3-Phenylcyclobutanone. A Convenient, One-step Synthesis from Phenylacetyl Chloride and Diazomethane

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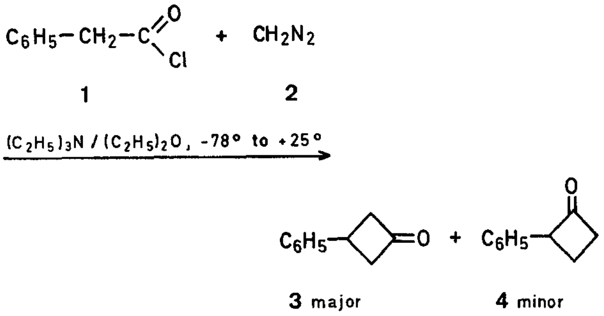
Although 2-phenylcyclobutanone can be readily prepared by a method involving spiroannelation of benzaldehyde[1], the published routes to 3-phenylcyclobutanone are laborious, require several steps, and proceed in only modest overall yield[2]. We wish to report that triethylamine promotes the reaction of phenylacetyl chloride (**1**) with excess diazomethane (**2**) at low temperature to give a mixture of 2- and 3-phenylcyclobutanone (**4** and **3**) from which the latter can be cleanly isolated in 34–48% overall yield via selective hydrogen sulfite adduct formation.



Phenylketene and phenylcyclopropanone represent likely intermediates in this transformation[3]. Acid chlorides with less acidic α-hydrogens, e.g. nonanoyl chloride, yield mainly diazoketones and very little (<10%) of the corresponding cyclobutanones under these conditions.

3-Phenylcyclobutanone (3):

A solution of triethylamine[4] (4.65 ml, 0.033 mol) and diazomethane[5] (0.1 mol) in anhydrous ether[4] (330 ml) is cooled to −78° under nitrogen in a baked-out 1-l three-necked Morton flask fitted with a low temperature thermometer, a mechanical stirrer, and a Hershberg constant addition funnel. Phenylacetyl chloride[6] (4.41 ml, 0.033 mol) in anhydrous ether[4] (30 ml) is then added dropwise with vigorous stirring over 40 min. The opaque yellow reaction mixture is stirred an additional 10 min at −78°, removed from the Dry Ice/acetone bath, and stirred for 90 min more. Dilution with water (200 ml) followed by successive washings of the organic phase with 10% acetic acid, water, saturated sodium hydrogen carbonate[7], water, and saturated sodium chloride, drying over magnesium sulfate, and evaporation of the solvent gives a light yellow oil; yield: 4.3–4.7 g (89–97%). By ^{1}H-N.M.R. analysis the product consists of 3-phenylcyclobutanone (**3**; 53–56%), 2-phenylcyclobutanone (**4**; 30–32%), and methyl phenylacetate (13%).

Isolation of the less hindered 3-phenylcyclobutanone (**3**) is achieved via selective hydrogen sulfite adduct formation[8]. Thus, to the above mixture at 0° is added the theoretical amount (3.00–3.47 ml, 0.0156–0.018 mol) of saturated aqueous sodium hydrogen sulfite solution (5.2 molar) followed by absolute ethanol (3.0 ml) with vigorous stirring. The mixture immediately thickens to a heavy white paste which is stirred an additional 30 min at 0° then diluted with absolute ethanol (5 ml). The solid adduct is filtered on a coarse fritted funnel, rinsed with 95% ethanol, and air dried. Stirring a suspension of the adduct in water (25 ml) with sodium carbonate monohydrate (5.8–6.7 g, 3 equivalents) for 1 h regenerates the ketone. After ether extraction, the organic phase is washed with water until neutral, then with saturated aqueous sodium chloride. Drying over magnesium sulfate and evaporation of the solvent gives 3-phenylcyclobutanone (**3**) as a light yellow oil, uncontaminated by the 2-isomer (<5%, by N.M.R.)[9]. This material slowly decomposes if left unprotected from light[2b]; yield: 1.66–2.32 g (34–48%, 73–88% recovery from the initial mixture).

I.R. (neat): $\nu = 3050, 3000, 2950, 1785, 1600, 1495, 1450, 1378, 1100, 1078, 757, 698\ \mathrm{cm}^{-1}$ (1100 more intense than $1078\ \mathrm{cm}^{-1}$).

^{1}H-N.M.R. (CCl_4): $\delta = 2.93$–3.45 (m, 4H), 3.45–3.78 (m, 1H), 7.18 ppm (s, 5H).

Treatment of the mother liquor with excess hydrogen sulfite and workup as above affords a mixture of the two cyclobutanones in which the 2-isomer (**4**) predominates. For comparison purposes, the spectral properties of pure 2-phenylcyclobutanone (**4**) are included here.

I.R. (neat): $\nu = 3050, 3000, 2950, 1785, 1600, 1495, 1450, 1378, 1100, 1078, 757, 698\ \mathrm{cm}^{-1}$ (1078 more intense than $1100\ \mathrm{cm}^{-1}$).

^{1}H-N.M.R. (CCl_4): $\delta = 1.87$–3.36 (m, 4H), 4.35 (t, 1H, $J = 9$ Hz), 7.08 ppm (s, 5H).

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[4] Distilled from sodium under nitrogen with a benzophenone indicator.

[5] *Org. Synth.* V, 351 (1973).

[6] Prepared from phenylacetic acid and thionyl chloride (95% yield).

[7] Caution, foaming.

[8] The isomeric phenylcyclobutanones can also be partially separated by careful preparative thin layer chromatography on silica gel (a) 2.5% ethyl acetate/petroleum ether (30–60°), 3 elutions: **4** ($R_f = 0.29$), **3** ($R_f = 0.24$); b) 1% butanone/petroleum ether (30–60°), 4 elutions: **4** ($R_f = 0.22$, contaminated with methyl phenylacetate), **3** ($R_f = 0.17$).

[9] Analytical gas chromatography on six different columns failed to separate the isomeric phenylcyclobutanones. No other peaks were observed in the gas chromatogram of purified 3-phenylcyclobutanone.