Friedel-Crafts Reactions. II.* Amidoalkylation by *N*-Acetoxymethyl-*N*-methylformamide in the Presence of Trifluoroacetic Acid

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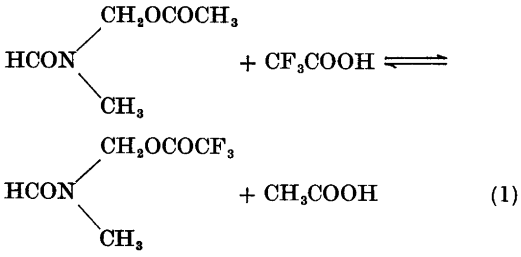
Amidoalkylation of aromatic compounds has received considerable attention, since it represents a convenient method for the synthesis of derivatives of benzylamines.[2] The reaction is generally carried out using *N*-hydroxymethylamides or *N*-hydroxymethylimides in the presence of a catalyst (proton or Lewis acids). The major limitation of the reaction often is the preparation of the *N*-hydroxymethylamide and its instability towards isolation, and it would therefore be an advantage to use the corresponding esters as starting materials.[2]

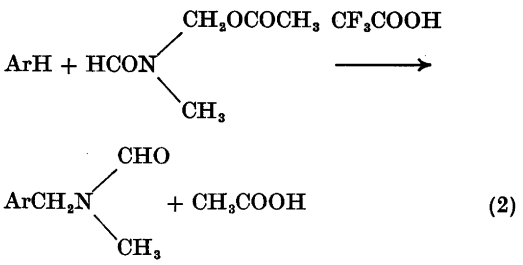
A direct synthesis of *N*-acetoxymethyl-*N*-methylformamide and *N*-formyloxymethyl-*N*-methylformamide has been achieved by anodic oxidation of *N*,*N*-dimethylformamide in acetic acid and formic acid, respectively.[3] The formyloxy derivative is capable of amidomethylating aromatic compounds in the presence of hydrochloric or sulfuric acid.[4]

When *N*-acetoxymethyl-*N*-methylformamide is dissolved in trifluoroacetic acid, an equilibrium is established, as can be shown by NMR, according to eqn. 1.



(1)

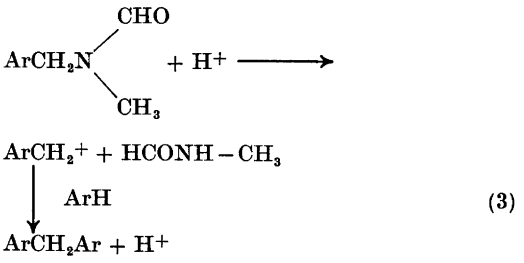
Upon addition of an aromatic compound a reaction takes place, leading to the formation of an *N*-benzyl-*N*-methylformamide derivative. The overall reaction is represented by eqn. 2. The rate of the reaction is determined by the concentration of trifluoroacetic acid as well as the nucleophilicity of the aromatic compound. Some examples of the synthetic scope of the reaction is shown in Table 1. The reactions with mesitylene, pentamethylbenzene and 1,3,5-trimethoxybenzene are very efficient under mild reaction conditions. Benzene, however, is a



(2)

weak nucleophile in this reaction and requires a considerable reaction period to give a reasonable yield of the product even in the presence of an additional catalyst (CF_3SO_3H).

The only side-reaction of any importance is the formation of diphenylmethanes. This probably takes place in an acid-catalyzed reaction according to eqn. 3.[1] However, the formation of



(3)

diphenylmethanes can be almost totally suppressed by selecting the reaction conditions properly (using equivalent amounts of acetate and aromatic compound, minimum amounts of catalyst).

Experimental. *N*-Acetoxymethyl-*N*-methylformamide was prepared in the following way using a concentric capillary gap cell.[5] A solution of *N*,*N*-dimethylformamide (5.0 mol), acetic acid (1.5 l) and Bu_4NBF_4 (0.023 mol) was electrolyzed at a current of 50 A and an applied voltage of 40 – 60 V with a temperature of 60 °C. When 2 F/mol of *N*,*N*-dimethylformamide had been passed, the electrolysis was interrupted. Acetic acid and *N*,*N*-dimethylformamide were removed by distillation up to 70 °C/20 mmHg. The product was then collected at 70 – 75 °C/1.5 mmHg (601 g; 92 % yield). The acetate has also been prepared on a 50 mol scale using a large electrolysis cell operating at 350 A.[6]

General procedure. Equivalent amounts of *N*-acetoxymethyl-*N*-methylformamide and the aromatic compound were dissolved in 25 ml of the solvent. Trifluoroacetic acid was added and the mixture was stirred (see Table 1 for details of the reaction conditions). When the reaction was over, trifluoroacetic acid and the solvent were removed by evaporation *in vacuo*. The residue was dissolved in ether, washed with sodium bicarbonate solution until neutral, washed with

* Part I, *cf.* Ref. 1.

Table 1. Yields of *N*-benzyl-*N*-methylformamides in the reaction between aromatic compounds (0.1 mol) and *N*-acetoxymethyl-*N*-methylformamide (0.1 mol) in the presence of trifluoroacetic acid.

ArH	CF_3COOH (mol)	Solvent	Reaction time (h)	Yield (%)
Benzene	0.5[a]	$CHCl_3$[b]	96	40
Mesitylene	0.25	CH_2Cl_2[c]	16	93
Pentamethyl benzene	0.25	$CHCl_3$[b]	5	85
1,3,5-Trimethoxy-benzene	0.1	CH_2Cl_2[c]	20	81

[a] CF_3SO_3H (0.01 mol) was used as an additional catalyst. [b] At reflux temperature. [c] At room temperature.

water, and finally dried over anhydrous sodium sulfate. After filtration and removal of the ether by evaporation *in vacuo* the product was isolated as shown below. The mixture from the reaction with 1,3,5-trimethoxybenzene was diluted with methylene chloride and worked up as above (the product was poorly soluble in ether).

N-*Benzyl-N-methylformamide.* The product was isolated by distillation, b.p. 148–150 °C/20 mmHg (6.0 g; 40 % yield). The NMR spectrum was in agreement with published data,[7] MS: *m/e* 149 (100 % abundance), 148 (18), 134 (11), 120 (7), 106 (18), 92 (10), 91 (73), 79 (15), 65 (14), 42 (18).

N-*(2,4,6-Trimethylbenzyl)*-N-*methylformamide.* The residue was dissolved in 50 ml of hexane. Crystallization took place at −20 °C giving the product, m.p. 59–61 °C (17.8 g; 93 % yield). NMR (in $CDCl_3$): δ 2.27 and 2.28 (9 H, $ArCH_3$), 2.72 and 2.80 (3 H, $N-CH_3$), 4.50 and 4.67 (2 H, $N-CH_2$), 6.90 (2 H, ArH), 8.20 (1 H, CHO). MS: *m/e* 191 (15), 133 (20), 132 (100), 117 (11).

N-*(2,3,4,5,6-Pentamethylbenzyl)*-N-*methylformamide.* The residue was dissolved in 50 ml of boiling hexane. After cooling, the precipitate was filtered off, giving the product, m.p. 87–89 °C (18.7 g; 85 % yield). NMR (in $CDCl_3$): δ 2.22 (15 H, $ArCH_3$), 2.58 and 2.75 (3 H, $N-CH_3$), 4.45 and 4.67 (2 H, $N-CH_2$), 8.00 and 8.08 (1 H, CHO). MS: *m/e* 219 (10), 161 (11), 160 (100), 145 (9).

N-*(2,4,6-Trimethoxybenzyl)*-N-*methylformamide.* The residue was dissolved in a mixture of 100 ml of cyclohexane and 25 ml of benzene at boiling. After cooling, the precipitate was filtered off, giving the product, m.p. 103–105 °C (19.3 g; 81 % yield). NMR (in $CDCl_3$): δ 2.72 (3 H, $N-CH_3$), 3.80 (9 H, CH_3O), 4.35 (2 H, $N-CH_2$), 6.12 (2 H, ArH), 8.25 (1 H, CHO). MS: *m/e* 239 (47), 210 (17), 182 (10), 181 (100), 180 (13), 168 (17), 136 (16), 121 (22).

Acknowledgements. This work was supported by grants from the Swedish Natural Science Research Council, the Carl Trygger Foundation, and the Royal Physiographic Society of Lund. Part of the cost for the analytical equipment was defrayed by a grant from the Knut and Alice Wallenberg Foundation.

1. Nyberg, K. *Chem. Scr. 4* (1973) 143. Part I.
2. Zaugg, H. E. and Martin, W. B. *Org. React. 14* (1965) 52.
3. Ross, S. D., Finkelstein, M. and Petersen, R. C. *J. Amer. Chem. Soc. 88* (1966) 4657.
4. Ross, S. D., Finkelstein, M. and Petersen, R. C. *J. Org. Chem. 31* (1966) 133.
5. Eberson, L., Nyberg, K. and Sternerup, H. *Chem. Scr. 3* (1973) 12.
6. Eberson, L. and Sternerup, H. *Unpublished results.*
7. Pine, S. H. and Sanchez, B. I. *J. Org. Chem. 36* (1971) 829.

Received August 1, 1974.