Nitration of 2-Phenylcyclohexanone

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Abstract

Nitration of 2-phenylcyclohexanone (1a) with mixed acid results in oxidative cleavage to a mixture of nitrobenzoic acids but use of copper(II) nitrate in acetic anhydride yields 2-(4′-nitrophenyl)cyclo-hexanone (1b) and smaller amounts of 6-(4′-nitrophenyl)-6-oxohexanoic acid (2).

Introduction

A study of the nitration of the title compound (1a) was undertaken with the aim of preparing 2-(4′-nitrophenyl)cyclohexanone (1b) for use in another project. Nitration of the open-chain analogue, 1-phenylpropan-2-one, with mixed sulfuric–nitric acids gives predominantly *ortho–para* substitution, although the actual ratios are not stated.[1] However, electronically similar compounds, such as ethyl phenylacetate and benzyl cyanide, undergo predominantly *para* substitution.[2a]

(1a) R = H
(1b) R = NO$_2$

(2)
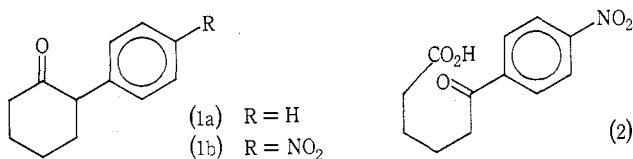
Results and Discussion

Reaction of (1a) with mixed sulfuric–nitric acids at 0°C, conditions which give good yields in the *para* nitration of benzyl cyanide,[3] resulted in extensive oxidation and cleavage of the cyclohexanone ring with the formation of mainly *para*- (60%) and *ortho*-nitrobenzoic acids (32%) and a smaller amount (8%) of the *meta*-isomer. The acids were identified by g.l.c. analysis of their methyl esters. The above results suggested that nitration of the aromatic ring had preceded cleavage as initial formation of benzoic acid followed by nitration would have yielded predominantly the *meta*-isomer. The presence of the nitro group on the benzene ring would enhance the enolization of the carbonyl group, thus facilitating the oxidative cleavage according to the accepted

[1] Baker, J. W., and Hey, L., *J. Chem. Soc.*, 1932, 2917.

[2] Hoggett, J. G., Moodie, R. B., Penton, J. R., and Schofield, K., 'Nitration and Aromatic Reactivity' (*a*) Ch. 9; (*b*) p. 93 (Cambridge University Press: 1971).

[3] Robertson, G. R., *Org. Synth.*, 1932, Coll. Vol. I, 397.

mechanism for such reactions.[4] Modification of the reaction conditions, similar to those employed for 1-phenylpropan-2-one (temperature-lowering and shorter reaction times), produced only oxidation products or unchanged starting material without the formation of appreciable amounts of new, neutral products. Accordingly other nitration conditions were sought.

Copper(II) nitrate in acetic anhydride has been used[5] for the nitration of sensitive compounds and when applied to (1a) gave good yields (c. 80%) of (1b), an unstable oil, characterized as its crystalline 2,4-dinitrophenylhydrazone.

Mass spectral (m/e 219) and infrared (peaks at 1525 and 1350 cm^{-1}) examination of the product confirmed the introduction of a nitro group into the aromatic ring.

The p.m.r. spectrum (CCl$_4$) showed benzylic proton absorption at δ 4·06–4·4 which, as expected, is downfield from similar absorption at 3·3–3·7 in 2-phenyl-cyclohexanone (1a). The aromatic proton pattern was complex and did not clearly define the expected *para* substitution. However, oxidation of the product with alkaline potassium permanganate solution gave only *para*-nitrobenzoic acid, which establishes the structure as (1b).

A minor acidic product, the yield of which is increased with higher proportions of reagent and longer reaction times, was also isolated. This product analysed for C$_{12}$H$_{13}$NO$_5$ and again showed aromatic nitro group absorptions at 1532 and 1355 cm^{-1} in the infrared spectrum. The p.m.r. spectrum (CCl$_4$) showed partly resolved triplets at δ 2·45 (2H) and 3·03 (2H), a partly resolved multiplet at 1·79 (4H) and a complex aromatic proton (4H) multiplet. Again oxidation with alkaline potassium permanganate solution gave only *para*-nitrobenzoic acid, thus establishing the structure of the acidic product as 6-(4'-nitrophenyl)-6-oxohexanoic acid (2), an intermediate in the complete oxidation to *para*-nitrobenzoic acid.

The high selectivity for *para*-substitution in this case contrasts with most nitrations involving acetyl nitrate, which is believed to be the active reagent formed from copper(II) nitrate and acetic anhydride,[5] where a higher ratio of *ortho* to *para* substitution is obtained than when mixed acid is used.[2b] Further studies are in progress with copper(II) nitrate–acetic anhydride on a variety of aromatic systems to see if this high selectivity of orientation is general.

Experimental

P.m.r. spectra were measured with a Hitachi Perkin–Elmer R20 instrument on carbon tetrachloride solutions with tetramethylsilane as internal reference. Infrared spectra were measured on carbon tetrachloride solutions with a Hitachi instrument; polystyrene lines were used for calibration. G.l.c. analyses were carried out on a Hewlett-Packard 5720A machine. Microanalyses were by the Australian Microanalytical Service, Melbourne. Mass spectra were recorded by Mr N. Keats with an AEI MS30 instrument. Melting points were determined in open capillaries by standard thermometers.

Nitration of 2-Phenylcyclohexanone

(i) *With mixed acid.*—Powdered 2-phenylcyclohexanone[6] (0·5 g) was added to a well stirred mixture of concentrated HNO$_3$ (5 ml) and concentrated H$_2$SO$_4$ (5 ml) at −2°. The temperature rose

[4] Waters, W. A., 'Mechanisms of Oxidation of Organic Compounds' Ch. 7 (Methuen: London 1964).

[5] Fieser, L. F., and Fieser, M., 'Reagents for Organic Synthesis' Vol. I, p. 163; Vol. II, p. 87 (John Wiley: New York 1967, 1969).

[6] Newman, M. S., and Forbman, M. D., *J. Am. Chem. Soc.*, 1944, **66**, 1550.

to 5° and then dropped slowly as a yellow colour and frothing developed in the mixture. Stirring was continued for an additional 30 min at 0–5° then the mixture was poured into ice-water (20 ml). The sticky yellow solid was taken into ether (2 × 20 ml), the combined ethereal extracts were washed with water, and then shaken with saturated $NaHCO_3$ solution (2 × 10 ml). Neutral material remaining in the ethereal solution amounted to only 6 mg. Acidification of the $NaHCO_3$ extracts yielded a pale yellow solid which was taken into ether. Drying ($MgSO_4$) of the ethereal extract, followed by removal of the solvent, left 0·42 g of pale yellow solid. This was esterified with anhydrous methanol and a drop of concentrated H_2SO_4 in the usual way and the crude methyl esters were analysed by g.l.c. (OV-1 on Chromosorb W at 130°, 1-m column, flow rate 60 ml/min). Samples were injected in ethyl acetate solutions and the reported retention times are measured from the ethyl acetate peak. Standards: *ortho*, 2·51 min; *meta*, 3·43 min; *para* 3·08 min. Reaction product: 2·50 min (32%); 3·08 min (60%); 3·44 min (8%).

(ii) *With copper*(II) *nitrate trihydrate–acetic anhydride.*—Powdered $Cu(NO_3)_2,3H_2O$ (5·324 g, 0·022 mol) was added to a stirred solution of 2-phenylcyclohexanone (3·48 g, 0·02 mol) in acetic anhydride (40 ml) at 14°. After an induction period of about 5 min, the temperature rose gradually to 48° and then dropped. The mixture was stirred at room temperature for 1 h, then poured into water (100 ml) and stirred to hydrolyse the acetic anhydride. The heavy, yellow insoluble oil was taken into carbon tetrachloride (2 × 25 ml), the combined organic extracts were washed (H_2O, saturated $NaHCO_3$ solution), dried ($MgSO_4$), and the solvent was removed leaving a pale yellow oil (3·80 g). T.l.c. (Eastman Chromagram silica gel, solvent benzene) showed a trace component (R_F *c.* 0·7) and a major component (R_F *c.* 0·3), cf. 2-phenylcyclohexanone (R_F *c.* 0·5). The oil darkened with time and attempts to purify it by short-path distillation led to extensive decomposition. Thick-layer chromatography (silica gel H, benzene) gave chromatographically pure (1b) as a very pale yellow oil (Found: m/e 219. $C_{12}H_{13}NO_3$ requires m/e 219). ν_{max} 1718 (C=O), 1525 and 1350 cm^{-1} (aromatic NO_2). N.m.r. δ 2·25–2·50, m, CH_2CO; 4·06–4·40, m, ArCH; 7·1–8·2, 4ArH. The *2,4-dinitrophenylhydrazine* crystallized from ethanol as yellow needles, m.p. 163–164° (Found: C, 53·7; H, 4·4; N, 17·7. $C_{18}H_{17}N_5O_6$ requires C, 54·1; H, 4·3; N, 17·5%). N.m.r. δ 3·77, t, ArCH(CH$_2$)CO.

Acidification of the $NaHCO_3$ wash from above gave a cream-coloured solid (0·34 g), the yield of which was increased in subsequent runs employing more reagent and longer reaction times. Recrystallization from aqueous methanol gave pale yellow flakes of *6-(4'-nitrophenyl)-6-oxohexanoic acid*, m.p. 85–86° (Found: C, 57·4; H, 5·5; N, 5·4; mol. wt (titration), 243. $C_{12}H_{13}NO_5$ requires C, 57·4; H, 5·2; N, 5·6%; mol. wt, 251). N.m.r. δ 1·79, t, CH_2CO_2H; 2·45 t, CH_2COAr; 3·03, m, $HO_2CCH_2CH_2CH_2COAr$; 7·4–8·1, m, 4ArH; 9·45, s, CO_2H, disappears on D_2O exchange. ν_{max} 2700–3300 (OH of CO_2H), 1715 (broad, C=O and CO_2H), 1532 and 1355 cm^{-1} (aromatic NO_2).

Oxidation of (1b) with Alkaline Potassium Permanganate

Crude (1b) (1·004 g) was heated under reflux with a solution of $KMnO_4$ (6 g) and Na_2CO_3 (4 g) in water (50 ml) for 30 min, by which time the permanganate colour was discharged. The precipitated MnO_2 was filtered off under suction and washed with hot water (5 ml). The combined filtrate and washings were chilled and acidified with 10 M HCl. The crystalline precipitate was collected and dried (0·52 g, 68%), m.p. and mixed m.p. with an authentic sample of *para*-nitrobenzoic acid, 237–238°. Continuous ether extraction of the aqueous filtrate gave an additional quantity (0·13 g, total yield 86%). Methylation of the product and g.l.c. analysis as before showed the presence of only the *para*-isomer.