A Convenient Preparation of Tetrahydro-4*H*-pyran-4-one

J. Chem. Soc. C,
2401-03 (1970)

By **G. R. Owen** and **C. B. Reese,*** University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW

Tetrahydro-4*H*-pyran-4-one has been prepared in a two-stage process from 3-chloropropionyl chloride, in 45% overall yield.

In connection with our work on oligoribonucleotide synthesis,[1] we have recently advocated the use of the methoxytetrahydropyranyl [1,2] (I) instead of the tetrahydropyranyl group for the protection of the hydroxy-functions of optically active alcohols. The reagent required for methoxytetrahydropyranylation, 4-methoxy-5,6-dihydro-2*H*-pyran (II), may be readily prepared [2] from tetrahydro-4*H*-pyran-4-one (III). However, as it is difficult to obtain compound (III) on a 100 g or larger scale by any published procedure (see later), an attempt was made to develop a more convenient laboratory preparation.

We now report that when 1,5-dichloropentan-3-one (V) is heated with *ca.* 2 mol. equiv. of sodium dihydrogen phosphate in aqueous dioxan, tetrahydro-4*H*-pyran-4-one (III) is obtained in satisfactory yield. 1,5-Dichloropentan-3-one (V) was first prepared by Catch *et al.*[3] by the aluminium chloride-catalysed Friedel–Crafts acylation of ethylene with 3-chloropropionyl chloride (IV). The reported yield (30%) was later improved by Baddeley *et al.*,[4] and has now been further improved so that it is

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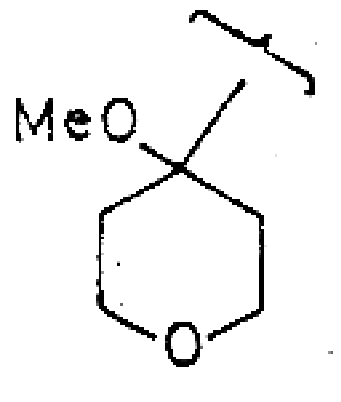
[1] See D. P. L. Green, T. Ravindranathan, C. B. Reese, and R. Saffhill, *Tetrahedron*, 1970, **26**, 1031 and previous papers in this series.

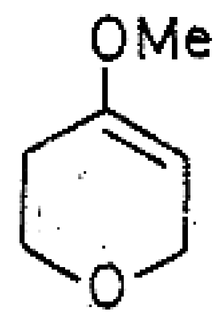
[2] C. B. Reese, R. Saffhill, and J. E. Sulston, *J. Amer. Chem. Soc.*, 1967, **89**, 3366; *Tetrahedron*, 1970, **26**, 1023.

[3] J. R. Catch, D. F. Elliott, D. H. Hey, and E. R. H. Jones, *J. Chem. Soc.*, 1948, 278.

[4] G. Baddeley, H. T. Taylor, and W. Pickles, *J. Chem. Soc.*, 1953, 124.

virtually quantitative. It is both unnecessary and undesirable to purify the crude 1,5-dichloropentan-3-one (V) obtained. When the latter is hydrolysed in the presence of sodium dihydrogen phosphate under the conditions mentioned, tetrahydro-4*H*-pyran-4-one (III) may be isolated in 45% overall yield [based on the readily available 3-chloropropionyl chloride (IV) as starting material].


(I)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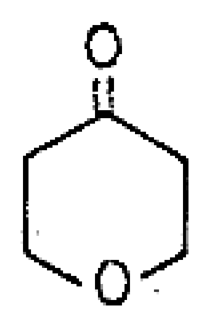
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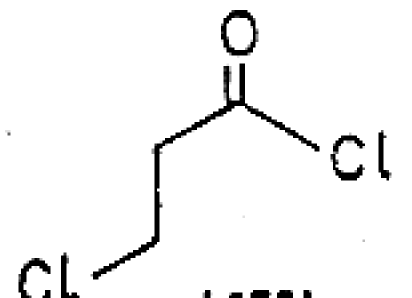
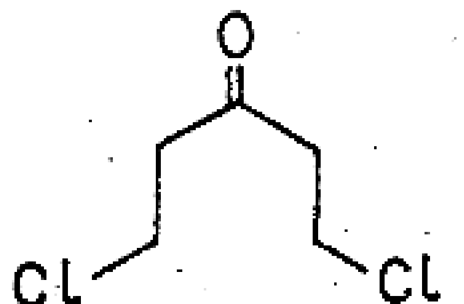
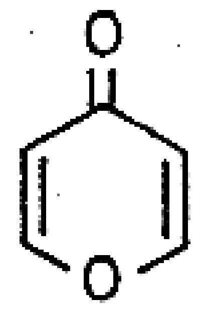
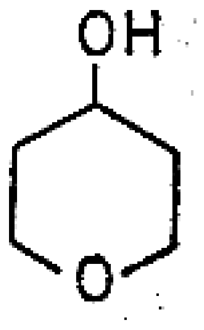

(IV)


(V)

The hydrolysis conditions for the conversion [(V) ⟶ (III)] appear to be critical. Thus the desired product (III) is not formed at a significant rate if the temperature of the reaction mixture is below 90°, and it is obtained in lower yield under more acidic conditions (see Experimental section).


(VI)


(VII)

Our method, which is suitable for the preparation of 100 g or larger quantities of (III), seems more convenient than any of the reported methods. Thus 4*H*-pyran-4-one (VI) may only be prepared readily on a small scale,[5] and its conversion into compound (III) by catalytic hydrogenation[5,6] also gives tetrahydro-4*H*-pyran-4-ol (VII) as a by-product. The latter compound (VII), which is the other common precursor of (III), is less easily accessible[7] than 1,5-dichloropentan-3-one (V), and its oxidation, by chromic acid, leads to variable yields[7] of compound (III). Finally, compound (V) may be prepared on a large scale more readily than any of the related acyclic precursors of compound (III), which have been described in the Russian literature.[8-11]

EXPERIMENTAL

N.m.r. spectra (100 MHz) were measured with a Varian HA 100 spectrometer, with tetramethylsilane as internal standard. I.r. spectra were measured with Unicam SP 200 and Perkin-Elmer 357 spectrometers, and mass spectra with an A.E.I. MS9 spectrometer. 3-Chloropropionyl chloride (IV), b.p. 46·5—47° at 17 mmHg (lit.,[12] 144° at 760 mmHg), was prepared in 90—95% yield by treatment of commercially available 3-chloropropionic acid (Koch–Light Ltd.) with thionyl chloride.

1,5-*Dichloropentan*-3-*one* (V).—3-Chloropropionyl chloride (500 g, 3·94 mol) was added slowly to a stirred suspension of powdered anhydrous aluminium chloride (735 g, 5·51 mol) in dichloromethane (550 ml), contained in a cooled (ice-water bath) three-necked flask (3 l). Ethylene gas (dried over KOH and anhydrous $CaSO_4$) was bubbled into the reaction mixture, which was allowed to warm to 20°. After 3 h, i.r. spectroscopic analysis * of the products indicated that the reaction had gone to completion.

The products were then added slowly to a cooled (ice-salt bath) mixture of dichloromethane (500 ml), hydrochloric acid, and ice (2 l of aqueous layer; *ca.* 1M with respect to HCl), so that the temperature did not rise above 20°. The organic layer was separated, washed with water (3 × 2 l), and dried ($MgSO_4$). The solvent was then evaporated under reduced pressure to leave crude 1,5-dichloropentan-3-one (578 g, 95%) as a dark brown oil.

Distillation of this material (50 g) led to the evolution of hydrogen chloride and gave a pale yellow liquid which consisted of 1,5-dichloropentan-3-one, contaminated with a more volatile compound; yield of distillate, 37·5 g; b.p. 65—70·5° at 0·2 mmHg (lit.,[4] 78° at 0·8 mmHg). Redistillation of this material gave virtually pure 1,5-dichloropentan-3-one, $\nu_{max.}$ (film) 1718 cm^{-1}, τ ($CDCl_3$) 6·27 (t, *J ca.* 6·5, 4H) and 7·08 (t, *J ca.* 6·5, 4H), *m/e* 154 and 156 (1·53 : 1, M^+), and 55 (base peak).

Tetrahydro-4H-*pyran*-4-*one* (III).—(*a*) The crude 1,5-dichloropentan-3-one (300 g, 1·94 mol) was added to a suspension of sodium dihydrogen phosphate (510 g, 3·7 mol) in water (600 ml) and dioxan (600 ml), contained in a three-necked flask (3 l). The slowly stirred mixture was heated on a sand-bath (*ca.* 140°) so as to maintain a gentle rate of reflux (internal temperature 91—92°). After 5 h, the products were cooled (ice–water bath), neutralized (to pH 5) with 30% aqueous sodium hydroxide, and extracted with ether (3 × 350 ml). The dried ($MgSO_4$), combined extracts were distilled under reduced pressure to give tetrahydro-4*H*-pyran-4-one (92 g, 45% overall yield based on 3-chloropropionyl chloride as starting material), b.p. 59—60° at 13 mmHg (lit.,[7c] 57—59° at 11 mmHg); $\nu_{max.}$

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* The progress of the reaction was monitored in the following way. A small quantity (*ca.* 0·1 ml) of the mixture was treated with water (0·1 ml) and the organic layer was separated and dried ($MgSO_4$). After evaporation of the solvent, the residual oil was examined by i.r. spectroscopy. A comparison of the intensities of the carbonyl-stretching bands at 1790 (starting material) and 1718 cm^{-1} (product) indicated the extent of reaction.

[5] R. Cornubert, R. Delmas, S. Monteil, and J. Viriot, *Bull. Soc. chim. France*, 1950, 36.

[6] R. Cornubert and P. Robinet, *Bull. Soc. chim. France*, 1933, **53**, 565; R. Mozingo and H. Adkins, *J. Amer. Chem. Soc.*, 1938, **60**, 669; E. Sorkin, W. Krähenbühl, and H. Erlenmeyer, *Helv. Chim. Acta*, 1948, **31**, 65.

[7] (*a*) M. I. Farberov, E. P. Tepenitsyna, and N. K. Shemyakina, *Doklady Akad. Nauk S.S.S.R.*, 1954, **99**, 793; *Zhur. obshchei Khim.*, 1955, **25**, 133 (*Chem. Abs.*, 1955, **49**, 8315b); (*b*) E. Hanschke, *Chem. Ber.*, 1955, **88**, 1053; (*c*) S. Olsen and R. Bredoch, *ibid.*, 1958, **91**, 1589.

[8] I. N. Nazarov and I. V. Torgov, *Bull. Acad. Sci.*, *U.S.S.R.*, *Classe sci. chim.*, 1946, 495 (*Chem. Abs.*, 1948, **42**, 7736a).

[9] S. A. Vartanyan and A. O. Tosynyan, *Izvest. Akad. Nauk Armyan, S.S.R. Khim. Nauki*, 1958, **11**, 177 (*Chem. Abs.*, 1959, **53**, 3048b).

[10] S. G. Matsoyan, G. A. Musakhanyan, and S. A. Vartanyan, *Izvest. Akad. Nauk Armyan. S.S.R.*, *Khim. Nauki*, 1958, **11**, 421 (*Chem. Abs.*, 1959, **53**, 21,653h).

[11] S. G. Matsoyan, G. A. Chukhadzhyan, and S. A. Vartanyan, *Zhur. obshchei Khim.*, 1959, **29**, 451 (*Chem. Abs.*, 1959, **53**, 21,913f).

[12] R. Wolffenstein and J. Rolle, *Chem. Ber.*, 1908, **41**, 733.

(film) 1715 cm^{-1}, τ ($CDCl_3$) 6·07 (t, *J ca.* 6 Hz, 4H) and 7·55 (t, *J ca.* 6 Hz, 4H), *m/e* 100 (M^+) and 42 (base peak); 4-phenylsemicarbazone, m.p. 171·5—172° (lit.,[7b] 170—171°) (Found: C, 61·5; H, 6·6; N, 17·8. Calc. for $C_{12}H_{15}N_3O_2$: C, 61·8; H, 6·5; N, 18·0%).

(*b*) The crude 1,5-dichloropentan-3-one (300 g, 1·94 mol) was added dropwise with stirring during 1 h to heated (steam-bath) 0·5N-sulphuric acid (1200 ml). After a further 1 h, the products were cooled (ice–water bath) and carefully neutralized (to pH 6) with 30% aqueous sodium hydroxide. The resultant solution was extracted with ether (3 × 600 ml), and the extract was dried ($MgSO_4$) and distilled to give tetrahydro-4*H*-pyran-4-one (63 g, 31% overall yield, based on 3-chloropropionyl chloride).