the solvent and the excess of amine, the residue was distilled under reduced pressure to give dimethyl α-(bromomethyl) fumarate (**2**), yield 11.02 g (73%); b.p. 81°C/0.1 Torr. (Lit.[9] 72°/0.1 Torr); IR: 1725 (C=O), 1635 (C=C), 1280 (C-Br); ^1H NMR ($CDCl_3$): 3.86 and 3.93 (2s, 6H), 4.73 (s, 2H), 6.85 (s, 1H); ^{13}C NMR ($CDCl_3$): 22.5 (t, CH_2-Br), 52.3, 53.1 (2q,$2CH_3-O$), 128.3 (d, $CH=C$), 142.8 (s, $C=CH$), 165.0, 165.2 (2s, 2CO).

One-pot synthesis of 4-methoxycarbonyl-1-N-alkyl-Δ³-pyrrolin-2-one (7): Typical procedure. *n*-Propylamine (20 mmoles) was added to a solution of dimethyl α-(bromomethyl) fumarate **2** (2.37 g, 10 mmoles) in boiling bromobenzene (10 mL). After stirring for 20 min, the mixture was cooled and filtered. The removal of solvent under reduced pressure, gave a solid which on purification by column chromatography on silica gel, using CH_2Cl_2/ethyl acetate (9:1) as eluent given crude pyrrolin-2-one **7a**. Crystallization from a pet. ether-hexane (40-60) mixture yielded 1.21 g (66%) of the pure product **7a** as white crystalline solid.

4-Methoxycarbonyl-1-N-propyl-Δ³-pyrrolin-2-one (7a). IR: 1719 (COOMe), 1694 (C=O), 1619 (C=C) ^1H NMR ($CDCl_3$): 0.90 (t, 3H, J=7 Hz), 1.33-1.78 (m, 2H), 3.36 and 3.30 (AA′, 2H), 3.45 (t, 2H, J=7 Hz), 3.70 (s, 3H), 7.37 (s, 1H), ^{13}C NMR ($CDCl_3$): 11.1 (q, CH_3-CH_2), 22.3 (t, CH_2-CH_3), 36.4 (t, $=C-CH_2-N$),44.1 (t, CH_2-CH_2-N), 51.3 (q, CH_3-O), 108.3 (s, $-CH=C$), 143.4 (d, $-CH=C$), 163.6 (s, $COOCH_3$), 176.1 (s, CO), m/z: (1%): 183 (M^+, 100), 141 (11), 124 (57), 82 (37).

4-Methoxycarbonyl-1-N-i-propyl-Δ³-pyrrolin-2-one (7b). IR: 1719 (COOMe), 1691 (C=O), 1617 (C=C), ^1H NMR ($CDCl_3$): 1.24 (d, 6H, J=7 Hz), 3.26 and 3.30 (AA′, 2H), 3.73 (s, 3H), 4.00-4.63 (m, 1H), 7.48 (s, 1H), ^{13}C NMR ($CDCl_3$): 21.6 (2q, CH_3-CH), 36.9 36.9 (t, $=C-CH_2-N$), 43.4 (t, $-CH-N$), 51.4 (q, CH_3-O, 108.7 (s, $-CH=C$); 140.4 (d, $-CH=C$), 163.7 (s, $COOCH_3$), 175.6 (s, CO), m/z: (1%): 183 (M^+, 100), 154 (16), 125 (6).

4-Methoxycarbonyl-1-N-butyl-Δ³-pyrrolin-2-one (7c). IR: 1721 (COOMe), 1694 (C=O), 1619 (C=C), ^1H NMR ($CDCl_3$): 0.90 (t, 3H, J=7 Hz), 1.16-1.83 (m, 4H), 3.26 and 3.30 (AA′, 2H), 3.50 (t, 2H, J=7 Hz), 3.73 (s, 3H), 7.40 (s, 1H), ^{13}C NMR ($CDCl_3$) 13.4 (*q*, CH_3-CH_2), 19.6 (t, CH_3-CH_2-), 30.8 (t, $-CH_2CH_2-CH_2$), 36.3 (t, $-C-CH_2-N$), 42.0 (t, CH_2-CH_2-N), 51.1 (q, CH_3-O), 108.2 (s, $-CH=C$), 143.2 (d, $-CH=C$), 163.4 (s, $COOCH_3$), 175.9 (s, CO), m/z: (1%): 197 (M^+, 97), 138 (85), 126 (100), 82 (38).

4-Methoxycarbonyl-1-N-cyclohexyl-Δ³-pyrrolin-2-one (7d). 1720 (COOMe), 1695 (C=O), 1620 (C=C), ^1H NMR ($CDCl_3$) 1.26-1.93 (m, 11H), 3.26 and 3.30 (AA′, 2H), 3.73 (s, 3H), 7.50 (s, 1H), ^{13}C NMR ($CDCl_3$): 25.4 (t, *p*-CH_2), 25.6 (t, 2m-CH_2), 32.4 (t, 2*o*-CH_2), 37.0 (t, $=C-CH_2-N$), 51.0 (d, $CH-N$), 51.5 (q, CH_3-O), 108-5 (s, $-CH=C$), 141.1 (d, $-CH=C$), 175.9 (s, $COOCH_3$), 183.9 (s, CO), m/z (1%): 223 (M^+, 84), 164 (19), 141 (100), 82 (47).

4-Methoxycarbonyl-1-N-benzyl-Δ³-pyrrolin-2-one-(7e). IR: 1722 (COOMe), 1695 (C=O); 1619 (C=C). ^1H NMR ($CDCl_3$): 3.33 and 3.36 (AA′, 2H), 3.70 (s, 3H), 4.63 (s, 2H), 7.30 (s, 5H), 7.36 (s, 1H). ^{13}C NMR ($CDCl_3$): 36.5 (t, $=C-CH_2-N$), 46.2 (t, Ph-CH_2-N), 51.5 (q, CH_3-O), 109.0 (s, $-CH=C$), 128.1, 128.4, 129.2 (3d, 5 CH_{arom}), 135.8 (s, C_{arom}), 142.8 (d, $-CH=C$), 163.5 (s, $COOCH_3$), 176 (s, CO), m/z: (1%): 231 (M^+, 43), 172 (7), 126 (4), 91 (100).

4-Methoxycarbonyl-1-N-p-chlorobenzyl-Δ³-pyrrolin-2-one (7f). IR: 1725 (COOMe), 1697 (C=O), 1620 (C=C), ^1H, NMR ($CDCl_3$): 3.33 and 3.36 (AA′, 2H), 370 (s, 3H), 4.61 (s, 2H), 7.23 (m, 4H), 7.43 (s, 1H). ^{13}C NMR ($CDCl_3$): 36.4 (t,

$=C-CH_2-N$), 45.5 (t, Ph-CH_2-N), 51.5 (q, CH_3-O), 109.0 (s, $-CH=C$), 129.3, 129.4 (2d, 4 CH_{arom}), 134.3 (s, C_{arom}), 142.5 (d, $-CH=C$), 163.4 (s, $COOCH_3$), 175.8 (s, CO), m/z: (1%): 265 (M^+, 42), 206 (3), 126 (14), 125 (100).

4-Methoxycarbonyl-1-N-(ethoxycarbonylmethyl)-Δ^3-pyrrolin-2-one (7g). IR: 1731 (COOEt), 1724 (COOMe), 1699 (C=O), 1622 (C=C); ^1H, NMR ($CDCl_3$): 1.21 (t, 3H, $J=7$Hz), 3.36 and 3.30 (AA', 2H), 3.70 (s, 3H), 4.15 (q, 2H), $J=7$ Hz), 4.20 (s, 2H), 7.35 (s, 1H), ^{13}C NMR ($CDCl_3$): 13.9 (q, CH_3-CH_2-), 35.6 (t, $=C-CH_2-N$), 43.1 (t, Ph-CH_2-N), 51.2 (q, CH_3-O), 61.8 (t, $-CH_2-O$), 108.8 (s, $-CH=C$), 142.6 (d, $-CH=C$), 163.2 (s, $COOCH_3$), 165.5 (s, $COOCH_2CH_3$), 175.6 (s, CO), m/z: (1%): 227 (M^+, 75), 154 (100), 126 (78), 92 (12).

Isolation of the intermediate dimethyl α-benzylamino-β-methylene succinate (5e). Coupling reaction of dimethyl α-(bromomethyl) fumarate (**2**) (10 mmoles) and benzylamine (10 mmoles) was carried out under the same conditions described above. Compound **5e** was obtained after purification on silica gel as pale yellow oil. IR (ν cm^{-1}): 3340 (N−H), 1745 (C=O), 1720 (C=O), 1630 (C=C), ^1H NMR: 2.30 (s, 1H, 3.71 and 3.76 (2s, 6H), 3.24 (s, 2H), 4.16 (s, 1H), 5.80 and 6.33 (2s, 2H), 7.30 (s, 5H).

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