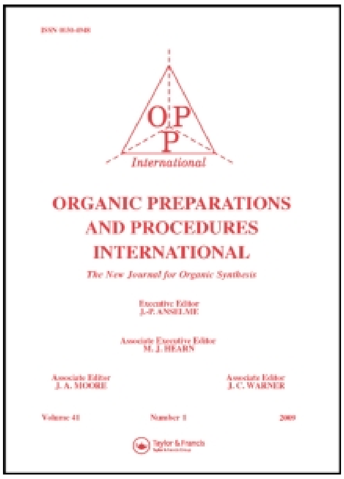

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A CONVENIENT PREPARATION OF ETIWL 7-BROMOHEPTANOATE

Stefano Canonica[a]; Marinella Ferrari[a]; Massimo Sisti[a]
[a] Dipartimento di Chimica Organica ed Industriale, Universita' degli Studi di Milano, Milano, ITALY

To cite this Article Canonica, Stefano , Ferrari, Marinella and Sisti, Massimo(1989) 'A CONVENIENT PREPARATION OF ETIWL 7-BROMOHEPTANOATE', Organic Preparations and Procedures International, 21: 2, 253 — 254
To link to this Article: DOI: 10.1080/00304948909356378
URL: http://dx.doi.org/10.1080/00304948909356378

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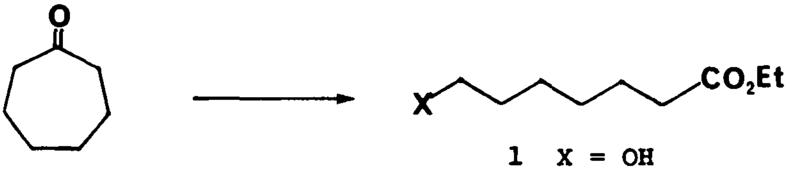
A CONVENIENT PREPARATION OF ETHYL 7-BROMOHEPTANOATE

Submitted by
(04/18/88)

Stefano Canonica, Marinella Ferrari and Massimo Sisti*

Universita' degli Studi di Milano
Dipartimento di Chimica Organica ed Industriale
Via Venezian, 21-20133 Milano, ITALY

As part of a program[1] aimed at the synthesis of prostaglandins[2] and their analogues,[3] we needed ethyl 7-bromohepanoate (2). Compound 2 has been obtained from tetrahydropyran by conversion to 5-chloropentyl acetate and treatment with diethyl sodium malonate followed by hydrolysis and decarboxylation[4] or by reaction of monoethyl suberate with red mercury (II) oxide and bromine.[5] The first method gives acceptable overall yield (about 40% in our hands) but suffers from time-consuming and tedious manipulations, while the second gives poor yields (25%) and utilizes toxic materials.



1 X = OH

2 X = Br

We now report that the reaction of cycloheptanone with three equiv. of potassium persulfate in the presence of sulfuric acid and ethanol was complete in 8 hrs at 15° affording ethyl 7-hydroxyheptanoate 1 in 85% yield (pure by GLC).[6] Higher temperatures or different ratios between the oxidizing agent and cycloheptanone had a deleterious effect on the yield of 1. Subsequent treatment of ethyl 7-hydroxyheptanoate with phosphorus tribromide in toluene gave the title compound 2 in 60% yield after distillation. This method is simple, short and proceeds in good yield, from inexpensive starting materials and may be run on a preparative useful scale.The oxidative procedure gives better yields than the methods using trifluoroperacetic acid[7] or sodium perborate.[8]

EXPERIMENTAL SECTION

Ethyl 7-Bromoheptanoate (2).- A mixture of sulfuric acid (142 ml, 95%), water (48 ml) and ethanol (200 ml) was cooled to 15°. Potassium persulfate (145.8 g, 0.54 mol) was added gradually with stirring, at 10-15°. A solution of cycloheptanone (20.2 g, 0.18 mol) in ethanol (60 ml) was added dropwise at 15° and the mixture was allowed to react at this temperature. After 8 hrs, the starting material was consumed (GLC on Carbowax 20M). The mixture was diluted with water (1.5 l) and exhaustively extracted with diethyl ether (7 x 100 ml). After drying (sodium sulfate) and evaporation *in vacuo*, ethyl 7-hydro- xyheptanoate (1) (26.6 g, 85%) was obtained (pure by GLC). Its physical and spectral data were identical to those reported.[7]

To a solution of ethyl 7-hydroxyheptanoate (1) (17.4 g, 0.1 mol) in anhydrous toluene (42 ml), was added phosphorus tribromide (17.4 ml, 0.18 mol) in anhydrous toluene (42 ml) dropwise at room temperature. After 4 hrs, the mixture was carefully diluted with water (200 ml), the layers were separated and the organic extract was washed with a saturated solution of potassium carbonate (3 x 50 ml), dried over potassium carbonate and evaporated under reduced pressure. The crude residue was distilled *in vacuo* and pure ethyl 7-bromoheptanoate 2 (14.3 g, 60%) was obtained; bp. 120°/5 mm (lit.[4] 112°/5 mm); IR ($CHCl_3$): 1725 cm^{-1}; ^1H-NMR ($CDCl_3$, 80 MHz): δ 1.18 (t, 3H, J = 7.3 Hz), 1.95-1.30 (m, 8H), 2.23 (t, 2H, J = 7.2 Hz), 3.32 (t, 2H, J = 6.8 Hz), 4.05 (q, 2H, J = 7.3 Hz); mass spectrum (70 ev) m/e (relative intensity) 238-236 (M^+, 14), 193-191 (52), 157 (33), 111 (53), 101 (38), 83 (100).

Anal. Calcd for $C_9H_{17}BrO_2$: C, 45.57; H, 7.17. Found: C, 45.49; H, 7.13

Acknowledgements.- We thank Prof. G. Jommi for helpful discussions and the Consiglio Nazionale delle Ricerche (Progetto Finalizzato Chimica Fine e Secondaria, CNR, Roma) for financial support.

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