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FAVORSKII REARRANGEMENT OF 1-BROMO-7,7-DIMETHYLNORBORNANONE[1a]

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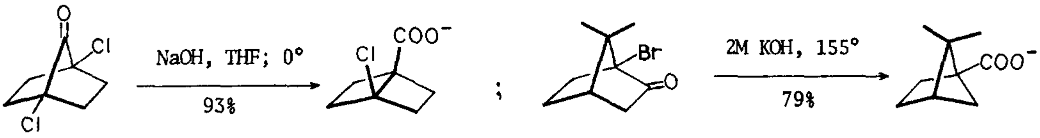
Derivatives of bicyclo[2.1.1]hexane bearing a functional substituent at the 1-position are still accessible only with difficulty, despite considerable effort directed toward that objective.[2,3] In view of the striking ease with which many 1-halo-7-keto norbornane derivatives undergo Favorskii rearrangement to bicyclo[2.2.0]hexanes (e.g. 1 → 2[4]), we decided to attempt the analogous reaction in a 1-halo-2-keto norbornane. The title compound (3) was selected for trial because it could readily be synthesized and because the expected rearrangement product, 5,5-dimethylbicyclo[2.1.1]hexane-1-carboxylic acid (4), is a known compound[3] although 3 presents a particularly severe test of the proposed reaction in view of the probable mechanism.



1 2 3 4

Ketone 3 was prepared by brominative decarboxylation of ketopinic acid[5] by a modification of the Cristol-Firth procedure:[6] ketopinic acid (0.11 mol.), red mercuric oxide (0.11 mol.) and $MgSO_4$ (10g) in 195 ml dichloromethane were heated to reflux and stirred during the dropwise addition of 0.12 mol. bromine. The mixture was refluxed for two hours and worked up by filtering the organic phase and washing it successively with 15% aqueous KI, 15% aqueous $Na_2S_2O_3$ and saturated $NaHCO_3$. Evaporation of the dried dichloromethane solution gave crude 3 in 84% yield. A purified sample gave satisfactory analytical data, had m.p. 192-193° (193-195°),[7] and the following characteristic absorbances: ir($CHCl_3$): 1752(s), 1412(w), 1390(w), 1373(w), 968(w), 949(m), 864(w) cm^{-1}; nmr: CH_3-singlets at 0.90 and 1.03 δ.

Initial attempts to effect rearrangement of 3 under mild conditions[4] gave only starting material. Reaction of 3 with 5.6 M refluxing methanolic KOH for 45 hours gave, after work-up, a neutral fraction (58 wt-% of initial 3) consisting of at least eight products, all of shorter r.t. than 3 and an acidic fraction (30 wt-%) which was esterified with diazomethane and found to give at least 27 peaks on gc analysis. The peak of second shortest r.t. comprised about 12% of the acidic material and was identified as 4-methyl ester by gc, ir and nmr comparison with an authentic sample.[3] Reasoning that the by-products must be arising at least in part by [probably reversible] intermolecular condensations of 3 and by the reducing action of potassium methoxide, we finally attempted to effect rearrangement in dilute aqueous solution: 260 ml of 2 M aq. KOH and 500 mg of 3 were heated to 155° under nitrogen in a metal bomb and rocked for 18 hours. Work-up gave recovered 3 (220 mg) and an acidic fraction (176 mg) which was esterified and found by gc to contain 89% of a methyl ester 4. Thus under these conditions the yield of 4 is 79% based on unrecovered starting material.

The severe conditions required to bring about rearrangement of 3 deserve comment: while the enolate anion of 3 is surely present under the reaction conditions, cyclization to a cyclopropanone seems wildly improbable, so the reaction must proceed by the semibenzilic mechanism.[8] The required intermediate from 3, the ketone hydrate-anion (or dianion) is very unfavorable compared to the corresponding species from 1 owing the steric effect of the 7-methyl, the lesser relief of ring strain in going from sp^2 to sp^3 hybridization at C-2 versus C-7 and the diminished inductive destabilization of the carbonyl with one instead of two α-halogens. Despite these unfavorable circumstances, our results demonstrate the feasibility of the Favorskii rearrangement as a route to bicyclo[2.1.1]hexanes.

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2. e.g. K.B. Wiberg and B.R. Lowry, *J. Am. Chem. Soc.*, **85**, 3188 (1963); A. Cairncross and E.P. Blanchard, Jr., *ibid.*, **88**, 496 (1966); H.O. Larson, T.C. Ooi, W.K.H. Luke and K. Ebisu, *J. Org. Chem.*, **34**, 525 (1969).
3. K. Ebisu, L.B. Batty, J.M. Higaki and H.O. Larson, *J. Am. Chem. Soc.*, **88**, 1995 (1966); R.S.H. Liu and G.S. Hammond, *ibid.*, **89**, 4936 (1967). We are indebted to Prof. Larson for an authentic sample of 4.
4. K.V. Scherer, Jr., *Tetrahedron Letters*, 5685 (1966).
5. P.D. Bartlett and L.H. Knox, *Org. Syn.*, **45**, 14 (1965).
6. S.J. Cristol and W.C. Firth, Jr., *J. Org. Chem.*, **26**, 280 (1961).
7. V.J. Spaziano, dissertation, Villanova Univ., 1970.
8. A.S. Kende, *Org. Reactions*, **11**, 261 (1960).