SYNTHESIS OF FLUORINATED KETONES BY MEANS OF ORGANOLITHIUM COMPOUNDS AND N, N-DIALKYL AMIDES OF FLUORINATED ACIDS

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Fluorinated ketones have not been easily available hitherto; a number of methods have been proposed for their synthesis, increasing importance being attached to those methods which employ organometallic compounds. Organomagnesium compounds in reactions with nitriles, and organozinc and organocadmium compounds with acyl chlorides of fluorinated acids give fluorinated ketones [1], in many cases with a good yield (up to 50-60 %). However, the synthesis is complicated and the initial compounds are often not readily available. In recent years, organolithium and organomagnesium compounds have been increasingly used for the synthesis of fluorinated ketones, as follows [2]:

$$C_6H_5Li + CHF_2COOH \rightarrow C_6H_6 + CHF_2COOLi$$

$$CHF_2COOLi + C_6H_5Li \rightarrow CHF_2COC_6H_5$$

The yield reaches 80%, but only half the organolithium compound is consumed on the formation of the ketone. This represents one of the shortcomings of the method, which may be eliminated by the use of salts of fluorinated acid [3]. We considered it of interest to find a method for preparing fluorinated ketones, convenient in the synthetic aspect, using readily available initial materials such as N,N-dialkyl amides of fluorinated acids. The reaction between organomagnesium and organolithium compounds and fluorine-free acid amides has been investigated by a number of authors [4]. Here again an excess of the organometallic compound is necessary, because part of it is decomposed by the hydrogen atoms of the amide group. Considerable heating is required to complete the reaction. With organolithium and organomagnesium compounds, N,N-dialkyl amides of acids form the corresponding aldehydes or ketones with a fairly good yield [5]. There are no data on the synthesis of fluorinated ketones by this method. The most readily available of the fluorinated acid derivatives is the diethyl amide of difluoroacetic acid [6], which is the starting point for obtaining the acid, its salts and acyl chloride.

In the present work we investigated the reaction of this amide and, to a lesser extent, the diethyl amide of trifluoroacetic acid with organosodium and organolithium compounds in various solvents at different temperatures to check the possibility of the formation of fluorinated ketones of the aliphatic, aromatic and heterocyclic series and to find the optimum conditions for their synthesis. The initial compounds were obtained by methods described in the literature. The diethyl amide of difluoroacetic acid was obtained from the acyl chloride of trifluoroacetic acid and diethylamine in ether. The diethyl amide of difluoroacetic acid reacts readily with phenyl lithium, but at room temperature a product which does not contain fluorine is formed. However, as we indicated, at a temperature of -65° in a medium of ether, ω, ω-difluoroacetophenone may be obtained with a 72 % yield

$$CHF_2CON(C_2H_5)_2 + C_6H_5Li \rightarrow CHF_2COC_6H_5$$

If ether is replaced by toluene the yield is reduced considerably. ω, ω-Difluoroacetophenone is also formed with phenyl sodium, but with a lower yield. Similarly, ω, ω, ω-trifluoroacetophenone is obtained from phenyl lithium and the diethyl amide of trifluoroacetic acid (yield 74 %). With thienyl lithium these amides give ω, ω-difluoroacetothienone (74 %) and ω, ω, ω-trifluoroacetothienone (39 %). From butyl lithium and the diethyl amide of difluoroacetic acid we obtained difluoromethyl butyl ketone (32.6 %). With the diethyl amide of fluorochloroacetic acid, phenyl lithium gives ω, ω-fluorochloroacetophenone with a yield of 53 %. The initial amides are the principal admixture in the unpurified fluorinated ketone obtained by this method. Purification of the end product is simplified if excess of the organolithium compound is used. Therefore, we found that a more convenient method for obtaining fluorinated ketones was by the action of amides of fluorinated acids of the $RCONR_2$ type on organolithium compounds.

EXPERIMENTAL

Work with lithium, sodium, organolithium and organosodium compounds was carried out in an atmosphere of dry purified nitrogen. N,N-dialkyl amides of fluorinated acids were introduced into the reaction with organolithium and organosodium compounds at a temperature of 65–70°.

Preparation of ω, ω-difluoroacetophenone

a) From the diethyl amide of difluoroacetic acid and phenyl lithium in ether. A quantity of 0.1 M phenyl lithium in 240 ml of dry ether was placed in a four-necked flask equipped with a stirrer with a mercury seal, a dropping funnel, thermometer and a gas feed [7]. The reaction flask was cooled with a mixture of dry ice in alcohol to -70° and 17.2 g (0.11 M) of the diethyl amide of difluoroacetic acid [6] in 50 ml of absolute ether was added dropwise in 40 minutes at such a rate that the temperature of the mixture did not exceed -65°. The viscous mass formed was stirred at -75° for 2 hours; in this period all the phenyl lithium reacted. A Gilman color test with Michler's ketone gave a negative result. The reaction mixture was poured onto a mixture of ice and hydrochloric acid, the ethereal layer was separated, the aqueous layer was extracted three times with ether; the ethereal extract was washed with water and dried with sodium sulfate; the ether was driven off and the residue was distilled under vacuum. We obtained 13 g of a substance with a b.p. of 63-65° (10-12 mm); n_D^{20} 1.4900; the yield was 83%, calculated on the amide. According to literature data [8], ω, ω-difluoroacetophenone has a b.p. of 84-85° (26-27 mm); n_D^{20} 1.4984.

b) From the diethyl amide of difluoroacetic acid and phenyl lithium in toluene. In the apparatus described in the previous experiment we placed 12.5 g (0.12 M) of crystalline phenyl lithium [9] with a 79% C_6H_5Li content and 150 ml of dry toluene; the mixture was stirred for 15-20 minutes at room temperature and cooled to - 70°. A quantity of 17.2 g (0.11 M) of the diethyl amide of difluoroacetic acid in 50 ml of dry toluene was added to the mixture in 35 minutes; it was stirred for 2 hours at - 70° (Gilman test negative) and treated as in the previous experiment. The solvent was distilled under vacuum. In this case, redistillation was necessary. The yield of ω, ω-difluoroacetophenone with a b.p. of 82.5-85° (25 mm) was ~ 11.5 g (67 %).

c) From the diethyl amide of difluoroacetic acid and phenyl sodium in toluene. Phenyl sodium was obtained in the reaction flask from 11.5 g (0.5 g- atom) [7] of sodium chips, 22.5 g (0.2 M) of chlorobenzene and 150 ml of toluene; it was cooled to - 70° and 15.1 g (0.1 M) of the diethyl amide of difluoroacetic acid in 15 ml of dry toluene was added in 10 minutes. The mixture was stirred for 2 hours at - 70° (Gilman sample negative). The reaction mixture was decomposed with absolute alcohol and was treated as in the previous experiments. We obtained 4.5 g (29 %) of ω, ω-difluoroacetophenone.

Preparation of Difluoro - α - Acetothienone

We obtained α-thienyl lithium from 0.186 M of butyl lithium in 280 ml of ether and 0.126 M of thiophene [10]. The butyl lithium was first filtered from unreacted lithium and its concentration was determined by the usual method. An equivalent amount of the diethyl amide of difluoroacetic acid in an equal volume of ether was added (about one hour) to the suspension of thienyl lithium at a temperature below - 65°. The reaction mixture was stirred for about another hour at this temperature and was poured into a mixture of ice and hydrochloric acid. After the usual treatment we obtained a substance with a b.p. of 77-80° (11 mm) with a yield of ~ 75 % of the theoretical. The synthesis may be carried out without preliminary filtration and analysis of butyl lithium (taking into account its possible yield). In one of the experiments, from 1.29 M of lithium, 0.555 M of butyl chloride, 0.476 M of thiophene and 0.476 M of the diethyl amide of difluoroacetic acid we obtained 57 g of a product with a b.p. of 80° (13 mm), i.e. 74 % of the theoretical. In this case, care is required when decomposing the reaction mixture (lumps of unreacted lithium remain). Found: F 23.00, 23.25 %. $C_6H_4OF_2S$. Calculated: F 23.43 %.

Preparation of ω, ω, ω-Trifluoroacetophenone

a) From the diethyl amide of trifluoroacetic acid and phenyl lithium in ether. A quantity of 10 g (0.06 M) of the diethyl amide of trifluoroacetic acid in 35 ml of ether was added to 0.06 M of phenyl lithium in 64 ml of ether. After redistillation we obtained 8 g (74 %) of the substance with a b.p. of 66-68° (37 mm); n_D^{20} 1.4578. According to literature data [8], ω, ω, ω-trifluoroacetophenone has a b.p. of 66-67° (37 mm); n_D^{20} 1.4576.

b) From the diethyl amide of trifluoroacetic acid and phenyl lithium in toluene. A quantity of 14.5 g (0.086 M) of the diethyl amide of trifluoroacetic acid in 50 ml of toluene was added gradually to 8 g (0.075 M) of crystalline phenyl lithium (with a C_6H_5Li content of 79 %) in 150 ml of toluene. After the mixture had been stirred (at -75°) for 2.5 hours, a Gilman test gave a positive result. After the usual treatment the product obtained was distilled. We obtained 7.1 g (54.5%) of ω, ω, ω, -trifluoroacetophenone.

Preparation of ω, ω, ω-Trifluoroacetothienone.

A quantity of 15 g (0.09 M) of the diethyl amide of trifluoroacetic acid in 15 ml of ether was added to the α-thienyl lithium obtained from 0.146 M of butyl lithium in 110 ml of ether and 11.7 g (0.14 M) of thiophene [10]. The reaction mixture was stirred for an hour and left overnight at -80°. We obtained 6.3 g (39 %) of the product, with a b.p. of 67° (23-24 mm). Found: F 31.10 %. $C_6H_3OF_3S$. Calculated: F 31.60%.

Preparation of the Diethyl Amide of Trifluoroacetic acid.

A quantity of 82 g (115.5 ml) of diethylamine in 180 ml of absolute ether was placed in a round-bottomed flask equipped with a stirrer with a mercury seal, a reflux condenser, dropping funnel and thermometer, and a solution of 60 g of the acyl chloride of trifluoroacetic acid in 100 ml of absolute ether (cooled by dry ice) was added at 0°. The white precipitate was filtered at the pump, the ethereal layer was washed twice with water and dried with sodium sulfate. The ether was driven off and the residue was distilled under vacuum. We obtained 36 g (47.4 %) of the diethyl amide of trifluoroacetic acid with a b.p. of 74-75° (43 mm).

Preparation of ω, ω-Fluorochloroacetophenone.

A quantity of 150 ml (0.158 M) of an ethereal solution of phenyl lithium was placed in the apparatus and 23.8 g (0.142 M) of the diethyl amide of fluorochloroacetic acid [6] in 70 ml of absolute ether was added over a period of one hour. The mixture was stirred for a further 2 hours at -70°. The Gilman reaction was negative. The light-brown transparent liquid obtained was poured with vigorous stirring onto a mixture of ice and hydrochloric acid. We obtained 13 g (53 %) of the substance, with a b.p. of 91° (11 mm). Found: F 11.78 %. C_8H_6OFCl. Calculated: F 11.02%.

Preparation of Difluoromethyl Butyl Ketone from the Diethyl Amide of Difluoroacetic Acid and Butyl Lithium.

A quantity of 40.8 g (0.27 M) of the diethyl amide of difluoroacetic acid in 60 ml of absolute ether was added dropwise to the butyl lithium obtained from 33 g (0.36 M) of butyl chloride and 5 g (0.72 g-atom) of lithium. Addition of the diethyl amide took ~ 2 hours; the reaction mass was then stirred for another hour at the same temperature. The Gilman reaction was negative. The contents of the flask were poured through a metal sieve into a mixture of ice and hydrochloric acid and treated as usual. We obtained 12 g (32.6%) of product with a b.p. of 104-110°; after redistillation the b.p. was 111-112°. Found: F 28.30, 28.20%. $C_6H_{10}OF_2$. Calculated: F 27.93%.

SUMMARY

1. A convenient method was found for the synthesis of fluorinated ketones from organolithium compounds and N, N-dialkyl amides of fluorinated acids.

2. ω, ω, ω-trifluoro- α-acetophenone, ω, ω-difluoro- α-acetothienone and difluoromethyl butyl ketone were synthesized for the first time.

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