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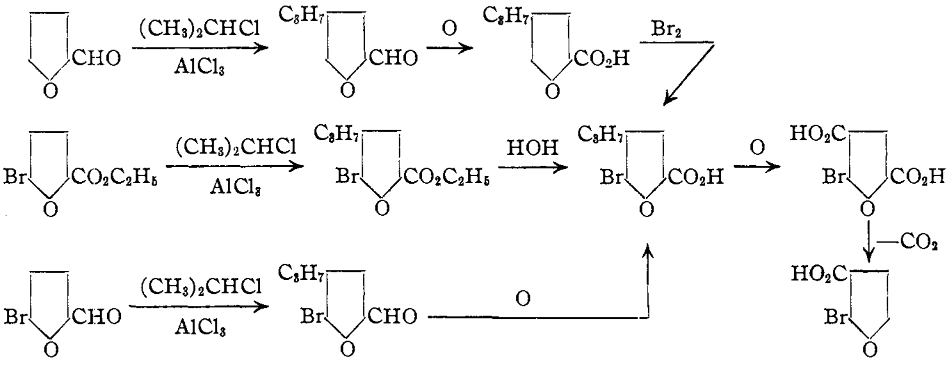
Orientation in the Furan Series. IX. The Friedel–Crafts Reaction with 2-Furfural

BY HENRY GILMAN, NATHANIEL O. CALLOWAY AND ROBERT R. BURTNER

Introduction

The compound obtained by the Friedel–Crafts reaction of 2-furfural and isopropyl chloride[1] is 4-isopropyl-2-furfural. The following transformations were used in the proof of structure



The formation of 4-isopropyl-2-furfural was wholly unexpected because a nuclear substituent has hitherto assumed an α-position if one were available.[2] In the earlier studies[1] of the Friedel–Crafts reactions of furans it was shown that the entering group, in alkylations and acylations, went to an α-position. However, the following paper describes some other anomalous Friedel–Crafts reactions with 2-furfurals.

Experimental Part

2-Furfural and Isopropyl Chloride.—The general procedure described earlier[1] was followed in this study. It is recommended that vigorous stirring be used when the reaction mixture is poured upon cracked ice, and that the carbon disulfide layer be quickly separated and washed with water and sodium acetate solution. The previously determined physical constants for the 4-isopropyl-2-furfural were checked.

Anal. Calcd. for $C_8H_{10}O_2$: C, 69.51; H, 7.31. Found: C, 69.16 and 69.63; H, 7.87 and 7.80.

The 4-isopropyl-2-furoic acid obtained by oxidation of the aldehyde gave a neutralization equivalent of 153.9 (calcd., 154.1).

4-Isopropyl-5-bromo-2-furoic Acid.—This acid, melting at 103–104° when recrystallized from an alcohol–water solution, was obtained by: (1) bromination of 4-isopropyl-2-furoic acid; (2) oxidation (by silver oxide) of 4-isopropyl-5-bromo-2-furfural; and (3) alcoholic potash hydrolysis of ethyl 4-isopropyl-5-bromo-2-furoate. The acids obtained by these three procedures were shown to be identical by the method of mixed melting points.

Anal. Calcd. for $C_8H_9O_3Br$: Br, 34.33. Found: Br, 33.80.

The 4-isopropyl-5-bromo-2-furfural which underwent decomposition during distillation was oxidized directly to the acid by means of silver oxide.

Ethyl 5-Bromo-2-furoate and Isopropyl Chloride.—The ester (0.1 mole) was alkylated in accordance with the general directions for the alkylation of methyl 2-furoate,[1] to give 9 g. of ethyl 4-isopropyl-5-bromo-2-furoate which distilled at 141–144° (17 mm.); n^{25}_D 1.5072.

Anal. Calcd. for $C_{10}H_{13}O_3Br$: Br, 30.65. Found: Br, 30.50.

Oxidation of 4-Isopropyl-5-bromo-2-furoic Acid.—The acid was first converted to 4-isopropyl-5-bromo-2-furoyl chloride in 85% yield by means of thionyl chloride. The acid chloride distilled at 129–131° (15 mm.).

Anal. Calcd. for $C_8H_8O_2ClBr$: Cl, 14.08; Br, 31.82. Found: Cl, 14.43; Br, 31.67.

The isopropyl group resists conversion to a carboxyl group by standard oxidation procedures. Accordingly, a combination of stepwise procedures was used: (1) bromination of the isopropyl group, (2) hydrolysis of the poly-brominated isopropyl group, (3) silver oxide oxidation of the possible di-aldehydo-carbinol to a possible intermediate dicarboxycarbinol which lost carbon dioxide to give a probable —CH_2OH in place of the original isopropyl group and (4) oxidation by potassium ferricyanide to give a carboxyl group.

The 4-isopropyl-5-bromo-2-furoyl chloride (33 g. or 0.13 mole) was placed in a 250-cc. three-necked Corex flask which was illuminated by a Corex mercury vapor lamp. A total of 104 g. (0.65 mole) of dry bromine was added dropwise with vigorous stirring over a period of four hours and with a bath temperature of 125–140°. Hydrogen bromide was evolved at once, and the reaction mixture gradually darkened with very little resinification. Hydrolysis of the mixture was then effected by refluxing for one and one-half hours with 600 cc. of water. The ether extract of the chilled hydrolysate was dried over sodium sulfate and the solvent then removed to yield a dark oily residue which gave a positive Schiff test. The oil was refluxed for four hours with alkaline silver oxide, the silver filtered off, the hot filtrate decolorized with Norite and the chilled filtrate acidified. Acidification was ac-

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[1] Gilman and Calloway, THIS JOURNAL, **55**, 4197 (1933), and *ibid.*, **56**, 745 (1934).

[2] Gilman and Wright, *Chem. Rev.*, **11**, 330 (1932).

companied by a vigorous evolution of carbon dioxide. Ether extraction yielded a dark partly crystallized oil which was oxidized to the bromo-dibasic acid by refluxing with 100 g. of potassium ferricyanide and 40 g. of potassium hydroxide in 600 cc. of water for four hours. Acidification and ether extraction gave the crude bromo-dibasic acid which was washed with chloroform and then sublimed under reduced pressure to yield 1 g. of pure 5-bromo-2,4-furandicarboxylic acid. There was no depression in a mixed melting point determination with an authentic specimen.[3] Additional confirmation of the identity of the 5-bromo-2,4-furandicarboxylic acid was secured by removal of the α-carboxyl group by the mercuric chloride procedure[4] to give the known 2-bromo-3-furoic acid[3] (mixed m. p.).

3-Isopropylfuran.—The 4-isopropyl-2-furoic acid (4 g.) was decarboxylated in accordance with Johnson's procedure by heating with quinoline and copper bronze at 220–240° until carbon dioxide evolution ceased. The yield of 3-isopropylfuran was 1.6 g.; b. p. 111–112°; d^{20}_{20} 0.8929; n^{20}_{D} 1.4369. Mercuration in the customary manner gave 3-isopropyl-2-furylmercuric chloride which melted at 90° after crystallization from an ethanol–water solution.

Anal. Calcd. for C_7H_9OClHg: Hg, 58.11. Found: Hg, 58.39.

The isomeric α-mercurial, 4-isopropyl-2-furylmercuric chloride, was prepared from 4-isopropyl-2-furoic acid, in accordance with the procedure for replacing an α-carboxyl group by a chloromercuri group,[4] and melted at 119–120°.

Anal. Calcd. for C_7H_9OClHg: Hg, 58.11. Found: Hg, 58.15.

The formation of these isomeric α-chloromercuri compounds from β-isopropylfuran compounds is additional confirmatory evidence for the 4-isopropyl-2-furfural. This follows from two facts: (1) a β-alkylated furan orients the chloromercuri group to a contiguous α-position; (2) an α-carboxyl group is preferentially and reliably replaced by a chloromercuri group.

Summary

The Friedel-Crafts reaction with 2-furfural and isopropyl chloride gives 4-isopropyl-2-furfural. This anomalous reaction is apparently the first unequivocal evidence of a β-substitution reaction of furan when an α-position is available.

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(3) THIS JOURNAL, **55**, 2903 (1933).

(4) *Ibid.*, **55**, 3302 (1933).

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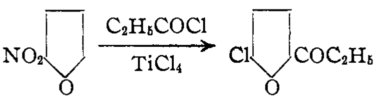
The Friedel–Crafts Reaction with Nitro Compounds

BY HENRY GILMAN, R. R. BURTNER, N. O. CALLOWAY AND J. A. V. TURCK, JR.

Introduction

Nitrobenzene has completely resisted acylation by means of the Friedel–Crafts reaction.[1] Furthermore, nitrobenzene is sometimes used as a medium in the Friedel–Crafts reaction. The alkylations of the negatively substituted ethyl 2-furoate and ethyl 5-bromo-2-furoate, described in the preceding paper, suggested the possibility of effecting a Friedel–Crafts reaction with an aromatic nucleus containing a nitro group. This appeared more reasonable when it was demonstrated that dimethyl 3,4-furandicarboxylate, which is rather resistant to nuclear substitution, could be acetylated by means of acetic anhydride and stannic chloride, a condensing agent used effectively in many Friedel–Crafts transformations.

The nitro compound first selected was 2-nitrofuran because of the greater ease of nuclear substitution reactions evidenced by furans. 2-Nitrofuran and propionyl chloride gave 5-chloro-2-furyl ethyl ketone.



The replacement of the nitro group by chlorine defeated an object of the experiment because there was no decisive way of determining whether such replacement preceded or was coincident with acylation. It was next shown in a corresponding experiment using ethyl 5-nitro-2-furoate in place of 2-nitrofuran that practically all of the nitro ester was recovered unchanged. This was not surprising from the point of view of furan chemistry because of the extreme difficulty of effecting β-substitution when both α-positions are occupied by relatively strong negative groups.

Nitrobenzene was next used. In the expectation that if a Friedel–Crafts reaction did occur it would take place slowly, a mixture of nitrobenzene, isobutyl bromide and aluminum chloride was set aside at room temperature for thirty days. The products isolated were almost equal quantities of *o*-chloroaniline and *p*-chloroaniline. Isopropyl bromide also gave a mixture of *o*-

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(1) Stockhausen and Gattermann, *Ber.*, **25**, 3521 (1892). The more aromatic *o*-nitroanisole and *o*-nitrophenetole can be acylated.