

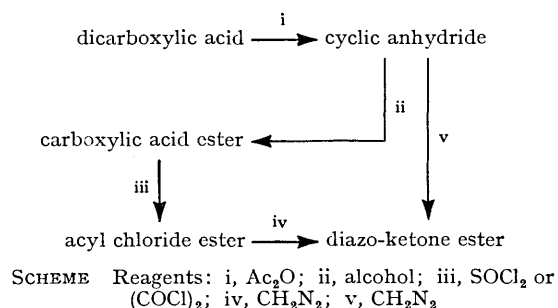
Lengthening the Chain of a Dicarboxylic Acid by One Carbon Atom

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The normal five-step procedure for the process indicated in the title has been shortened to three steps by using the reaction between diazomethane and a cyclic anhydride to prepare the intermediate diazo-ketone ester. This is illustrated by the synthesis of methyl 2-(1-benzyl-5-methoxycarbonylpyrrolidin-2-yl)acetate from 1-benzylpyrrolidine-2,5-dicarboxylic anhydride.

IN order to lengthen the chain of a dicarboxylic acid by one carbon atom it is necessary to protect one of the carboxy-groups before proceeding with the usual Arndt-Eistert synthesis.^{1,2} The normal procedure for doing this is shown in the Scheme (steps i—iv).



When the diazo-ketone ester has been produced it can then undergo the Wolff rearrangement to yield whichever carboxylic acid derivative is required.^{1,2} This reaction sequence is aptly illustrated by the synthesis of diethyl tetrahydrohomophthalate (2) from tetrahydrophthalic acid (1)³ (see also ref. 4).

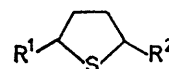
This process can be shortened to three steps by preparing the diazo-ketone ester directly from the cyclic anhydride (step v). This reaction does not appear to have been used previously as part of a synthesis presumably because it is reported to require several days and to produce a mixture of compounds.^{5,6} However, we have found that if a large excess of diazomethane is used the diazo-ketone ester is readily produced and is suitable for further reactions. In fact the diazo-ketone ester (8) prepared directly from tetrahydrothiophen-2,5-dicarboxylic anhydride (3)⁷ and diazomethane was of comparable purity to the product obtained *via* the acyl chloride ester (7) (i.r.⁸ and t.l.c.).

This shortened procedure has proved successful in a situation where the usual approach failed. Thus, 1-benzylpyrrolidine-2,5-dicarboxylic anhydride (4)⁹ was

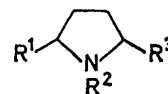
converted into the half ester (10) by a similar procedure to that used for the sulphur analogue. Only intractable tars were isolated when we attempted to convert this



- (1) $\text{R}^1 = \text{R}^2 = \text{CO}_2\text{H}$ (3) $\text{X} = \text{S}$
 (2) $\text{R}^1 = \text{CO}_2\text{Et}$, $\text{R}^2 = \text{CH}_2\text{CO}_2\text{Et}$ (4) $\text{X} = \text{N}\cdot\text{CH}_2\text{Ph}$



- (5) $\text{R}^1 = \text{R}^2 = \text{CO}_2\text{Me}$
 (6) $\text{R}^1 = \text{CO}_2\text{Me}$, $\text{R}^2 = \text{CO}_2\text{H}$
 (7) $\text{R}^1 = \text{CO}_2\text{Me}$, $\text{R}^2 = \text{COCl}$
 (8) $\text{R}^1 = \text{CO}_2\text{Me}$, $\text{R}^2 = \text{CO}\cdot\text{CHN}_2$



- (9) $\text{R}^1 = \text{R}^3 = \text{CO}_2\text{Me}$, $\text{R}^2 = \text{CH}_2\text{Ph}$
 (10) $\text{R}^1 = \text{CO}_2\text{Me}$, $\text{R}^2 = \text{CH}_2\text{Ph}$, $\text{R}^3 = \text{CO}_2\text{H}$
 (11) $\text{R}^1 = \text{CO}_2\text{Me}$, $\text{R}^2 = \text{CH}_2\text{Ph}$, $\text{R}^3 = \text{COCl}$
 (12) $\text{R}^1 = \text{CO}_2\text{Me}$, $\text{R}^2 = \text{CH}_2\text{Ph}$, $\text{R}^3 = \text{CO}\cdot\text{CHN}_2$
 (13) $\text{R}^1 = \text{CO}_2\text{Me}$, $\text{R}^2 = \text{CH}_2\text{Ph}$, $\text{R}^3 = \text{CH}_2\cdot\text{CO}_2\text{Me}$

material into the acyl chloride ester (11) by using either thionyl chloride or oxalyl chloride. However treatment of the cyclic anhydride (4) with an excess of dried ethereal diazomethane yielded the diazo-ketone ester (12), which was converted into the acetate derivative (13) by boiling in methanol in the presence of silver oxide. The ¹H n.m.r. spectrum of the diester (13) suggested that this product was a mixture of geometrical isomers. Since the Wolff rearrangement is reported to proceed with retention of configuration,¹ the major component (85%) was identified as the *cis*-isomer.

This shortened procedure may prove advantageous in other situations, especially as it eliminates the need to use thionyl chloride, which sometimes has adverse effects.

¹ L. L. Rodina and I. K. Korobitsyna, *Russ. Chem. Rev.*, 1967, **36**, 260.

² W. E. Bachman and W. S. Struve, *Org. Reactions*, 1942, **1**, 38.

³ F. D. Brutcher and D. D. Rosenfeld, *J. Org. Chem.*, 1964, **29**, 3154.

⁴ K. M. Baker and B. R. Davis, *Tetrahedron*, 1968, **24**, 1955.

⁵ A. Bhati, *J. Org. Chem.*, 1962, **27**, 1183.

⁶ W. Bradley and R. Robinson, *J. Amer. Chem. Soc.*, 1930, **52**, 1558.

⁷ V. Horak, *Chem. listy*, 1950, **44**, 34 (*Chem. Abs.*, 1952, **46**, 103).

⁸ P. Yates, B. L. Shapiro, N. Yoda, and J. Fugger, *J. Amer. Chem. Soc.*, 1957, **79**, 5756.

⁹ E. W. Della and M. Kendall, unpublished data.

EXPERIMENTAL

I.r. spectra were measured with a Perkin-Elmer 237 spectrophotometer, and ^1H n.m.r. spectra with a Varian A-60A instrument (Me_4Si as internal standard). G.l.c. was effected on an Aerograph Autoprep A-705 instrument [10 ft \times 1/8 in stainless steel column packed with SE-30 (20%) on Chromosorb P]. T.l.c. was carried out on Fluka alumina type D5 (chloroform as solvent); spots were developed with iodine vapour. Microanalyses were performed by the Australian Microanalytic Service, Melbourne.

5-Methoxycarbonyltetrahydrothiophen-2-carboxylic Acid (6).—A solution of tetrahydrothiophen-2,5-dicarboxylic anhydride (3) (7.9 g) ⁷ in dry methanol (150 ml) was stirred at room temperature (2.3 h) then evaporated under reduced pressure. Distillation of the residual oil (b.p. 114—118° at 0.05 mm Hg) yielded the *half ester* (6) (7.8 g, 83%), which soon solidified and crystallised from light petroleum (b.p. 60—80°) as white plates, m.p. 50—53° (Found: C, 44.3; H, 5.2. $\text{C}_7\text{H}_{10}\text{O}_4\text{S}$ requires C, 44.2; H, 5.3%), ν_{max} (Nujol) 1730s and 1700sh cm^{-1} , δ (CDCl_3) 3.75 (3H, s, CO_2Me) and 9.68 (1H, s, CO_2H , exchangeable).

Dimethyl Tetrahydrothiophen-2,5-dicarboxylate (5).—Methylation of the *half ester* (6) with diazomethane yielded the *dimethyl ester* as a liquid, b.p. 70° at 0.1 mmHg (Found: C, 46.7; H, 5.8. $\text{C}_8\text{H}_{12}\text{O}_4\text{S}$ requires C, 47.1; H, 5.9%), ν_{max} (neat) 1740s cm^{-1} , δ (CCl_4) 3.68 (6H, s, CO_2Me).

Methyl 5-Chloroformyltetrahydrothiophen-2-carboxylate (7).—The *half ester* (6) (0.5 g) was stirred with an excess of thionyl chloride (15 ml) at room temperature for 1 h. The excess of reagent was removed at room temperature leaving the acyl chloride ester (7) as a liquid that was not purified [ν_{max} (neat) 1780s and 1730s cm^{-1}]. This liquid was boiled in dry methanol; removal of the solvent under reduced pressure left an oil identical with the foregoing diester (5) (i.r., g.l.c., and t.l.c.).

Methyl 5-Diazoacetyltetrahydrothiophen-2-carboxylate (8).—(i) A solution of the acyl chloride ester (7) (0.5 g) in dry ether (50 ml) was slowly added (0.5 h) to a dried ethereal solution of diazomethane [from nitrosomethylurea (6 g)] at 0°. The mixture was allowed to warm to room temperature overnight and the ether was removed under reduced pressure leaving the diazo-ketone ester as a yellow liquid, ν_{max} (neat) 2100s, 1735s, and 1640 cm^{-1} .

(ii) A solution of tetrahydrothiophen-2,5-dicarboxylic anhydride (3) (3 g) in dry benzene (300 ml) was added to a dried ethereal solution of diazomethane [from nitrosomethylurea (60 g)] at 0°, and the mixture was allowed to warm to room temperature overnight. Evaporation left a yellow liquid, identical with that obtained in (i) (i.r. and t.l.c.).

1-Benzyl-5-methoxycarbonylpyrrolidine-2-carboxylic Acid (10).—A solution of 1-benzylpyrrolidine-2,5-dicarboxylic

anhydride (4) (6.93 g) ⁹ in dry methanol (150 ml) was stirred at room temperature (4 h), then evaporated under reduced pressure. The residual solid was re-crystallised from benzene–light petroleum (b.p. 50—60°) yielding the *half ester* (10) (7.32 g, 93%) as white needles, m.p. 67—68° (Found: C, 64.2; H, 6.5; N, 5.1. $\text{C}_{14}\text{H}_{17}\text{NO}_4$ requires C, 63.9; H, 6.5; N, 5.3%), ν_{max} (CCl_4) 1750s cm^{-1} , δ (CDCl_3) 3.63 (3H, s, CO_2Me), 3.90 (2H, s, $\text{N}\cdot\text{CH}_2$), 7.30 (5H, s, aromatic), and 11.20 (1H, s, CO_2H). The *picrate* crystallised from methanol as yellow prisms, m.p. 160—163° (Found: C, 48.5; H, 4.4; N, 11.2. $\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}_{11}$ requires C, 48.8; H, 4.1; N, 11.4%). The *hydrochloride* of (10) crystallised from ethanol–acetone as white needles, m.p. 149—150° (Found: C, 55.8; H, 6.2; Cl, 12.1; N, 4.5. $\text{C}_{14}\text{H}_{18}\text{NO}_4\text{Cl}$ requires C, 56.1; H, 6.0; Cl, 11.9; N, 4.7%).

Dimethyl 1-Benzylpyrrolidine-2,5-dicarboxylate (9).—Methylation of the *half ester* (10) with diazomethane yielded dimethyl 1-benzylpyrrolidine-2,5-dicarboxylate (9), b.p. 115° at 0.02 mmHg (lit.,¹⁰ 129—130° at 0.05 mmHg); lit.,¹¹ 148—152° at 0.02 mmHg), ν_{max} (neat) 1745s cm^{-1} , (CCl_4) 3.50 (6H, s, CO_2Me), 3.83 (2H, s, $\text{N}\cdot\text{CH}_2$), and 7.23 (5H, s, aromatic). The *picrate* crystallised from methanol–light petroleum (b.p. 50—60°) as yellow needles, m.p. 122° (Found: C, 49.7; H, 4.5; N, 11.0. $\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_{11}$ requires C, 49.8; H, 4.4, N, 11.1%).

Methyl 1-Benzyl-5-diazoacetylpyrrolidine-2-carboxylate (12).—To a solution of 1-benzylpyrrolidine-2,5-dicarboxylic anhydride (4) (4.8 g) in dry benzene (250 ml) was added a dried ethereal solution of diazomethane [from nitrosomethylurea (60 g)] at 0°. The mixture was allowed to warm to room temperature overnight and then evaporated under reduced pressure leaving the *diazo-ketone ester* (12) as a yellow liquid that was not purified, ν_{max} (neat) 2100s, 1735s, and 1640s cm^{-1} .

Methyl 2-(1-Benzyl-5-methoxycarbonylpyrrolidin-2-yl)-acetate (13).—Freshly prepared silver oxide (2 g) was added to a solution of the foregoing diazoketone (12) in dry methanol (300 ml), and the mixture was boiled under reflux (2 h). Decolourising charcoal was added to the mixture, which was then filtered hot, and the filtrate was concentrated under reduced pressure. Distillation of the residue afforded the *diester* (13) (3.3 g, 53%) as a pale yellow liquid, b.p. 117° at 0.05 mmHg (Found: C, 66.3; H, 7.1; N, 4.7. $\text{C}_{16}\text{H}_{21}\text{NO}_4$ requires C, 66.0; H, 7.3; N, 4.8%), ν_{max} (neat) 1735s cm^{-1} , δ (CCl_4) 2.35 (2H, m, $\text{CH}_2\cdot\text{CO}_2$), 3.47, 3.53 and 3.58 (total 6H, s, CO_2Me), 3.80 and 3.90 (total 2H, s, $\text{N}\cdot\text{CH}_2$), and 7.23 (5H, s, aromatic). G.l.c. analysis (185°) showed a single peak. The *picrate* crystallised from methanol as clusters of yellow needles, m.p. 108—109° (Found: C, 50.9; H, 4.8; N, 10.9. $\text{C}_{22}\text{H}_{24}\text{N}_4\text{O}_{11}$ requires C, 50.8; H, 4.7; N, 10.8%).

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¹⁰ S. W. Blackman and R. Baltzly, *J. Org. Chem.*, 1961, **26**, 2750.

¹¹ E. Schipper and W. R. Boehme, *J. Org. Chem.*, 1961, **26**, 3599.