Notes

A department for short papers of immediate interest.

Preparation and Properties of Tertiary Alkyl Formates

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Although Cottle[1] has reported the use of ion exchange resins as catalysts in the preparation of alkyl esters, he utilized special dry resins and limited his work to the acetate esters. In this work tertiary alkyl esters of formic acid have been prepared using ion exchange resins containing as much as 53% moisture.

Five tertiary alkyl formates were prepared by Barkenbus.[2] He made *tert*-butyl formate by the reaction of aluminum *tert*-butoxide with *n*-butyl formate and also, using sulfuric acid as the catalyst in the reaction of formic acid with isobutylene. The use of sulfuric acid as a catalyst in the addition of acids other than formic to alkenes has been reported.[3-5]

Earlier workers[6,7] have prepared tertiary alkyl formates but their yields have been poor and the esters impure.

The cationic exchange resins tested in this study were of the polystyrene divinylbenzene sulfonic acid type, the most effective resin being Dowex 50-X8 (200–400 mesh). Reactions were run using the resin as obtained from the supplier, that is, "wet" containing as much as 53% moisture. Other reactions were run using resins which had been dried at 100° for 24 hr. In addition both types of resin were reused several times without losing their effectiveness. The best yields of the ester were obtained when between 1–1.5% wet catalyst (based on the weight of formic acid) was used at a reaction temperature below 65°. Below this catalyst concentration the reaction rate was too slow to be efficient while above this concentration and temperature the formation of polymer by-product became appreciable.

It is of interest to note that no reaction took place when diisobutylene was treated with formic acid in the presence of Dowex 50-X8. This would seem to indicate that, although diisobutylene type material is a by-product in the formation of *tert*-butyl formate, the ion exchange resin is not a catalyst for the addition of acids to the higher polymers of isobutylene.

EXPERIMENTAL

tert-Butyl formate. A typical preparation is given. Formic acid (208 g., 4.5 moles) and "wet" Dowex 50-X8, 200–400 mesh (2.5 g., 1.2% by weight of formic acid) were placed in a gas washing bottle and isobutylene gas was bubbled through the system at the approximate rate of one mole per hour. After 4 hr. the gas flow was discontinued and the resin filtered off. The reaction mixture was washed with eight portions of ice water and then dried over anhydrous magnesium sulfate. Vacuum distillation of the product gave *tert*-butyl formate (43.6% yield): b.p. 83°/760 mm., n_D^{25} 1.3790, d_4^{25} 0.8717 (reported,[2] n_D^{25} 1.3783, d_4^{25} 0.8718, b.p. 82.8/760 mm.).

Anal. Calcd. for $C_5H_{10}O_2$: C, 58.9; H, 9.8. Found: C, 59.2; H, 9.7.

tert-Amyl formate. Anhydrous formic acid (50 g., 1.09 moles) and 2 methyl butene-2 (72 g., 1.03 moles) were agitated occasionally for two days at room temperature in a 4-oz. glass stoppered bottle using "wet" Dowex 50-X8, 200–400 mesh (0.3 g., 0.6% by weight of formic acid) as the catalyst. The resin was filtered off and the filtrate was washed six times with ice water. After drying over anhydrous magnesium sulfate the sample was distilled. There were obtained. 2-methyl-2-butene boiling at 41° and *tert*-amyl formate (23.8%) b.p. 112.1°, n_D^{25} 1.3952, d_4^{25} 0.8821 (reported[2] n_D^{25} 1.3951, d_4^{25} 0.8853, b.p. 112.9°).

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.0; H, 10.7. Found: C, 62.1; H, 10.4.

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Reduction of Fluorenonecarboxylic Acids to Fluorenecarboxylic Acids[1]

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Many of the syntheses in the fluorene series are rendered difficult by the inaccessibility of the fluorenecarboxylic acids. The reduction of the fluorenonecarboxylic acids to the corresponding fluorene acids is the step which seems to give the poorest yields. Several processes have been described for this reduction but the Clemmensen and

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Wolff-Kishner methods have been used most often. Thus, Gutmann and Albrecht[2] described a modified Clemmensen reduction of fluorenone-1-carboxylic acid during 40 hours reflux, and British workers[3,4] have used a shorter heating period. Sawicki and Chastain[5] report unsatisfactory yields or mixtures resulted from three different procedures for reduction of the fluorenone-1 acid.

Schiessler and Eldred[6] obtained 43% of fluorene-2-carboxylic acid by a Wolff-Kishner type reduction of fluorenone-2-carboxylic acid. It has also been prepared by a Grignard carbonation in 20% yield,[7] and by a 2-step processs, the last step of which involves iodine and phosphorus reduction.[6,8]

The method of Suzuki[9] was tried in the present work, employing some variations. This worker reduced fluorenone-4-carboxylic acid to fluorene-4-carboxylic acid using hydriodic acid and phosphorus in acetic acid during 10 hr. heating at 130–140°. This work was repeated in refluxing acetic or propionic acids as solvents, and was extended to the other fluorenonecarboxylic acids. In each case, the corresponding fluorenecarboxylic acids were formed in good yields in the refluxing solvent, and the process is adaptable to large scale work. Propionic acid is advantageous in that the fluorenonecarboxylic acids are more soluble in it at the boiling point, and a higher reaction temperature may be realized, but the use of acetic acid is more economical.

Enough solvent was employed to keep the fluorenonecarboxylic acids in solution throughout the reaction. As the other isomeric fluorenonecarboxylic acids are less soluble than fluorenone-4-carboxylic acid, a greater volume of solvent was required for their solution. The solubility of the fluorenone-2-carboxylic acid was so low that it was found to be more convenient to reduce its ethyl ester. During the course of the reduction, the ester was hydrolyzed by the hydriodic acid and fluorene-2-carboxylic acid was isolated. The methyl ester of fluorenone-3-carboxylic acid was employed for reduction in the 3 series. In all of the reductions, no unchanged fluorenonecarboxylic acids were detected in the products under the conditions used.

EXPERIMENTAL

Melting points are uncorrected and were taken on a Fisher-Johns melting point block.

In view of the results of Suzuki, it is probable that the reflux time may be shortened but this was not done in order to ensure completeness of the reaction. Descriptions of the reduction of fluorenone-1-carboxylic acid and fluorenone-2-carboxylic ethyl ester are given as representative examples of the process. Yields ranged from 83% to nearly theoretical.

Fluorene-1-carboxylic acid. A solution of 3.44 g. of fluorenone-1-carboxylic acid in 250 ml. of glacial acetic acid was mixed with 5.5 g. of red phosphorus and 6 ml. of 47–50% hydriodic acid. This mixture was refluxed for 46 hr. and then most of the solvent distilled. The residue was diluted to 350 ml. with cold water and after several hours standing was filtered and the product was washed. It was stirred with an excess of warm dilute potassium carbonate solution and filtered from phosphorus. The filtrate was acidified with hydrochloric acid and left overnight. The acid was filtered, washed, and dried. It weighed 3.18 g. or 99%. After several recrystallizations from acetone–petroleum ether at low temperatures, it had a melting point of 242–247° with previous sintering (Lit. 245–247° Corr.[2]). A run which was refluxed 70 hr. gave a nearly theoretical yield of slightly better quality acid. The reduction was also carried out in propionic acid as solvent with a 40-hr. reflux period.

Fluorene-2-carboxylic acid. The ethyl ester of fluorenone-2-carboxylic acid was prepared by overnight refluxing of the acid in ethanol containing a little sulfuric acid. This ester (10.96 g.) was dissolved in 250 ml. of hot acetic acid and treated with 15 g. of red phosphorus and 17 ml. of 47–50% hydriodic acid. The mixture was refluxed 30 hr. and worked up as with the 1 isomer. Decolorization with a little Norit was carried out in potassium carbonate solution and the acid precipitated with hydrochloric acid. A yield of 8 g. or 88% of air-dried acid was obtained. It sintered about 200° and discolored above 220° with melting 255–272°. One recrystallization from ethanol gave a product sintering at 235° and m.p. 265–275°. The literature melting points vary from 265–277°.[5,7] A reduction in propionic acid as solvent gave a crude yield of 97%.

If the free fluorenone-2-carboxylic acid is reduced in acetic acid, 300–350 ml. of boiling solvent is required for solution of 2 g. The fluorenone-2-carboxylic acid should be finely ground and refluxed for complete solution in excess acetic acid before adding the other reagents, which are best introduced near the boiling point. Though this is wasteful of acetic acid, a nearly theoretical yield of fluorene-2-carboxylic acid was obtained of good melting point without recrystallization. Propionic acid is slightly better as a solvent for the acid.

Fluorene-2-carboxylic acid was esterified by refluxing its solution in an excess of absolute ethanol containing some sulfuric acid for 16 hr. and isolating as usual. A nearly quantitative yield of ethyl ester was obtained which was recrystallized from ether–petroleum ether and acetone-water. It had m.p. 81–82°. The ethyl ester does not seem to have been prepared previously.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.67 H, 5.88. Found: C, 80.63 H, 5.61.

Fluorene-3-carboxylic acid. The reduction of the methyl ester of fluorenone-3-carboxylic acid has already been described.[10] In general it was similar to the method employed with the 2 isomer and fluorene-3-carboxylic acid was obtained in 99% yield.

Fluorene-4-carboxylic acid. In two experiments, fluorenone-4-carboxylic acid was reduced in propionic acid solution using 24 and 42 hr. reflux time. In both cases, 87% of fluorene-4-carboxylic acid was obtained. After recrystallization from

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aqueous acetone, this acid had m.p. 191–193° (Lit.[9] 189–191°).

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Synthesis of Some β-Phenethylamine Derivatives. I

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β-Phenethylamines are well known for their sympathomimetic activity, which is modified by the presence of substituents both in the side chain as well in the aromatic nucleus.[1] With a view to studying the effects on the physiological activity of different substituent groups like alkyl, alkoxyl, and halogen in various positions in the nucleus a number of β-phenethylamines were synthesized.

These amines were synthesized by the condensation of aromatic aldehydes with nitromethanes in acetic acid solution,[2] to yield the corresponding β-nitrosytrenes. The latter were then reduced with lithium aluminum hydride[3] to the β-phenethylamine derivatives, which were characterized as their picrates and wherever possible as their hydrochlorides.

2,3,5- (XIII) and 2,3,6- (XIV) -Trimethoxy-β-phenethylamines are hitherto unknown analogs of Mescaline. The starting material for the synthesis of XIII was 2,3,5-trimethoxybenzaldehyde.[4] The latter was prepared[5] by the Elb's persulfate oxidation of *o*-vanillin to 2,5-dihydroxy-3-methoxybenzaldehyde and subsequent methylation.

For the synthesis of 2,3,6-trimethoxy-β-phenethylamine, the starting material was 2,3,6-trimethoxybenzaldehyde,[5] whose synthesis was attempted by different routes. The easiest approach to its synthesis appeared to be through 2-hydroxy-6-methoxybenzaldehyde,[6] which on Elb's persulfate oxidation and subsequent methylation, would yield 2,3,6-trimethoxybenzaldehyde. Accordingly, 2,6-dihydroxybenzaldehyde (A) was prepared by the hydrolysis of the known 8-formyl-7-hydroxy-4-methylcoumarin[7] or from 2,6-dihydroxy-3-methoxycarbonylbenzaldehyde[8] by boiling with excess of water. The first method gave very poor yields of (A) and was abandoned. The second afforded a 48% yield of (A). However, persulfate oxidation of 2-hydroxy-6-methoxybenzaldehyde under different conditions proved to be unsuccessful. 2,3,6-Trimethoxybenzaldehyde was finally prepared as described by Merchant *et al.*[5]

During the course of the synthetic work, the decarboxylation of 3-carboxy-2-hydroxy-6-methoxybenzaldehyde, 3-carboxy-2,5-dihydroxy-6-methoxybenzaldehyde, and their respective anils, was studied under different conditions. It has been observed by Weijlard *et al.*[9] that the anil of opianic acid could be decarboxylated by heating with copper bronze. However, in the above two cases the desired decarboxylated product could not be isolated. Methylation of 3-carboxy-2,5-hydroxy-6-methoxybenzaldehyde resulted in the formation of 3-methoxycarbonyl-2,5,6-trimethoxybenzaldehyde, obtained as an oil and characterized by the preparation of a 2,4-dinitrophenylhydrazone. Hydrolysis of the above oily product gave instead of the expected 3-carboxy-2,5,6-trimethoxybenzaldehyde, a substance of melting point 224–225°, having a different molecular composition. From the analytical data, no definite structure could be assigned to it.

A detailed account regarding the pharmacological properties of the amines will be published elsewhere.

EXPERIMENTAL[10]

β-Nitrostyrenes. A mixture of 5 g. of the aldehyde, 5 ml. of nitromethane, 2 g. of ammonium acetate, and 20 ml. of glacial acetic acid, was refluxed at 130° for 2 hr. The reaction mixture was cooled, and the solid which separated was collected and crystallized from methanol or acetic acid. If no solid separated, the resulting solution was poured into ice water, and the precipitated semisolid mass or oil was extracted with ether. The ether solution was washed with water, dried, and the solvent distilled, when either a solid or an oil was left behind. The solid was purified by crystallization, whereas the oil was directly subjected for reduction.

β-Phenethylamines. The reduction of the β-nitrostyrene with lithium aluminum hydride, to the corresponding β-phenethylamine, was carried out according to the general method followed by Erne and Ramirez.[3]

A solution of 3 g. of the β-nitrostyrene in dry ether was added dropwise to a well stirred suspension of 2 g. of lithium aluminum hydride, in 100 ml. of dry ether. A mixture of ether and benzene was employed for styrenes which were sparingly soluble in ether. The reaction mixture was gently refluxed for 2 hr., and then decomposed with 2*N* sulfuric acid. To the aqueous layer, solid lithium carbonate was

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