Acta Chemica Scandinavica B 33 (1979) 69—72

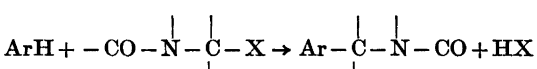
Friedel-Crafts Reactions. III.* Electrophilic Amidoalkylation of 1,3,5-Trimethoxybenzene with Cyclic *N*-Formylimmonium Ion Precursors

MATS MALMBERG and KLAS NYBERG **

Division of Organic Chemistry 1, Chemical Center, University of Lund, P.O. Box 740, S-220 07 Lund, Sweden

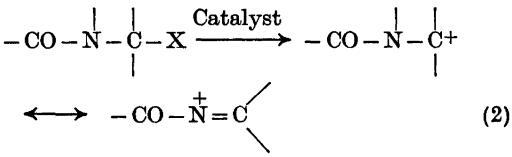
Cyclic *N*-formyl-2-methoxyamines (pyrrolidine, piperidine, 1*H*-hexahydroazepine, morpholine), *N*-formyl-1-methoxy-1,2,3,4-tetrahydroisoquinoline and 5-methoxy-*N*-methyl-2-pyrrolidone react with 1,3,5-trimethoxybenzene using methanesulfonic acid or trifluoroacetic acid as a catalyst, yielding amidoalkylated products in 54 – 82 % yields. The reactions are reversible. as shown by the exchange of the *N*-formylimmonium ion part under acid catalysis. The product from the reaction between *N*-formyl-2-methoxypyrrolidine and 1,3,5-trimethoxybenzene was converted into 4-(2,4,6-trimethoxyphenyl)-1-(*N*,*N*-dimethylamino)butane *via* reduction with $LiAlH_4$, methylation with CH_3I and cathodic reduction. Thus a method for ω-aminoalkylation of aromatics is available.

Amidoalkylation of aromatic compounds is a well-established method for the synthesis of *N*-acylated α-aminoalkylarenes [2,3] (Eqn. 1).



(1)

The reaction is catalyzed by protonic or Lewis acids and it is believed that an *N*-acylimmonium ion is the reactive intermediate (Eqn. 2) attacking the arene. The major limitation of the amidoalkylation



(2)

reaction lies in the choice of the electrophilic reagent, the *N*-acylimmonium ion precursor. In general, the reagent contains a CH_2-group between the nitrogen and the leaving group. Some exceptions are found among alkylidene and arylidene bisamides. Few cyclic reagents, mostly hydantoin derivatives where the nitrogen and the α-carbon is part of the ring, have been used. This is due to the lack of methods for preparing such reagents. Among more recent work it is worth noting the use of glyoxylic acid derivatives as electrophilic reagents.[4–6] In a recent paper we described the facile anodic synthesis of cyclic *N*-formyl-2-methoxyamines by the oxidation of the corresponding *N*-formylamines in methanol.[7] We have thus produced reagents of potential value for amidoalkylation reactions, in which the reactive position is part of a ring. In this work we describe the use of these reagents in the amidoalkylation of 1,3,5-trimethoxybenzene.[8] The latter was chosen as a model substrate because of its high reactivity in amidoalkylation.[1]

RESULTS

The reactions were carried out by mixing 1,3,5-trimethoxybenzene, the methoxyamide

* Part II, see Ref. 1.

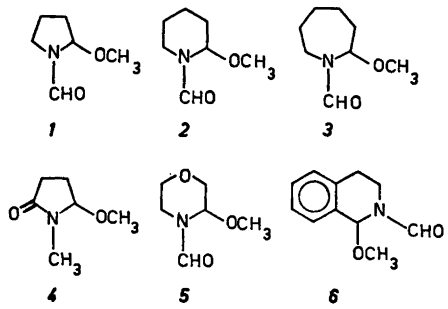
** Author to whom correspondence should be addressed at: AB Bofors, Nobel Kemi, P.O. Box 800, S-690 20 Bofors, Sweden.

0302-4369/79/010069-04$02.50

Table 1. Yields of amidoalkylated products *8*.

Amide	mol	7/mol	Catalyst	mol	Yield of *8* (%)
1	0.03	0.025	CH_3SO_3H	0.05	54
2	0.03	0.025	CH_3SO_3H	0.05	55
3	0.03	0.025	CH_3SO_3H	0.05	58
4	0.03	0.025	CH_3SO_3H	0.05	64
5	0.06	0.05	CF_3COOH	0.1	82
6	0.06	0.05	CF_3COOH	0.1	80

in a slight excess, and either methanesulfonic acid or trifluoroacetic acid as the catalyst, in dichloromethane. The reaction mixture was allowed to stand at room temperature for one day before work-up, but in general 80 – 90 % of the 1,3,5-trimethoxybenzene had reacted after 1 h. GLC analysis of the reaction mixtures before work-up showed 70 – 90 % yield of the amidoalkylated products. Reagents *1* – *6* have



1 *2* *3*

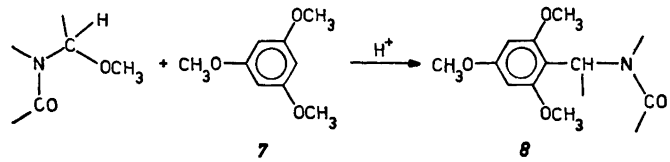
4 *5* *6*

been used. Scheme 1 shows the overall reaction. Isolated yields are given in Table 1. If the intention is to use an amidoalkylated product for further synthesis it is not necessary to isolate it in a pure state.

One of our interests in the amidoalkylated products was the conversion of the nitrogen-containing ring into an open chain. It is well-known that a benzyl-nitrogen bond can be cleaved either by catalytic hydrogenation [9] or by cathodic reduction.[10] A quaternary ammonium compound is cleaved more rapidly than a tertiary amine, and an amide is fairly difficult to cleave. We therefore tried to cleave the benzyl-nitrogen bond in compound *9*, but this was unsuccessful. Instead *9* was converted into the *N*-methyl derivative by $LiAlH_4$ reduction. Attempts to cleave this compound also failed. Finally the quaternary ammonium derivative *10* was prepared. This was smoothly cleaved by cathodic reduction yielding *11*. When the reaction sequence shown in Scheme 2 was carried out without isolation of intermediates in a pure state, *11* was obtained in an overall yield of 60 %. The combination of amidoalkylation and subsequent cleavage of the benzyl-nitrogen bond thus gives a method for the synthesis of *N*,*N*-dialkylaminoalkylarenes. The length of the alkyl chain in the final product will then be related to the size of the ring in the methoxylated amide. When we applied the same reaction sequence to *N*-formyl-2-methoxypiperidine, it was, however, not possible to obtain a selective cleavage of the benzyl – nitrogen bond. The cathodic reduction yielded a 3:1 mixture of debenzylation and demethylation products.

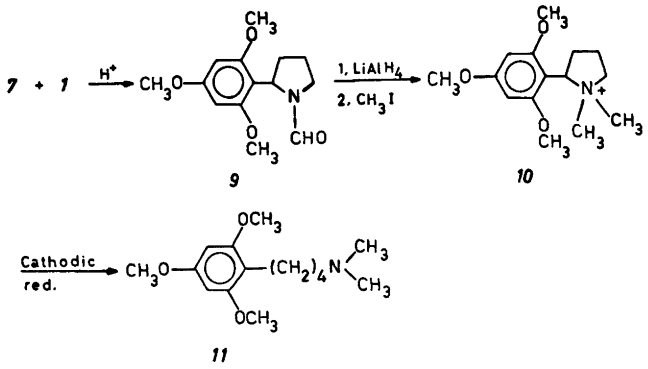
The failure to cleave the benzyl – nitrogen bond in *9* as well as its reduced form and the unselectivity in the reduction of the quaternary piperidine derivative are presumably due to the presence of the methoxy groups in the *ortho* positions of the aromatic ring. These might shield the benzyl – nitrogen bond making it less susceptible for attack by the reducing agent.

Since the amidoalkylation of 1,3,5-trimethoxybenzene worked well we tried to extend the reaction to other aromatic compounds of lower reactivity. However, when anisole or alkylbenzenes, such as mesitylene or toluene, were treated with any of the methoxy compounds *1* – *6* in the presence of methanesulfonic acid or trifluoroacetic acid



7 *8*

Scheme 1.



Scheme 2.

only traces of the desired products were obtained, although the methoxy compounds were consumed. We believe that this is due to the formation of enamides that polymerize under the reaction conditions.[11] An *N*-formylimmonium ion is probably the common intermediate for the formation of the amidoalkylated product as well as the enamide. Under the reaction conditions anisole or the alkylbenzenes are too unreactive to compete with the enamide formation. We are currently looking for other catalysts that might reduce the ease of enamide formation, since we believe that the use of cyclic *N*-acylimmonium ion precursors might open up new routes to arylsubstituted nitrogen-containing heterocycles and to aminoalkylarenes.

We have also shown that the amidoalkylation reaction is reversible. When *9* was treated with *2* in the presence of methanesulfonic acid an equilibrium mixture of *9* and its piperidine analogue was formed.

EXPERIMENTAL

General procedure for amidoalkylation. The methoxylated amide[7] was added slowly to a solution of the catalyst and 1,3,5-trimethoxybenzene in dichloromethane (15 ml). Table 1 gives the amounts used. The resulting solution was allowed to stand for one day. Dichloromethane (100 ml) was added and the solution was shaken with dilute NaOH solution. The aqueous phase was further extracted with dichloromethane (50 ml). The combined organic phases were washed twice with water (50 ml) and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent by evaporation *in vacuo* gave the amidoalkylated product in a crude state. If this is to be used for further transformation no purification is necessary. The pure product was obtained by subjecting the crude material to column chromatography on neutral alumina using dichloromethane as eluent (about 400 ml), followed by removal of the solvent and crystallization of the residue from hexane (charcoal was sometimes used for decolorization). The product from the methoxyamide *6* was obtained without column chromatography by crystallization from methanol.

The purity of the products was checked by GLC analysis using a Hewlett-Packard HP-5830 instrument on a 2 m × 0.3 cm 3 % OV 17 on Chromosorb W column. ^{1}H NMR analysis was performed on a Jeol 100 MHz spectrometer using $CDCl_3$ as solvent. MS analysis was carried out on an LKB 9000 spectrometer at 70 eV. None of the products has previously been reported in the literature.

N-Formyl-2-(2,4,6-trimethoxyphenyl)-pyrrolidine. Yield 54 %, m.p. 79–81.5 °C. Anal. $C_{14}H_{19}NO_4$: C, H, N. MS *m/e* (% rel. int.): 265 (100, M), 236 (56, M-CHO), 234 (76, M-CH_3O), 168 (74). ^{1}H NMR: δ 1.70–2.30 (4 H, m), 3.30–3.80 (2 H, m), 3.78 (6 H, s), 3.82 (3 H, s), 5.22–5.46 (1 H, m), 6.16 (2 H, s), 7.90 (1 H, s).

N-Formyl-2-(2,4,6-trimethoxyphenyl)-piperidine. Yield 55 %, m.p. 89–91 °C. Anal. $C_{15}H_{21}NO_4$: C, H, N. MS *m/e* (% rel. int.): 279 (40, M), 250 (20, M–CHO), 248 (100, M–CH_3O), 168 (36). ^{1}H NMR: δ 1.20–2.82 (7 H, m), 3.78 (6 H, s), 3.82 (3 H, s), 4.46–4.96 (2 H, m), 6.16 (2 H, s), 7.78 (1 H, s).

N-Formyl-2-(2,4,6-trimethoxyphenyl)-1H-hexahydroazepine. Yield 58 %, m.p. 99–105 °C. Anal. $C_{16}H_{23}NO_4$: C, H, N. MS *m/e* (% rel. int.): 293 (72, M), 264 (52, M–CHO), 262 (100, M–CH_3O), 168 (76). ^{1}H NMR: δ 1.10–2.40 (8 H, m), 3.10–4.30 (2 H, m), 3.78 (6 H, s), 3.82 (3 H, s), 5.10–5.30 (1 H, m), 6.12 (2 H, s), 8.08 and 8.12 (1 H, s).

N-Methyl-5-(2,4,6-trimethoxyphenyl)-2-pyrrolidine. Yield 64 %, m.p. 109–111 °C. Anal.

$C_{14}H_{19}NO_4$: C, H, N. MS *m/e* (% rel. int.): 265 (100, M), 250 (38, M − CH_3), 234 (18, M − CH_3O), 208 (60), 98 (62), 97 (30). ^{1}H NMR: δ 1.90 − 2.60 (4 H, m), 2.54 (3 H, s), 3.78 (6 H, s), 3.82 (3 H, s), 5.14 − 5.34 (1 H, m), 6.16 (2 H, s).

N-Formyl-3-(2,4,6-trimethoxyphenyl)-morpholine. Yield 82 %, m.p. 88.5 − 91 °C. Anal. $C_{14}H_{19}NO_5$: C, H, N. MS *m/e* (% rel. int.): 281 (100, M), 252 (42, M − CHO), 250 (66, M − CH_3O), 220 (70), 194 (40), 179 (53), 168 (56). ^{1}H NMR: δ 2.82 − 3.14 (4 H, m), 3.42 − 4.50 (2 H, m), 3.80 (6 H, s), 3.84 (3 H, s), 5.04 − 5.20 (1 H, m), 6.16 (2 H, s), 7.80 (1 H, s).

N-Formyl-1-(2,4,6-trimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline. Yield 80 %, m.p. 146 − 150 °C. Anal. $C_{19}H_{21}NO_4$: C, H, N. MS *m/e* (% rel. int.): 327 (88, M), 298 (100, M − CHO), 296 (86, M − CH_3O), 168 (46). ^{1}H NMR: δ 2.80 − 3.02 (2 H, m), 3.30 − 3.90 (1 H, m), 3.60 and 3.74 (6 H, s), 3.82 (3 H, s), 4.08 − 4.34 (1 H, m), 6.16 (2 H, s), 6.20 and 6.36 (1 H, s), 6.74 − 7.22 (4 H, m), 8.16 and 8.34 (1 H, s).

Synthesis of 4-(2,4,6-trimethoxyphenyl)-1-(N,N-dimethylamino)butane, 11. A. Amidoalkylation: A solution of *1* (0.03 mol), *7* (0.025 mol), and methanesulfonic acid (0.05 mol) in dichloromethane (25 ml) gave by the usual procedure crude *9* (5.67 g).

B. $LiAlH_4$ reduction: A solution of *9* (5.67 g) in toluene (20 ml) was added dropwise to $LiAlH_4$ (0.61 g; 0.016 mol) in dry ether (30 ml). The mixture was stirred for 4 h and then decomposed by adding successively water (0.61 g), 15 % NaOH (0.61 g) and water (1.83 g). The inorganic precipitate was filtered off and washed with ether. The amine was extracted into aqueous HCl, which was then made alkaline with NaOH. The amine was extracted back into ether, the solution dried over anhydrous magnesium sulfate and the ether was removed by evaporation *in vacuo* leaving the crude amine (4.62 g).

C. Methylation with CH_3I: To a chilled solution of the crude amine (4.62 g) in abs. ethanol (20 ml) was added dropwise CH_3I (0.028 mol). After 17 h at room temperature conc. NH_3 (2 ml) was added and the solution was heated to 60 °C. After 1 h the mixture was concentrated by evaporation *in vacuo* leaving an oily residue. This was dissolved in water, extracted with dichloromethane and the extract was dried over anhydrous magnesium sulfate, filtered and finally evaporated *in vacuo*. The oily residue was further concentrated at 70 °C yielding *10* (6.79 g).

D. Cathodic reduction: The electrolysis cell consisted of a water-jacketed beaker equipped with an Hg cathode (surface area 15 cm^2), a graphite anode and a ceramic cell divider. The catholyte consisted of *10* (2.37 g; 0.006 mol) in methanol (70 ml) containing tetraethylammonium bromide (0.03 mol), while the anolyte consisted of the same solution without *10*. Electrolysis was carried out with a constant current of 0.75 A until 4.1 F/mol had been passed. Methanol was removed from the combined catholyte and anolyte solutions by evaporation *in vacuo*, and ether and 0.5 M NaOH were added to the residue. After shaking this mixture the aqueous phase was separated and extracted with ether. The combined ether phases were washed with a small amount of water, dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo* yielding *11* (1.39 g; overall yield 60 %). GLC analysis showed only one peak. MS *m/e* (% rel. int.): 267 (100, M), 181 (25, M − $(CH_3)_2N(CH_3)_2$). The amine was dissolved in dry ether, which was then saturated with HCl. The precipitate was filtered off and recrystallized from ethanol yielding *11.HCl*, m.p. 204 − 205 °C. ^{1}H NMR: δ 1.35 − 1.92 (4 H, m), 2.47 − 2.69 (2 H, m), 2.79 (6 H, s), 2.91 − 3.15 (2 H, m), 3.79 (9 H, s), 6.14 (2 H, s).

Acknowledgements. This work was supported by grants from the Swedish Natural Science Research Council and the Royal Physiographic Society of Lund. Part of the cost for the mass spectrometric analysis was defrayed by a grant from the Knut and Alice Wallenberg Foundation.

REFERENCES

1. Nyberg, K. *Acta Chem. Scand. B 28* (1974) 825. Part II.
2. Zaugg, H. E. and Martin, W. B. *Org. React. 14* (1956) 52.
3. Zaugg, H. E. *Synthesis* (1970) 49.
4. Ben-Ishai, D., Satati, I. and Berter, Z. *Chem. Commun.* (1975) 349.
5. Ben-Ishai, D., Satati, I. and Bernstein, Z. *Tetrahedron 32* (1976) 1571.
6. Ben-Ishai, D., Altman, J. and Peled, N. *Tetrahedron 33* (1977) 2715.
7. Nyberg, K. and Servin, R. *Acta Chem. Scand. B 30* (1976) 640.
8. This work was presented at the Electrochemical Society Spring Meeting, Seattle, Washington, May 21 − 26, 1978. Abstract No. 499.
9. Freifelder, M. *Practical Catalytic Hydrogenation*, Wiley, New York 1971, p. 413.
10. Horner, L. and Röder, H. *Chem. Ber. 101* (1968) 4197.
11. Nyberg, K. *Synthesis* (1976) 545.

Received September 11, 1978.