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Friedel-Crafts Reactions. IV.* The Use of Cyclic *N*-Formyl-2-Methoxyamines in Electrophilic Amidoalkylation of Aromatic Compounds

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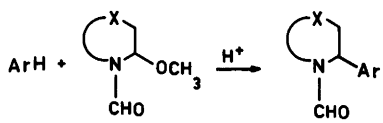
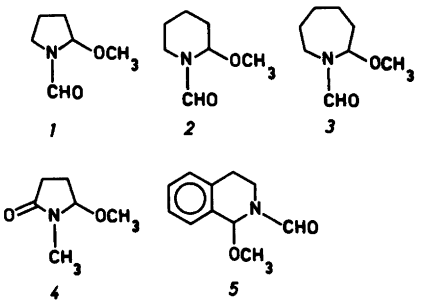
Aromatic compounds react with cyclic *N*-formyl-2-methoxyamines in proton or Lewis acid catalyzed reactions, yielding 2-aryl substituted nitrogen heterocyclic compounds.*** These products are easily converted to the corresponding $N-H$ and $N-CH_3$ derivatives by acid hydrolysis and $LiAlH_4$ reduction, respectively.

Recently, we reported the use of cyclic *N*-formyl-2-methoxyamines as reagents for the electrophilic amidoalkylation of 1,3,5-trimethoxybenzene [eqn. (1), Ar = 2,4,6-trimethoxyphenyl], a suitable model compound for this type of reaction.[1,4] Protic acids, such as methanesulfonic acid or trifluoroacetic acid, were used as catalysts, providing mild reaction conditions and high yields of amidoalkylated products. It was also shown that the products could be converted into ω-aminoalkylbenzene derivatives after reductive cleavage of the heterocyclic ring, thus providing a new and simple method for ω-functionalization of aromatics.



X: see 1-5 (1)

When we tried to apply the same reaction conditions to the amidoalkylation of less activated substrates, the expected products were formed in low yields or not at all. This was because a competitive reaction, acid-catalyzed elimination of methanol from the aminoalkylation reagent became the predominant reaction path.[3] The primary product from this reaction, an enamide, reacted further to give polymeric material. When formic acid was used as catalyst and solvent, significant amounts of dimers were formed. As an example, the dimeric product *6* was isolated in 56% yield from the reaction with *2*. Amidoalkylation was not observed in formic acid. Amidoalkylation of less reactive aromatic substrates than 1,3,5-trimethoxy-



* Part III, see Ref. 1.

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*** This synthetic principle, to form a C–C bond at the α position of amines *via* a key electrochemical step, was first described in 1966 (Ross, S. D., Finkelstein, M. and Petersen, R. C. *J. Am. Chem. Soc. 88* (1966) 4657) and later applied in thisLaboratory in a number of ways (see, *e.g.*, Refs. 1–4, 22). Somewhat surprisingly, it appeared as "new" in 1981 (Shono, T., Matsumura, Y. and Tsubata, K. *J. Am. Chem. Soc. 103* (1981) 1172).

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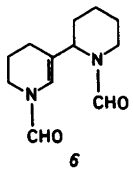

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benzene was accomplished by using Lewis acids as catalysts instead of protic acids,[2] and we now present a full report on the scope of the amidoalkylation reaction of eqn. (1).

RESULTS

The cyclic *N*-formyl-2-methoxyamines, *1*–*5*,[4] were used as amidoalkylation reagents. Generally, the reactions were carried out by adding the amide, dissolved in a molar excess of the aromatic reactant, to a stirred mixture of $AlCl_3$ in the same solvent. It was necessary to use an excess of the nucleophile in order to obtain high yields of the desired products. For example, amidoalkylation of benzene or toluene gave product yields lower than 15% when a 1:1 mol ratio of nucleophile to amide was used. Considerably higher yields were obtained with a 10:1 molar ratio, as shown in Table 1. The effect of an excess of the aromatic reactant became less dramatic with more reactive aromatics such as 1,4-dimethylbenzene. Improvements of the yields could also be obtained by heating the reaction mixtures.

Table 1. Isolated yields (%) of products derived from amidoalkylation of aromatic compounds.

Substituent R in (*1*)	Amidoalkylation reagent *1*	*2*	*3*	*4*	*5*
Methylphenyl	59[a,b]	52[a]	69[a]		
2,5-Dimethylphenyl	72	54			
2,4,6-Trimethylphenyl	74	58		57	34
Naphthyl	67	63			30[a]
Chlorophenyl	52[a,b]	39[a]			
2-Thienyl	58	46	68		73
2,5-Dimethoxyphenyl		57			
Phenyl[c]	52[b,d]	44[d]	55[d]		40
Phenyl[e]	70[b]	84	85	75	72

[a] Two isomers of product; the isomer distribution is given in the experimental section. [b] Previously prepared; Ref. 6. [c] 1.4:1 mol ratio of $AlCl_3$ to amide. [d] For experimental details, see Ref. 2. [e] 2:1 mol ratio of $AlCl_3$ to amide.

Napthalene and thiophene could not be amidoalkylated with $AlCl_3$ as the catalyst, since they react with it.[5] We found, however, that $TiCl_4$ or BF_3 functioned well as catalysts with these reactants. Slightly modified reaction conditions were also employed in the amidoalkylation of 1,4-dimethoxybenzene (see Experimental). Product yields are shown in Table 1.

Chlorobenzene and toluene each afforded at least two isomeric amidoalkylated products, according to GLC/MS analysis. In the reaction between naphthalene and the bulky *N*-formyl-1-methoxy-1,2,3,4-tetrahydroisoquinoline, two isomers were also formed. No attempt was made to isolate the isomers. A few deactivated aromatic compounds, nitrobenzene and methyl benzoate, were also tried as reactants but with no success. The reason for this might be loss of reactivity of the catalyst due to complex formation with the functional groups of the aromatic substrates,[5] together with the anticipated low reactivity of these substrates towards electrophiles.

In our previous work involving benzene we used a mol ratio of $AlCl_3$ to amide of 1.4:1.[2] Further experiments have now shown that an increased ratio will increase the yield of amidoalkylated product. These results are included in Table 1. Complex formation of the catalyst with the amide groups of starting materials and products may be responsible for this effect. In experiments involving the more activated aromatic compounds this effect seems less pronounced.

During the work with the amidoalkylation reagents we noticed differences in the reactivity between the cyclic *N*-formyl-2-methoxyamines, *e.g.* low reactivity of *2* and high reactivity of *5*. The differences in reactivity were further investigated by competion experiments. The reactions were carried out by dissolving two methoxylated amides together with a small quantity of 1,3,5-trimethoxybenzene in dichloromethane (the mol proportions of amide A – amide B – 1,3,5-trimethoxybenzene were 10:10:1). The catalyst was added and, after 30 min at room temperature, the reaction mixture was subjected to GLC analysis. 1,3,5-Trimethoxybenzene was chosen because of its almost complete reaction within a reasonable time (30 min) in the presence of methanesulfonic acid, used as catalyst in order to provide homogeneous reaction conditions. From the GLC analyses relative rate constants for the different pairs of products were obtained, and the

relative rate constants of the five compounds could be calculated: *1*: 4 – 5, *2*: 1, *3*: 3 – 4, *4*: 30, *5*: 2×10^2. These results are supported by data from amidoalkylations of active methylene compounds[2] to be presented in a forthcoming paper.

The *N*-formyl compounds in Table 1 are easily converted to the corresponding *N*-methyl or N – H derivatives by $LiAlH_4$ reduction or hydrolysis, respectively. The *N*-formyl-2-phenyl derivatives of pyrrolidine, piperidine and 1*H*-hexahydroazepine were hydrolyzed under acidic conditions, giving the N – H derivatives in isolated yields of 84, 96, and 82%, respectively. All three compounds are known from the literature.[9,10,15,16] The $LiAlH_4$ reduction has been described in a previous paper.[1] In contrast to the *N*-formyl compounds in Table 1, many of the corresponding N – H and $N-CH_3$ derivatives are known from the literature. The last steps of their synthesis usually involve one of the following procedures: reduction and cyclization of *β*-aroylpropionitriles[9,10]; reaction of *ω*-chloronitriles with aromatic Grignard reagents and, after cyclization, reduction of the partially unsaturated nitrogen-containin ring[7,8,15]; reaction of lactams with aromatic Grignard reagents followed by reduction of the heterocyclic moiety;[10,11,13,14,16] reduction of 2-aryl substituted pyrroles and pyridines;[18,19,20] rearrangement reactions.[12]

The facile electrochemical preparation of compounds *1* – *5* from simple starting materials,[4,21,22] together with good yields in the amidoalkylation reaction, call attention to this method as a different and useful route to 2-aryl substituted nitrogen hetrocyclic derivatives.

EXPERIMENTAL

Most experiments were performed using similar reaction conditions and work-up procedures. The following general procedure was used, unless otherwise indicated:

One mol equiv. methoxylated amide, dissolved in 2 mol equiv. aromatic compound, was added dropwise to a stirred mixture of 1.4 mol equiv. anhydrous $AlCl_3$ in 8 mol equiv. aromatic compound. After a sufficient time of reaction (0.5 to 24 h), checked by GLC analysis, water was added to the stirred reaction mixture and the resulting two-phase system was extracted twice with dichloromethane. The combined organic phases were washed twice with water, dried over magnesium sulfate, and the solvents were removed by evaporation *in vacuo*. The residue was finally distilled under reduced pressure, or recrystallized, to give the product.

The purity of the products was checked by GLC analysis, using a Hewlett-Packard HP-5830 instrument, equipped with (unless otherwise indicated) a 3m × 3 mm 5% OV 17 on Chromosorb W column. ^{1}H NMR spectra were recorded on a Jeol 100 MHz spectrometer using $CDCl_3$ as solvent. MS analysis were performed on an LKB 9000 spectrometer as 70 eV or on a Finnigan 4021 spectrometer at 70 eV. In the case where two isomers were formed these are indicated as A and B with respect to their order of appearance in GLC analysis. Unless otherwise indicated, a GLC inlet was used. All of the products derived from the amidoalkylation of benzene were subjected to elemental analysis. Among the other products a selection was made in order to provide one elemental analysis of each aromatic compound.

N-*Formyl-2-(methylphenyl)-pyrrolidine.* Compound *1* (0.1 mol) was reacted with toluene for 2 h at room temperature; yield 11.2 g (59%), b.p. 125 – 134 °C/0.7 – 1.0 mmHg. GLC: 2 m × 3 mm 10% Carbowax column; isomer distribution: 5:95. MS [*m/e* (% rel. int.)]: isomer A (5%): 189 (100, M); isomer B (95%): 189 (100, M). ^{1}H NMR: *δ* 1.60 – 2.58 (4H, m), 2.28, 2.31 and 2.33 (3H, s), 3.48 – 3.90 (2H, m), 4.70 – 4.92 and 4.96 – 5.18 (1H, m), 6.94 – 7.30 (4H, m), 8.09 and 8.37 (1H, s).

N-*Formyl-2-(methylphenyl)-piperidine.* Compound *2* (0.1 mol) and toluene were reacted for 3 h at room temperature; yield 10.5 g (52%), b.p. 133 – 140 °C/0.4 mm Hg. GLC: 2 m × 3 mm 10% Carbowax column. Poor separation of the isomers only permitted a rough estimation of the isomer distribution: 1:9. MS *m/e* (% rel. int.): isomer A (approx. 10%): 203 (70, M), 202 (100, M – H); isomer B (approx. 90%): 203 (56, M), 202 (100, M – H). ^{1}H NMR: *δ* 1.23 – 2.57 (6H, m), 2.33 (3H, s), 2.79 – 3.29 (2H, m), 3.31 – 3.59 and 3.91 – 4.21 (1H, m), 4.61 – 4.81 and 5.63 – 5.81 (1H, m), 6.97 – 7.43 (4H, m), 7.65, 8.16 and 8.27 (1H, s).

N-*Formyl-2-(methylphenyl)-1H-hexahydroazepine.* Compound *3* (0.1 mol) was reacted with toluene for 3 h at room temperature; yield 14.9 g (69%), b.p. 146 – 150 °C/0.5 mmHg. GLC: 2 m × 3 mm 10% FFAP column; isomer distribution: 20:80. Found: C 76.7; H 8.53; N 6.51. Calc. for $C_{14}H_{19}NO$: C 77.38; H 8.81; N 6.45. MS *m/e* (% rel. int.): isomer A (20%): 217 (100, M) isomer B (80%): 217 (89, M), 216 (100, M – H). ^{1}H NMR: *δ* 1.10 – 3.80 and 4.06 – 4.34 (10 H, m), 2.28, 2.31 and 2.34 (3H, s), 4.46 – 4.76 and 5.16 – 5.44 (1H, q, J 6 Hz), 6.96 – 7.36 (4H, m), 8.06, 8.14, 8.18 and 8.26 (1H, s).

N-*Formyl-2-(2,5-dimethylphenyl)-pyrrolidine.* Compound *1* (0.1 mol) was reacted with 1,4-dimethylbenzene for 2 h at room temperature; yield 14.7 g (72%), b.p. 140 – 150 °C/0.5 mmHg. MS *m/e* (% rel. int.): 203 (100, M). ^{1}H NMR: *δ*1.61 – 2.19 (3H, m), 2.19 – 2.81 (1H, m), 2.31 (6H, s), 3.59 – 3.87 (2H,

m), 4.97 – 5.31 (1H, m), 6.79 – 7.17 (3H, m), 8.09 and 8.41 (1H, s).

N-*Formyl-2-(2,5-dimethylphenyl)-piperidine.* Compound *2* (0.1 mol) and 1,4-dimethylbenzene were reacted for 2 h at room temperature. The product was recrystallized from ethyl acetate; yield 11.2 g (52 %), m.p. 95.5 – 98 °C. Anal. $C_{14}H_{19}NO$: C, H, N. MS *m/e* (% rel. int.): 217 (62, M), 216 (63, M – H), 202 (100, M – CH_3). ^{1}H NMR: δ 1.28 – 2.54 (6H, m), 2.25 (3H, s), 2.32 (3H, s), 2.74 – 3.62, 4.26 – 4.60 and 5.54 – 5.74 (3H, m) 6.94 – 7.32 (3H, m), 7.65 and 8.16 (1H, s).

N-*Formyl-2-(2,4,6-trimethylphenyl)-pyrrolidine.* Compound *1* (0.1 mol) was reacted with 1,3,5-trimethylbenzene and worked up after 1.5 h at room temperature; yield 16.1 g (74 %), b.p. 148 – 156 °C/0.3 mmHg. MS *m/e* (% rel. int.): 217 (28, M), 98 (100, M – C_9H_{11}). ^{1}H NMR: δ 1.79 – 2.71 (4H, m), 2.25, 2.29 and 2.33 (9H, s), 3.27 – 3.67 (1H, m), 3.67 – 4.05 (1H, m), 5.05 – 5.33 (1H, m), 6.81 and 6.87 (2H, s), 7.98 and 8.30 (1H, s).

N-*Formyl-2-(2,4,6-trimethylphenyl)-piperidine.* Compound *2* (0.1 mol) and 1,3,5-trimethylbenzene were allowed to react for 24 h before work-up. (The stirring of the reaction mixture was inhibited by a viscous oil that formed during the mixing of the reactants.) After evaporation of the solvents, the crude oil was dissolved in ether and crystals precipitated, which were filtered off and washed with ether.

Additional product was obtained when the concentrated mother liquors were treated with ether, as described previously. Yield: 13.5 g (58 %), m.p. 85.5 – 86.5 °C. MS *m/s* (% rel. int.): 231 (36, M), 112 (100, M – C_9H_{11}). ^{1}H NMR: δ 1.34 – 2.88 (7 H, m), 2.24 (3H, s), 2.34 (6H, s), 2.40 – 2.74 (2H, m), 6.86 (2H, s), 7.82 (1H, s).

N-*Methyl-5-(2,4,6-trimethylphenyl)-2-pyrrolidinone.* Compound *4* (0.1 mol), containing 8 % of *N*-methoxymethyl-2-pyrrolidinone, obtained as a by-product during the electrochemical preparation of *4* was reacted with 1,3,5-trimethylbenzene for 1.5 h. After evaporation of the solvents, the crude product was treated as described above; yield 12.4 g (57 %), m.p. 95 – 96 °C. Anal. $C_{14}H_{19}NO$:C, H, N. MS *m/e* (% rel. int.): 217 (66, M), 98 (100, M – C_9H_{11}). ^{1}H NMR: δ 1.68 – 2.82 (4H, m), 2.21 (3H, s), 2.28 (3H, s), 2.38 (3H, s), 2.62 (3H, s), 5.00 – 5.26 (1H, t, *J* 8.1 Hz), 6.90 (2H, s).

N-*Formyl-1-(2,4,6-trimethylphenyl)-1,2,3,4-tetrahydroisoquinoline.* Compound *5* (0.05 mol) was dissolved in 1,3,5-trimethylbenzene (25 ml) and dichloromethane (12 ml; the addition of dichloromethane was necessary to dissolve *5*), and added dropwise to a stirred mixture of anhydrous $AlCl_3$ (0.07 mol) in mesitylene (44 ml; 0.5 mol of mesitylene altogether). After 1 h at room temperature, the reaction mixture was subjected to the general work-up procedure. The isolated product was obtained after recrystallization from ether. Yield: 4.7 g (34 %), m.p. 140 – 141 °C. MS *m/e* (% rel. int.): 279 (34, M), 160 (100, M – C_9H_{11}). ^{1}H NMR: δ 2.07 (6H, s), 2.37 (3H, s), 2.68 – 3.65 (3H, m), 4.29 – 4.61 (1H, m), 6.15 and 6.31 (1H, s), 6.55 – 7.31 (6H, m), 7.91 and 8.23 (1H, s).

N-*Formyl-2-(1-naphthyl)-pyrrolidine.* Compound *1* (0.1 mol) and naphthalene (0.1 mol) dissolved in dichloromethane (20 ml) were added dropwise to a stirred solution of $TiCl_4$ (0.2 mol) in dichloromethane (80 ml). The resulting dark red solution was refluxed for 1.5 h before general work-up.

Since the oil remaining after evaporation of the solvents, resisted all attempts to achieve crystallization, a fraction (65 %) of the crude oil was distilled *in vacuo*. Yield: 9.7 g (43 %; corresponding to a total yield of 67 %), b.p. 200 – 206 °C/0.5 mmHg, GLC purity by 98 %. MS *m/e* (% rel. int.): 225 (72, M), 224 (100, M – H). ^{1}H NMR: δ 1.74 – 5.99 (1H, q, *J* 7.9 and 3.0 Hz), 7.07 – 8.13 (7H, m), 8.21 and 8.49 (1H, s).

N-*Formyl-2-(1-naphthyl)-piperidine.* The experimental procedures were similar to those used in the preparation of the previous compound, except for the time of reaction (2.5 h) and the use of *2* as electrophile. The crude product, after evaporation of the solvents, was recrystallized from a mixture of ethanol and ether (20 and 35 ml, respectively). Additional product was obtained from the concentrated mother liquors (recrystallized from ether).

Yield: 15.0 g (63 %), m.p. 114 – 116 °C. Found: C 79.7; H 7.35; N 5.72 Calc. for $C_{16}H_{17}NO$: C 80.30; H 7.16; N 5.85. MS *m/e* (% rel. int.); 239 (72, M), 238 (100, M – H). ^{1}H NMR: δ 1.26 – 2.50 (6H, m), 3.02 – 3.62 and 4.22 – 4.64 (2H, m), 4.96 – 5.20 and 6.20 – 6.40 (1H, q, *J* 4.2 Hz), 7.06 – 8.32 (8H, m; the singlets from the formyl proton could not be discerned).

N-*Formyl-1-naphthyl-1,2,3,4-tetrahydroisoquinoline.* A solution of *5* (0.05 mol) and naphthalene (0.05 mol in dichloromethane, 10 ml) was added dropwise to a stirred solution of $TiCl_4$ (0.1 mol) in dichloromethane (40 ml). The reaction mixture was worked up after 1.5 h at room temperature. The crude product was recrystallized from ether; yield 4.3 g (30 %), m.p. 123 – 146 °C; the wide melting range was not affected by repeated recrystallization, indicating the presence of more than one isomer. GLC: two peaks showing partial decomposition; the isomer distribution could not be determined. MS *m/e* (% rel. int.), direct inlet: 287 (100, M). ^{1}H NMR: δ 2.58 – 3.62 and 4.06 – 4.38 (4H, m), 5.84, 6.52 and 6.74 – 8.22 (12H, s and m), 8.55, 8.60, 8.76 and 8.84 (1H, s).

N-*Formyl-2-(chlorophenyl)-pyrrolidine.* Compound *1* (0.1 mol) was dissolved in chlorobenzene (20 ml) and added dropwise to a stirred mixture of

$AlCl_3$ (0.14 mol) in chlorobenzene (80 ml, 1 mol) at 100 °C. The reaction mixture was kept at 100 °C for 3.5 h before being worked up according to the general procedure. Yield: 11.0 g (52%), b.p. 140 – 152 °C/0.5 mm Hg. GLC: isomer distribution 43:57. Found: C 62.3; H 5.80; N 6.75; Cl 16.6 Calc. for $C_{11}H_{12}ClNO$: C 63.01; H 5.77; N 6.68; Cl 16.91. MS *m/e* (% rel. int.); isomer A (43%): 174 (100, M – Cl): isomer B (57%): 211 (33, M), 209 (100, M). ^1H NMR: δ 1.60 – 2.14 (3H, m), 2.14 – 2.72 (1H, m), 3.50 – 3.92 (2H, t, *J* 6.3 Hz), 4.76 – 5.52 (1H, m), 7.00 – 7.48 (4H, m), 8.11, 8.15, 8.38 and 8.42 (1H, s).

N-*Formyl-2-(chlorophenyl)-piperidine.* Chlorobenzene was amidoalkylated with 2 under the same conditions as those described for the preparation of the previous compound; yield 8.7 g (39%), b.p. 150 – 155 °C 0.7 mm Hg. GLC: 2 m × 3 mm 10% Carbowax column; isomer distribution 43:57. MS *m/e* (% rel. int.): isomer A (43%): 188 (100, M – Cl), isomer B (57%): 225 (14, M), 223 (45, M), 222 (100, M – H). ^1H NMR: δ 1.27 – 2.55 (6H, m), 2.63 – 4.31 (2H, m), 4.65 – 5.01 and 5.67 – 5.87 (1H, m), 7.11 – 7.57 (4H, m), 7.81, 8.17, 8.21 and 8.27 (1H, s).

N-*Formyl-2-(2-thienyl)-pyrrolidine.* Boron trifluoride diethyl etherate (0.14 mol) was added dropwise to a stirred and boiling solution of *1* (0.1 mol) in thiophene (100 ml, 1.12 mol). The reaction mixture was refluxed for 40 min before the addition of 2M sodium hydroxide solution (100 ml). (In some previous experiments, BF_3 was observed to give strong complexes with the products formed, unless the work-up was performed under alkaline conditions.) The rest of the work-up was performed as described under "general procedure". Yield: 10.5 g (58%), b.p. 140 – 146 °C/1.5 mmHg. MS *m/e* (% rel. int.): 181 (100, M). ^1H NMR: δ 1.69 – 2.63 (4H, m), 3.49 – 3.81 (2H, m), 5.15 – 5.27 and 5.33 – 5.55 (1H, s), 8.53 – 7.07 (2H, m), 7.07 – 7.39 (1H, m), 8.25 and 8.31 (1H, s).

N-*Formyl-2-(2-thienyl)piperidine.* Compound *2* (0.1 mol) was reacted with thiophene under the same conditions as described above, except for the time of reaction (3 h). Yield: 9.0 g (46%), b.p. 148 – 155 °C/2 mmHg. MS *m/e* (% rel. int.): 195 (100, M). ^1H NMR: δ 1.30 – 2.58 (6H, m), 2.76 – 3.60 and 4.04 – 4.32 (2H, m), 4.90 – 5.10 and 5.82 – 6.02 (1H, m), 6.86 – 7.12 (2H, m), 7.12 – 7.42 (1H, m), 8.16 and 8.22 (1H, s).

N-*Formyl-2-(2-thienyl)-1H-hexahydroazepine.* Compound *3* (0.1 mol) was reacted with thiophene under the same conditions as those described for the preparation of *N*-formyl-2-(2-thienyl)-pyrrolidine; yield 15.3 g (68%), b.p. 140 – 152 °C/0.6 – 1.2 mmHg. MS *m/e* (% rel. int.): 209 (100, M). ^1H NMR: δ 1.10 – 4.22 (10H, m), 4.70 – 4.96 and 5.52 – 5.76 (1H, q, *J* 11.0 and 6.8 Hz (4.70 – 4.96) and *J* 11.6 and 6.6 Hz (5.52 – 5.76)), 6.82 – 7.06 (2H, m), 7.06 – 7.38 (1H, m), 8.22 (1H, s).

N-*Formyl-1-(2-thienyl)-1,2,3,4-tetrahydroisoquinoline.* Boron trifluoride diethyletherate (0.07 mol) was added dropwise to a solution of *5* (0.05 mol) in thiophene (0.5 mol). The mixture was kept at 50 °C for 1.5 h before general work-up. After evaporation of the solvents the crude product was recrystallized from ether; yield 8.8 g (73%), m.p. 97.5 – 98.5 °C. Anal. $C_{14}H_{13}NOS$: C, H, N, S. MS *m/e* (% rel. int.): 243 (100, M). ^1H NMR: δ 2.66 – 3.74 and 4.18 – 4.48 (4H, m), 5.98, 6.66 – 7.00 and 7.06 – 7.40 (8H, s and m), 8.16 and 8.46 (1H, s).

N-*Formyl-2-(2,5-dimethoxyphenyl)-piperidine.* Compound *2*. (0.1 mol) and 1,4-dimethoxybenzene (0.1 mol) dissolved in dichloromethane (20 ml) was added dropwise to a stirred mixture of $AlCl_3$ (0.2 mol) in dichloromethane (80 ml). The reaction mixture was stirred for 24 h at room temperature before being subjected to the general work-up procedure. Yield: 14.2 g (57%), b.p. 170 – 183 °C/0.5 – 1.0 mmHg. Found: C 66.4; H 7.69; N 5.40. Calc. for $C_{14}H_{19}NO_3$: C 67.44; H 7.68; N 5.62. MS *m/e* (% rel. int.): 249 (100, M). ^1H NMR: δ 1.41 – 2.49 (6 H, m), 3.41 – 4.07 (2H, m), 3.77 (3H, s), 3.73 – 4.93 (1H, q, J 3.8 and 6.9 Hz), 6.65 – 7.01 (3H, m), 7.93 and 8.17 (1H, s).

N-*Formyl-2-phenylpyrrolidine.* Compound *1* (0.5 mol) was reacted with benzene. The reaction mixture was heated during the addition of *1* and, after complete addition, refluxed for 30 min. In order to avoid inconvenient precipitates during the first step of the work-up, the reaction mixture should preferably be added to water. After evaporation of the solvents the crude product was distilled under reduced pressure, using a 25 × 1.5 cm Vigreux column. Yield: 61.4 g (70%), b.p. 137 – 143 °C/1.2 mmHg, m.p. 35 – 38 °C. Anal. $C_{11}H_{13}NO$: C, H, N. MS *m/e* (% rel. int.): 175 (100, M). ^1H NMR: δ 1.71 – 2.57 (4H, m), 3.43 – 3.91 (2H, m), 4.77 – 4.99 and 4.99 – 5.21 (1H, q, *J* 4.8 and 6.6 Hz), 7.11 – 7.53 (5H, m), 8.11 and 8.39 (1H, s).

N-*Formyl-2-phenylpiperidine.* Compound *2* (0.5 mol) was reacted with benzene, following the same procedures as described for the preparation of the previous compound; yield 79.1 g (84%), b.p. 138 – 144 °C/0.9 – 1.0 mmHg. Anal. $C_{12}H_{15}NO$: C, H, N, MS *m/e* (% rel. int.): 189 (57, M), 188 (100, M – H). ^1H NMR: δ 1.23 – 2.57 (6H, m), 2.79 – 3.27 (1H, m), 3.33 – 3.59 and 3.97 – 4.23 (1H, m), 4.69 – 4.85 and 5.67 – 5.85 (1H, m), 7.07 – 7.55 (5H, m), 8.15 and 8.27 (1H, s).

N-*Formyl-2-phenyl-1H-hexahydroazepine.* This synthesis was identical to the preparation of *N*-formyl-2-phenylpyrrolidine except for the use of *3* as electrophile; yield 86.6 g (85%), b.p. 143 – 148 °C/0.8 – 1.0 mmHg. Anal. $C_{13}H_{17}NO$: C, H, N. MS *m/e* (% rel. int.): 203 (83, M), 202 (100, M – H). ^1H NMR: δ 1.02 – 2.96 and 3.12 – 3.44 (9H, m), 3.52 – 3.80 and 4.08 – 4.36 (1H, m), 4.52 – 4.80 and 5.20 – 5.44 (1H, q,

J 6.4 and 11.3 Hz (4.52 – 4.80), and *J* 5.8 and 12.3 Hz (5.20 – 5.44), 7.08 – 7.48 (5H, m), 8.14 and 8.28 (1H, s).

1-Methyl-5-phenyl-2-pyrrolidinone. Compound *4* (0.5 mol) was reacted with benzene, following the procedure described for the preparation of *N*-formyl-2-phenylpyrrolidine. As the starting material contained 8% 1-methoxy-methyl-2-pyrrolidinone, the isolated product (after distillation) contained 8% 1-phenylmethyl-2-pyrrolidinone as impurity. Yield: 66.2 g (76%), b.p. 119 – 122 °C/1.0 mmHg. Found C 74:3; H 7.74; N 7.80. Calc. for $C_{11}H_{13}NO$: C 75. 40, H 7. 48; N 8.00 MS *m/e* (% rel. int.): 1-methyl-5-phenyl-2-pyrrolidinone: 175 (47, M), 98 (100, M – C_6H_5), 1-phenylmethyl-2-pyrrolidinone: 175 (100, M). ^{1}H NMR (both isomers): δ 1.53 – 3.42 (4H, m), 2.68 (3H, s), 4.44 – 4.64 (1H, q, *J* 5.3 and 7.0 Hz), 7.10 – 7.54 (5H, m).

N-Fomyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline. Compound *5* (0.05 mol) dissolved in benzene (25 ml) was added dropwise to a stirred mixture of $AlCl_3$ (0.1 mol) in benzene (25 ml; 0.56 mol). The reaction mixture was kept below 40 °C during the addition of *5*, and thereafter stirred for 30 min before being worked up according to the general procedure. The crude product was recrystallized from ethanol; yield 8.6 g (72%), m.p. 73 – 75 °C. Anal. $C_{16}H_{15}NO$: C, H, N. MS *m/e* (% rel. int.): 237 (100, M). ^{1}H NMR: δ 2.59 – 3.67 and 4.06 – 4.35 (4H, m), 5.77 and 6.69 (1H, s), 6.87 – 7.38 (9H, m), 8.17 and 8.51 (1H, s).

An experiment with a 1.4 molar ratio of $AlCl_3$ to *5* was performed in a similar way; yield 40%.

Competitive amidoalkylation of 1,3,5-trimethoxybenzene. Methanesulfonic acid (0.007 mol) was added to a solution of two of the methoxylated amides (*1* – *5*, 0.005 mol of each) and 1,3,5-trimethoxybenzene (0.0005 mol) in dichloromethane (5 ml). After 30 min at room temperature, 5M sodium hydroxide solution was added and the mixture shaken. As the GLC response factors of the products were known, the relative molar yields could be calculated.

Acidic hydrolysis. A stirred mixture of the formamide (0.1 mol) and 5M hydrochloric acid (100 ml) was refluxed. After complete hydrolysis of the amide (GLC analysis), 5 M sodium hydroxide solution (120 ml) was added. The alkaline solution was extracted 3 times with dichloromethane and the combined organic layers were dried over magnesium sulfate and evaporated *in vacuo*. Finally, the residue was distilled under reduced pressure.

2-Phenylpyrrolidine. Time of reaction: 1.5 h; yield 12.4 g (84%), b.p. 104 – 108 °C/10 mmHg. MS *m/e* (% rel. int.): 147 (35, M), 118 (100, M – C_2H_5). ^{1}H NMR: δ 1.37 – 2.29 (4H, m), 1.87 (1H, s), 2.79 – 3.31 (2H, m), 3.95 – 4.19 (1H, t, *J* 7.7 Hz), 7.05 – 7.47 (5H, m).

2-Phenyl-1H-hexahydroazepine. Complete hydrolysis in 10 h; yield 14.3 g (82%), b.p. 125 – 127 °C/10 mmHg. Anal. $C_{12}H_{17}N$: C, H. MS *m/e* (% rel. int.): 175 (53, M), 132 (100, M – C_3H_7). ^{1}H NMR: δ 1.34 – 2.14 (9H, m, N – H probably at δ 1.70), 2.64 – 3.28 (2H, m), 3.64 – 3.88 (1H, q with further splitting, *J* approx. 4 and 8 Hz), 6.98 – 7.48 (5H, m).

2-Phenylpiperidine. Complete hydrolysis in 2 h; after the reaction mixture was made alkaline the product crystallized as the hydrate. The crystals were filtered off and washed several times with water. The product was pure according to GLC analysis and its melting range was not affected by recrystallization from ethanol/water (50/50). The NMR sample was obtained from distillation of the hydrate under reduced pressure. Yield (hydrate): 17.1 g (96%), m.p. 40 – 60 °C (reported: 71 °C [19]), b.p. 112 – 113 °C/10 mmHg. MS *m/e* (% rel. int.): 161 (68, M), 104 (100, M – C_4H_9). ^{1}H NMR: δ 1.24 – 2.10 (6H, m), 1.68 (1H, s), 2.60 – 2.94 (1H, m), 3.06 – 3.32 (1H, m), 3.44 – 3.70 (1H, m), 7.10 – 7.54 (5H, m).

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