Synthetic Applications of Crown Ethers; The Malonic Ester Synthesis

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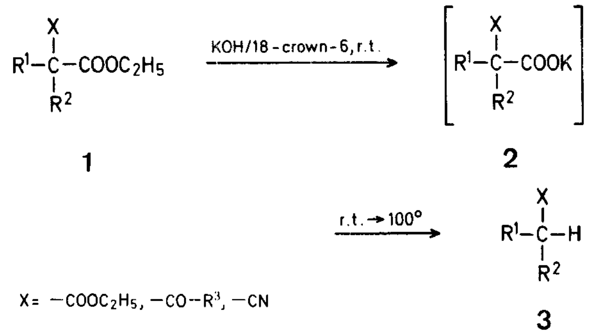
The traditional malonic ester synthesis[1,2] involves as part of the procedure the hydrolysis of the diester to the diacid, followed by thermal decarboxylation, and often reesterification of the monoacid. The thermal decarboxylation can require fairly high temperatures (up to 180°) and is often the overall yield determining step. In recent years several procedures have been developed for the direct decarboxyalkylation[3–9] of geminal diesters, β-keto and α-cyano esters in an attempt to reduce the number of steps involved and to operate under milder conditions. From studies of the catalytic effect of crown ethers upon the rate of decarboxylation of carboxylates in ether solvents[10,11], we have developed a convenient, high yield, one-pot method for the decarboxyalkylation of esters (**1**) with α-activating groups. In essence this improved procedure relies upon the ability of 18-crown-6 ether both to accelerate the hydrolysis of esters[12] by potassium hydroxide and also to allow the decarboxylation of potassium carboxylates (**2**) under mild conditions[10,11,13]. As indicated for the archetypal compounds shown in the Table, reactions could be run at either 80° (refluxing benzene, Procedure A) or at 100° (refluxing dioxan, Procedure B).



Although the yields of crude product (**3**) were high (75–90%) and it was often sufficiently pure for further use, the purified product (>99%) was obtained in yields certainly comparable to the multistep procedures, for example: ethyl caproate (73%) in this study cf to caproic acid (75%) in an *Organic Synthesis* preparation[14]; ethyl butyrate (59%) in this study cf 60%[15]; 2-heptanone (45%) in this study cf (52–61%) in an *Organic Synthesis* preparation[16].

The one-pot procedures involve two distinct steps. The substrate was first hydrolyzed to the potassium carboxylate with potassium hydroxide[17] in ~6 vol% ethanol/benzene (Procedure A) and an equimolar amount of 18-crown-6-ether[18]. With non-enolizable substrates the hydrolysis is very rapid at room temperature but up to 20 h can be required for particularly acidic substrates (e.g., diethyl phenylmalonate). The decarboxylation step usually involves heating to reflux for 2–20 h as indicated in the Table and product formation was followed by G.L.C. The decarboxylation is facilitated by removal of the ethanol by distillation as an azeotrope prior to the reflux period. If the carboxylate is particularly resilient to decarboxylation, the reflux temperature was increased by using dioxan instead of benzene (Procedure B). Solubility problems may also dictate the choice of solvent. For substrates with just one ester group, it is possible to use an of excess potassium hydroxide. This is particularly useful for systems that decarboxylate rapidly releasing carbon dioxide which consumes potassium hydroxide. Also water may be added to depress enolate formation for acidic substrates (e.g., camphor carboxylate ester) (Procedure C). Best results were obtained using a molar equivalent amount of 18-crown-6-ether and consequently a procedure for recovering the crown ether has been developed. The recovery procedure is included in the Experimental. The one-pot procedures outlined here were not successful for particularly acidic substrates ($pK_a < \sim 10$) such as diethyl nitromalonate and 2-carboxyethylcyclopentanone since the potassium hydroxide converted these preferentially to the unreactive enolate form. While for these substrates other procedures are favoured, it is for the less reactive compounds that the present procedure is particularly attractive. The procedures outlined here can also be applied to methyl esters which undergo prior and almost complete transesterification. Clearly this technique may have to be limited to compounds not containing base sensitive groups and in this sense it compliments the traditional procedure. Nevertheless a degree of selectivity to base is shown by the lack of hydrolysis of the amide group in the acetamidomalonate yielding protected amino acids in yields comparable to the traditional 2-step procedure[19].

Typical Procedures for the Malonic Ester Synthesis:

Distilled benzene contained ~100 μg water/ml and dioxan, distilled from hydride, contained ~30 μg water/ml. The reactions were conducted under argon. The respective compounds were identified by comparison with the N.M.R., G.L.C., b.p., or m.p.[20] data of pure compounds. The yields of crude product were calculated from the weight and N.M.R.-integration of the neat product and corrected for any remaining traces of solvent. The yields of purified products were based upon distilled product or sublimed product in the case of camphor. The product yields are uncorrected for recovered starting material.

Procedure A in Benzene: A benzene solution (20 ml) containing 1.1 normal potassium hydroxide in ethanol (2.8 ml, 3.1 mmol) was added dropwise over 25 minutes to a stirred solution of malonate diester or α-keto ester (3.0 mmol) and 18-crown-6 (3.0 mmol, 0.78 g) (see Table for cases where addition of crown was delayed) in benzene (30 ml) at 5–10°. After several hours stirring at room temperature, the solution was heated to reflux and the ethanol distilled as an azeotrope (10–15 ml). Refluxing was continued for 2–20 h and the solution cooled. (See below for methyl pentyl ketone isolation procedure). A 3 normal hydrochloric acid solution (1.5 ml) was added[21], then saturated potassium chloride solution (10 ml). The layers were separated and the benzene layer washed twice with saturated potassium chloride solution (15 ml). The combined aqueous washes were saved to recover the crown ether. After drying (Na_2SO_4), the benzene solution was filtered and the solvent removed under reduced pressure. Because methyl pentyl ketone is water soluble, the following modification was used. The benzene solution was diluted with pentane (100 ml), filtered through neutral alumina (~5 g), and the solvents removed under reduced pressure. The crown may be recovered by washing the alumina with 1–5% ethanol in dichloromethane.

Procedure B in Dioxan: The reaction was carried out as above using dioxan as solvent and addition of the potassium hydroxide/ethanol solution at <15°. The removal of ethanol by distillation was continued until the pot temperature reached 100° (15–30 ml distillate). After the reflux period (2–48 h), the solution was cooled and pentane (50 ml) added. (See below for acetamidoester isolation procedure.) Then 3 normal hydrochloric acid and saturated potassium chloride solution were added and the above washing procedure followed. After evaporation of the solvent, the crude material may be contaminated with crown ether (20–50 mg) which was removed by filtration of a pentane solution through neutral alumina (1–2 g) and reevaporation. Since the acetamidoester was sparingly soluble in pentane and soluble in water, after the reaction was completed, the solution was filtered and evaporated. The residue was taken up in dichloromethane (50 ml), washed four times with saturated potassium chloride solution, dried, and evaporated to yield 54% ester and 10% diester. The combined washes were continuously extracted with ether, which was dried and evaporated to yield 24% ester product.

Procedure C in Benzene and Water: To the compound (3.0 mmol) in benzene (50 ml) at 25° was added 5 normal aqueous

Table. Conditions and Yields for One-Pot Decarboxyalkylation Reactions

Substrate R[1]	R[2]	X	Procedure	Reaction time at 25°	Reaction time at reflux	Yields [%][a] of starting material	Yields [%][a] of crude product	Yields [%][a] of pure product[b]	m.p. or b.p./torr	Lit.[20] m.p. or b.p./torr
n-C_4H_9	H	$COOC_2H_5$	A	1 h	23 h	3	84	73	82–84°/45	168°/760
			A[c]	17 h	42 h	12	72	61	–	–
n-C_3H_7	H	$COOC_2H_5$	A	1 h	14 h	16	81	59	90–92°/125	146°/760
—$(CH_2)_5$—		$COOCH_3$[d]	A	1 h	20 h	3	87[e]	70[e]	100–102°/35	82–83°/12
C_6H_5	H	$COOC_2H_5$	A	20 h	2 h	9	78	65	122–124°/25	120°/20
			A[f]	17 h	1 h	14	66	–	–	–
H_3C—CO—NH	H	$COOC_2H_5$	B	0.5 h	16 h	10	78	55	m.p. 46–48°	m.p. 48°
n-C_4H_9	H	CO—CH_3	A[g,h]	4 h	16 h	<1	74	45	148–150°/745	148–150°/750
			A[f,g]	18 h	1 h	4	74	45	–	–
n-C_4H_9	H	CN	B[i]	1 h	48 h	–[j]	76	55	120–126°/250	163°/760
3-methoxycarbonyl-2-oxo-1,7,7-trimethylbicyclo[2.2.1]heptane[l]			C	0.5 h	28 h	2	73	–	–	–
			C[h]		11 h	<1	91	95[k]	m.p. 171–173°	m.p. 176–177°

[a] Crude yields are based upon 3 mmol scale; purified on 30 mmol scale.

[b] Purified products were >99% pure by G.L.C. (5 ft × 0.75 in column of 5% SE-30 on 45–60 Chromsorb P) and yields given are of distilled products.

[c] Ratio of (substrate/crown ether) = 5.

[d] Methyl ester used.

[e] Obtained as the ethyl ester.

[f] No crown ether added.

[g] 2–2.5 fold excess of potassium hydroxide.

[h] Crown ether added after 3.5 h.

[i] Crown ether added after 1 h.

[j] 21% of the cyano acid recovered.

[k] Ratio of (substrate/crown ether) = 3.

[l] Methyl camphor-3-carboxylate.

potassium hydroxide solution (3.5 mmol, 0.7 ml). (If crown was also present then 6 mmol of potassium hydroxide were added.) After 3.5 h reflux, 18-crown-6 (3.0 mmol) was added, the water distilled off as an azeotrope, and the solution refluxed for an additional 7.5 h. The isolation procedure of A was then followed.

Procedure D; Recovery of 18-Crown-6-ether: The acidic and saturated potassium chloride washes of several experiments were combined and evaporated to dryness on a rotary evaporator. The solid residue was transferred to a funnel and washed repeatedly with dichloromethane. The dichloromethane washes (~1 liter) were dried ($MgSO_4$), filtered, and evaporated. The resulting solid contains potassium chloride and may be either sublimed (130–140°/0.05 torr) or crystallized from acetonitrile[22] to give product containing 3–4% potassium chloride by weight. This latter mixture is sufficiently reactive in most crown ether-catalyzed reactions and is less hygroscopic than the purified crown ether, but can be further purified by sublimation (60–70°/0.05 torr). The recovery of crown ether by either method was 65–85%.

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