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THE RESOLUTION OF 3-CHLORO-2-BUTANONE

B. MODARAI
Department of Chemistry, Arya-Mehr University of Technology, Tehran, Iran

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Abstract—3-Chloro-2-butanone has been resolved into its optical antipodes by means of its 'menthydrazide' derivative.

Only a few cases of the resolution of ketones have been reported, since the resolution of carbonyl compounds are difficult to achieve.[1] An enolizable α-hydrogen causing racemization creates further problems in the resolution of 3-chloro-2-butanone.

3-Chloro-2-butanone was prepared by the method of Bruylants and Houssiau.[2] The product could be obtained only in 90% purity after several fractionations, containing 6% 1-chloro-2-butanone and 0·8% 2-butanone.

It was anticipated that stringent hydrolysis conditions for the regeneration of the ketone from a derivative would lead to racemization since the active centre is enolizable. Attempts were, therefore, made to choose a method for the resolution whereby the ketone could be regenerated under fairly mild conditions.

Resolution by enamine formation[3] failed. The resolving agent used for the resolution of the chloroketone was (−)-menthyl-N-aminocarbamate, '(−)-menthydrazide'.[1] The diastereoisomeric '(−)-menthydrazone' was formed in quantitative yield by adding the chloro-ketone (b.p. 114–117°) to a solution of the (−)-menthydrazide (m.p. 96–98°C, lit., 101–102°) in minimum quantity of absolute ethanol at 30°. Fractional crystallization of the white powdery condensation product from ethanol gave powdery amorphous solid with poor change in rotation. The derivative was soluble in cold methylene chloride and chloroform, fairly soluble in cold carbon tetrachloride and insoluble in n-hexane. Acetone, benzene, cyclohexane, toluene and ligroin were not suitable solvents for the crystallization. Although absolute ethanol at first seemed to be an unsuitable solvent, repeated crystallization from minimum quantity of boiling absolute ethanol ultimately gave the optically pure less soluble (−)-derivative as shiny crystalline needles. The (+)-from was isolated as a white powder by working up the mother liquors.

Regeneration of the ketone from the menthydrazone was not smooth. The derivative resisted hydrolysis under mild acid conditions used by Woodward.[1] Regeneration by the use of a reactive carbonyl compound, such as acetylacetone,[4] whereby the ketone could be recovered under mild conditions failed.

Regeneration of the ketone was achieved by means of a 50% (w/v) sulphuric acid solution under special conditions. In order to prevent racemization of the halo-ketone, contact of the regenerated ketone with the acid was kept at a minimum.

The optically active (−) and (+)-3-chloro-2-butanones had specific rotation of − 1·7° and + 0·72° respectively. In order to confirm the optical purity of the resolved halo-ketones, a sample of each of the optically active halo-ketones was reconverted to the menthydrazone; its specific rotation was measured and found to compare well with that of the respective pure diastereoisomer, indicating that racemization has not occurred during the hydrolysis.

The chemical purity of the optically active halobutanones was confirmed by GLC., NMR. and IR spectroscopy.

EXPERIMENTAL

Resolution of 3-chloro-2-butanone.- (−)-menthyl N-aminocarbamate (214 g, 1 mol), $[\alpha]_D^{25}$ − 79° (1 2 dm, *c* 2, in abs EtOH) was dissolved in the minimum quantity of cold abs EtOH. To the soln kept at 30°, (±)-3-chloro-2-butanone (106·5 g, 1 mol) was added. The white solid product which separated after 1 h was filtered off (185·2 g), $[\alpha]_D^{25}$ − 51·2° (1 4 dm, *c* 0·16 in abs EtOH), m.p. 161–165°C (dec). The solid was refluxed with abs EtOH (1·5 l), with exclusion of moisture, until a clear soln was obtained. The hot soln was allowed to cool to room temp within 30 h. Filtration gave white powdery solid (92 g), $[\alpha]_D^{25}$ − 62·5° (1 4 dm, *c* 0·1 in abs EtOH), m.p. 201–204° (dec). Crystallization of this solid, in the same manner, again gave powdery solid (71 g), $[\alpha]_D^{25}$ − 71·6° (1 4 dm, *c* 0·1 in abs EtOH), m.p. 221–223°C (dec). Three further crystallization yielded pure (−)-3-chloro-2-butanone (−)-menthydrazone (25 g) as shiny crystalline needles $[\alpha]_D^{25}$ − 81·5° (1 4 dm, *c* 0·1 in abs EtOH), m.p. 228–228·5°C (dec). Further crystallization did not alter the rotation of these crystals.

The original filtrate and the mother liquor from the first crystallization were combined and filtered. The filtrate obtained was evaporated under vacuum to 2/3 of its volume and then filtered. The mother liquor was then evaporated to dryness under vacuum at room temp. The solid was dissolved in the minimum quantity of boiling EtOH, allowed to cool to room temp and then filtered. The mother liquor was evaporated to dryness at room temp; the solid was subjected to a three stage fractional crystallization from EtOH to give (+)-3-chloro-2-butanone (−)-menthydrozone. $[\alpha]_D^{25}$ −40·3° (l 4 dm, *c* 0·2 in abs EtOH), m.p. 171–173° (dec).

Hydrolysis of the menthydrozones. Pure (−)-3-chloro-2-butanone (−)-menthydrazone (6·0 g) was refluxed in ether (1 l) in contact with 50% (w/v) H_2SO_4 (400 cm^3) with vigorous stirring until all the solid dissolved and then refluxed for 1 h longer. The ether layer was removed after cooling, washed with water and dried over $MgSO_4$. The ether was distilled off and the residue was warmed to 30° under high vacuum using two traps cooled to −78° to collect any of the halo-ketone. The solid left was placed in 1 l of ether, transfered to the same reaction flask and subjected to hydrolysis for 1 h longer. The ether layer was then withdrawn and treated as above. This procedure was repeated until no more solid was obtained after evaporation of the ether. Hydrolysis was performed on two further 6 g of pure (−)-derivative and the product from the three hydrolyses were combined and distilled to give (−)-3-chloro-2-butanone (1:1 g, 17%), b.p. 40–41° at 30 mmHg, 114–115° at atmospheric pressure, $[\alpha]_D^{25}$ −1·7° (l 1 dm, *c* 90 in CCl_4, α_D^{25} −1·53°). The (+)-3-chloro-2-butanone was obtained in the same way $[\alpha]_D^{25}$ +0·72° (l 1 dm, *c* 50 in CCl_4, α_D^{25} +0·36°).

(−)-3-Chloro-2-butanone (0·1105 g, 1·03 mmol) was reacted with (−)-menthyl N-aminocarbamate (0·2220 g, 1·03 mmol). The solid product, (menthydrazone), had $[\alpha]_D^{25}$ −80·0 (l 4 dm, *c* 0·1 in abs EtOH), m.p. 228–228·5° (dec). (+)-3-chloro-2-butanone was treated similarly and the corresponding menthydrazone had $[\alpha]_D^{25}$ −42·1°, m.p. 171–173·5° (dec).

The accuracy of polarimetric readings were ±0·01°.

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