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SELECTIVE MONOFORMYLATION OF 1,3-DIAMINOPROPANE DERIVATIVES

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ABSTRACT: A general procedure for regiospecific construction of *N*-aryl-*N'*-formyl-1,3-diaminopropanes **2** (R=H) by selective monoformylation of *N*-(3-aminopropyl)arylamines **1** is described. Compounds **1** are readily obtained with high yields by aminolysis of 3-bromopropylamine hydrobromide with aromatic amines. The present synthetic strategy was extended to the synthesis of other *N*-acyl-*N'*-aryl-1,3-diaminopropanes.

N-Acyl derivatives of *N*-substituted alkylenediamines represent key intermediates in the preparation of potentially bioactive compounds such as cyclic amidines[1] and *N,N'*-disubstituted α,ω-diaminoalkanes.[2]

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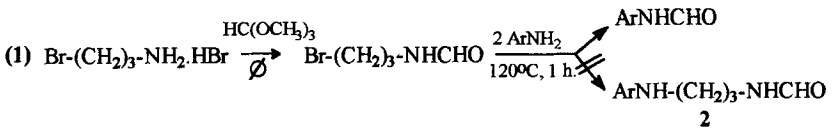
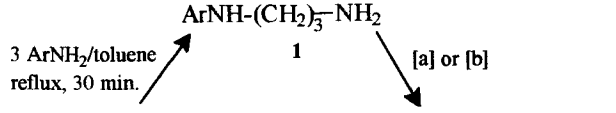
In the course of our research on nitrogen heterocycles having pharmacological interest, we recently needed to prepare some compounds of this type, namely *N*-aryl-*N'*-formyltrimethylenediamines **2** (R=H) as synthetic intermediates. In previous work, we reported a simple procedure that led to high yields of *N*-acyl-*N'*-aryl-1,3-diaminopropanes **2** (R=alkyl, aryl) by aminolysis of the corresponding *N*-(3-bromopropyl)amides.[2b] Attempts to extend such methodology to the synthesis of formyl derivatives were unsuccessful because of the low yields in the preparation of *N*-(3-bromopropyl)formamide and also due to a competitive transformylation reaction which led to *N*-formylanilines as main product in the aminolysis step[3] (Equation 1).



The present paper describes an alternative approach to the synthesis of *N*-aryl-*N'*-formyl-1,3-diaminopropanes **2a-g** (Scheme I) in good overall yields, from easily available starting materials. The method involves the condensation of 3-bromopropylamine hydrobromide with aromatic amines, followed by selective monoformylation of the resulting *N*-(3-aminopropyl)arylamines **1** with *p*-nitrophenyl formate. This methodology was also applicable to the synthesis of *N*-acyl-*N'*-aryl derivatives **2h,i**, employing the corresponding acid anhydrides as acylating agents.

Scheme I



[a] for R=H: $(p\text{-}NO_2C_6H_4)OCHO/THF$, -5°C, 1h

[b] for R= CH_3, C_6H_5: $(RCO)_2O/OH^-$, -5°C, 15 min

Compound (1, 2)	Ar	R	Yield (%) (overall)
a	C_6H_5	H	60
b	$p\text{-}ClC_6H_4$	H	69
c	$p\text{-}CH_3C_6H_4$	H	66
d	$o\text{-}CH_3C_6H_4$	H	71
e	$p\text{-}CH_3OC_6H_4$	H	56
f	$p\text{-}NO_2C_6H_4$	H	77
g	$o\text{-}NO_2C_6H_4$	H	68
h	$p\text{-}ClC_6H_4$	CH_3	79
i	$p\text{-}ClC_6H_4$	C_6H_5	82

Results and discussion

Condensation of 3-bromopropylamine hydrobromide with three moles of a primary aromatic amine in toluene afforded the desired *N*-(3-aminopropyl)arylamines **1a-e**, which crystallized in the reaction mixture as hydrobromides. By employing such reaction conditions it was possible to minimize formation of *N,N*-bis(3-aminopropyl)arylamines, without interfering the excess arylamine with further purification of the products. This procedure is operationally simple and leads to

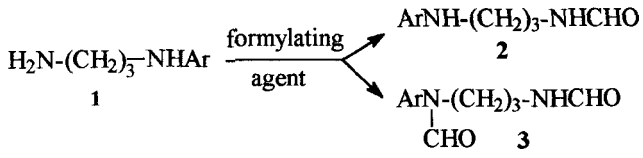
higher yields (78-94%) of compounds **1a-e** than those reported in the literature (17-39%)[4] employing the Ing-Manske modification of the Gabriel synthesis of primary amines.

The preparation of nitroaryl derivatives **1f,g** by the above route requires very drastic conditions and affords low yields. Such compounds were prepared from 1,3-diaminopropane and the corresponding halonitrobenzene.[1b]

As optimum reaction conditions for the aminolysis step were readily achieved, the only problem lay on the selection of a suitable formylating agent. Although literature describes some examples of chemoselective *N*-formylations in bifunctional molecules containing additional S[5] and O[5,6] nucleophilic groups, data concerning selective *N*-monoformylation of diamines are, to our knowledge, absent. Examination of the literature[7] showed that formylation of amino groups is generally achieved by reaction of the amine with mixed anhydrides of formic and other carboxylic acids[7a,8], themselves more stable than formic anhydride[9] which decomposes above -40°C. Alternatively, formic acid has been used in combination with dicyclohexylcarbodiimide in the synthesis of certain *N*-formyl aminoacid esters and peptides.[10] The main disadvantage of this procedure is the formation of dicyclohexylurea as side product, which often complicates the isolation and purification of the products. In some cases, *N*-formylation has been performed with formic acid[11] or its derivatives like formamide[12] or alkyl formates[13], which are less reactive. The use of active formate esters as formylating agents[5,6,14], instead, leads to better results, both in terms of product yields and ease of isolation.

In our case, compound **1e** was chosen to evaluate the selectivity of different formylating agents, because of the higher nucleophilicity of the arylamino moiety. Comparative yields of compound **2e** and *N,N'*-diformyl-*N*-(*p*-methoxyphenyl)trimethylenediamine **3e** obtained in each case are listed in **Scheme II**.

Scheme II



Formylating agent	**2e** % yield	**3e** % yield
Ethyl formate	35	-
Formamide	10	62
Formic acetic anhydride	-	47
Formic acetic anhydride generated *in situ*	24	5
Formic acid	55	5
p-Nitrophenyl formate	72	-

Reaction of **1e** with ethyl formate led to low yields of **2e**, and 52% of the starting material was recovered unreacted after 12 hours reflux. Formamide did not react with **1e** at room temperature, and showed no selectivity at reflux, leading almost exclusively to diformyl derivative **3e**. Formic acetic anhydride[7a] at 0°C was not selective, and formic acetic anhydride generated *in situ*[8a] afforded a mixture of formyl and acetyl derivatives.

Acceptable yields of compounds **2** were obtained in all cases by treatment with formic acid at reflux. The only exception was the *o*-tolyl derivative **1d**, which did

not react after 10 hours reflux. The best results regarding both reactivity and selectivity, even in the case of compound **1d**, were accomplished by the use of *p*-nitrophenyl formate. Employing a molar ratio of 1:1 with the substrate, and working at -5°C, this reagent led to the highest yields, affording exclusively the monoformyl derivatives **2a-g**. Additional advantages of this reagent include easy handling, mildness of reaction conditions, a significative shortening in reaction times and cleanness of the crude products, with concomitant simplification of their purification.

The use of acylatig agents such as acetic and benzoic anhydrides also allowed for selective monoacylation of *N*-(3-aminopropyl)arylamines **1**, leading respectively to compounds **2h,i** in overall yields higher than those previously reported by our group.[1b,2b,15]

The extension of this method to the preparation of unsymmetrical *N*-alkyl-*N'*-formyl-1,3-diaminopropanes is limited due to the similar reactivity of primary and secondary alkylamino moieties towards acylating agents in general.

Experimental

Melting points were determined with a Büchi capillary apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker MSL 300 MHz spectrometer, using deuteriochloroform as the solvent. Chemical shifts are reported in ppm (δ) relative to TMS as an internal standard. D_2O was employed to confirm exchangeable protons (ex.). Splitting multiplicities are reported as singlet (s), broad signal (bs), doublet (d), double doublet (dd), triplet (t), double triplet (dt), quartet (q), pentet (p) and multiplet (m). Mass spectra (EI) were recorded

with a GC-MS Shimadzu QP-1000 spectrometer operating at 20 eV. TLC analyses were carried out on aluminium sheets Silica Gel 60 F_{254} using chloroform-methanol (9:1), ethyl acetate-methanol (20:1) or diethyl ether-isopropylamine (10:1) as the solvent. Flash column chromatographies were performed on Silica Gel 60 (0.040-0.063 mm).[16] Reagents, solvents and starting materials were purchased from standard sources and purified according to literature procedures.

_N_-(3-Aminopropyl)arylamines 1a-e. General procedure.

3-Bromopropylamine hydrobromide (10 mmol) was added to a solution of the corresponding arylamine (30 mmol) in toluene (30 ml). After refluxing for 30 minutes, the mixture was cooled (room temperature) and filtered. The precipitate was washed twice with toluene and dried. The solid was treated with 20% aqueous sodium hydroxide, and the mixture extracted with methylene chloride (2 x 30 ml). The organic layer was washed with water (5 ml) and dried over anhydrous sodium sulphate. The solvent was removed *in vacuo*, and the crude product purified by flash column chromatography (diethyl ether-isopropylamine 10:0 to 10:1).

N-(3-Aminopropyl)aniline[4] (**1a**) (81%); ^{1}H NMR: δ= 7.17 (2H, dt, 2 meta H), 6.69 (1H, dt, para H), 6.44 (2H, dd, 2 ortho H), 3.19 (2H, t, C*H*$_2$NHAr), 2.85 (2H, t, C*H*$_2$NH$_2$), 1.77 (2H, p, CH$_2$C*H*$_2$CH$_2$), 1.60 (2H, bs, ex., NH$_2$).

N-(3-Aminopropyl)-p-chloroaniline[4] (**1b**) (94%); ^{1}H NMR: δ=7.10 (2H, dd, 2 meta H), 6.51 (2H, dd, 2 ortho H), 3.15 (2H, t, C*H*$_2$NHAr), 2.84 (2H, t, C*H*$_2$NH$_2$), 1.75 (2H, p, CH$_2$C*H*$_2$CH$_2$), 1.60 (2H, bs, ex., NH$_2$).

N-(3-Aminopropyl)-p-toluidine[4] (**1c**) (82%); ^{1}H NMR: δ=6.98 (2H, d, 2 meta H), 6.54 (2H, d, 2 ortho H), 3.80 (1H, bs, ex., NHAr), 3.17 (2H, t, C*H*$_2$NHAr), 2.83 (2H, t, C*H*$_2$NH$_2$), 2.25 (3H, s, ArCH$_3$), 2.00 (2H, bs, ex., NH$_2$), 1.75 (2H, p, CH$_2$C*H*$_2$CH$_2$).

N-(3-Aminopropyl)-o-toluidine (**1d**).

The product was obtained as an oil (89%).

MS: m/z= 164 ($M^{+\cdot}$).

^{1}H NMR: δ= 7.16-7.04 (3H, m, 2 meta and para H), 6.63 (1H, t, 2 ortho H), 3.16 (2H, t, CH_2NHAr), 2.88 (2H, t, CH_2NH_2), 2.14 (3H, s, ArCH_3), 1.82 (2H, p, $CH_2CH_2CH_2$), 1.05 (2H, bs, ex., NH_2).

Anal. calcd. for $C_{10}H_{16}N_2$: C 73.13, H 9.82, N 17.06; found: C 73.25, H 9.89, N 17.18.

N-(3-Aminopropyl)-p-methoxyaniline[4] (**1e**) (78%); ^{1}H NMR: δ=6.78 (2H, dd, 2 ortho H), 6.58 (2H, dd, 2 meta H), 3.74 (3H, s, ArOCH_3), 3.14 (2H, t, CH_2NHAr), 2.84 (2H, t, CH_2NH_2), 2.05 (2H, bs, ex., NH_2), 1.75 (2H, p, $CH_2CH_2CH_2$).

N-Aryl-N'-formyl-1,3-diaminopropanes 2a-g. General procedure.

A solution of *p*-nitrophenyl formate (5 mmol) in dry tetrahydrofurane (10 ml) was added to a solution of the corresponding N-(3-aminopropyl)arylamine (5 mmol) in dry tetrahydrofurane (10 ml) with stirring, during 30 minutes in an ice-salt bath. After complete dissapearance of the starting material was checked by TLC (ethyl acetate-methanol 9:1), the solvent was removed *in vacuo* at room temperature. The crude products were purified by flash column chromatography (ethyl acetate-methanol 10:0 to 20:1).

N-Formyl-N'-phenyl-1,3-diaminopropane (**2a**).

The product was obtained as an oil (74%).

MS: m/z= 178 ($M^{+\cdot}$).

^{1}H NMR: δ=8.12 (1H, s, CHO), 7.18 (2H, dt, 2 meta H), 6.73 (1H, dt, para H), 6.61 (2H, dd, 2 ortho H), 6.25 (1H, bs, ex., NHCO), 3.95 (1H, bs, ex., NHAr), 3.37 (2H, q, CH_2NHCO), 3.16 (2H, t, CH_2NHAr), 1.79 (2H, p, $CH_2CH_2CH_2$).

Anal. calcd. for $C_{10}H_{14}N_2O$: C 67.39, H 7.92, N 15.72; found: C 67.25, H 7.84, N 15.85.

N-(p-Chlorophenyl)-N'-formyl-1,3-diaminopropane (**2b**).

The product was obtained as an oil (73%).

MS: m/z= 212 ($M^{+\cdot}$).

^{1}H NMR: δ=8.19 (1H, s, CHO), 7.10 (2H, dd, 2 meta H), 6.54 (2H, dd, 2 ortho

H), 5.95 (1H, bs, ex., NHCO), 4.05 (1H, bs, ex., NHAr), 3.41 (2H, q, CH_2NHCO), 3.16 (2H, t, CH_2NHAr), 1.80 (2H, p, $CH_2CH_2CH_2$).

Anal. calcd. for $C_{10}H_{13}ClN_2O$: C 56.47, H 6.16, N 13.17; found: C 56.59, H 6.23, N 13.08.

N-Formyl-N'-(p-tolyl)-1,3-diaminopropane (**2c**).

The product was obtained as an oil (81%).

MS: m/z= 192 ($M^{+\cdot}$).

^{1}H NMR: δ=8.16 (1H, s, CHO), 6.99 (2H, dd, 2 meta H), 6.55 (2H, dd, 2 ortho H), 5.91 (1H, bs, ex., NHCO), 3.42 (2H, q, CH_2NHCO), 3.18 (2H, t, CH_2NHAr), 2.21 (3H, s, $ArCH_3$), 1.81 (2H, p, $CH_2CH_2CH_2$).

Anal. calcd. for $C_{11}H_{16}N_2O$: C 68.72, H 8.39, N 14.57; found: C 68.83, H 8.44, N 14.44.

N-Formyl-N'-(o-tolyl)-1,3-diaminopropane (**2d**).

The product was obtained as an oil (80%).

MS: m/z 192= ($M^{+\cdot}$).

^{1}H NMR: δ=8.19 (1H, s, CHO), 7.12 (1H, t, meta H), 7.06 (1H, d, meta H), 6.66 (1H, t, para H), 6.61 (1H, d, ortho H), 5.89 (1H, bs, ex., NHCO), 3.80 (1H, bs, ex., NHAr), 3.43 (2H, q, CH_2NHCO), 3.25 (2H, t, CH_2NHAr), 2.16 (3H, s, $ArCH_3$), 1.86 (2H, p, $CH_2CH_2CH_2$).

Anal. calcd. for $C_{11}H_{16}N_2O$: C 68.72, H 8.39, N 14.57; found: C 68.69, H 8.47, N 14.62.

N-Formyl-N'-(p-methoxyphenyl)-1,3-diaminopropane (**2e**).

The product was obtained as an oil (72%).

MS: m/z= 208 ($M^{+\cdot}$).

^{1}H NMR: δ=8.18 (1H, s, CHO), 6.79 (2H, dd, 2 ortho H), 6.60 (2H, dd, 2 meta H), 5.84 (1H, bs, ex., NHCO), 4.30 (1H, bs, ex., NHAr), 3.76 (3H, s, $ArOCH_3$), 3.44 (2H, q, CH_2NHCO), 3.16 (2H, t, CH_2NHAr), 1.82 (2H, p, $CH_2CH_2CH_2$).

Anal. calcd. for $C_{11}H_{16}N_2O_2$: C 63.44, H 7.74, N 13.45; found: C 63.31, H 7.80, N 13.37.

N-Formyl-N'-(p-nitrophenyl)-1,3-diaminopropane (**2f**).

The product had mp 126 °C (90%).

MS: m/z=223 ($M^{+\cdot}$).

^{1}H NMR: δ=8.25 (1H, s, CHO), 8.10 (2H, dd, 2 meta H), 6.55 (2H, dd, 2 ortho H), 5.74 (1H, bs, ex., NHCO), 5.36 (1H, bs, ex., NHAr), 3.46 (2H, q, CH_2NHCO), 3.32 (2H, q, CH_2NHAr), 1.81 (2H, p, $CH_2CH_2CH_2$).

Anal. calcd. for $C_{10}H_{13}N_3O_3$: C 53.81, H 5.87, N 18.82; found: C 53.72, H 5.94, N 18.70.

N-Formyl-N'-(o-nitrophenyl)-1,3-diaminopropane (**2g**).

The product had mp 72°C (78%).

MS: m/z=223 ($M^{+\cdot}$).

^{1}H NMR: δ=8.22 (1H, s, CHO), 8.15 (1H, dd, meta H), 7.43 (1H, dt, meta H), 6.83 (1H, d, ortho H), 6.55 (1H, t, para H), 5.99 (1H, bs, ex., NHCO), 3.46 (2H, q, CH_2NHCO), 3.38 (2H, q, CH_2NHAr), 1.97 (2H, p, $CH_2CH_2CH_2$).

Anal. calcd. for $C_{10}H_{13}N_3O_3$: C 53.81, H 5.87, N 18.82; found: C 53.98, H 5.92, N 18.73.

Formylation of compound 1e with ethyl formate.

Compound **1e** (5 mmol) and ethyl formate (10 ml) were heated under reflux for 12 hours. The solution was cooled and the excess ethyl formate removed *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate-methanol 20:1 to 7:3) to afford 35% of **2e** and 52% of **1e**.

Formylation of compound 1e with formamide.

Reaction of compound **1e** with formamide was performed following the procedure described in the literature.[12b] The crude product was purified by flash chromatography (ethyl acetate-methanol 10:1 to 4:1) affording 10% of **2e** and 62% of *N,N'*-diformyl-*N*-(*p*-methoxyphenyl)-1,3-diaminopropane (**3e**), MS: m/z= 236 ($M^{+\cdot}$); ^{1}H NMR δ=8.28 (1H, s, ArNCHO), 8.20 (1H, s, NHC*H*O), 7.10 (2H, dd, 2 ortho H), 6.95 (2H, dd, 2 meta H), 6.63 (1H, bs, ex., NH), 3.83 (2H, t,

CH_2NArCHO), 3.73 (3H, s, $ArOCH_3$), 3.30 (2H, q, CH_2NHCHO), 1.72 (2H, p, $CH_2CH_2CH_2$).

Anal. calcd. for $C_{12}H_{16}N_2O_3$: C 61.00, H 6.83, N 11.86; found: C 60.89, H 6.90, N 11.75.

Formylation of compound 1e with formic acetic anhydride.

Formic acetic anhydride [7a] (5 mmol) was added to a chloroform solution of **1e** (5 mmol) in an ice/salt bath, followed by 4% aqueous sodium hydroxide solution (5 ml). The mixture was vigorously shaken during 10 minutes, after which the organic layer was separated. The aqueous solution was extracted with chloroform (2 x 5 ml). The organic layers were pooled, washed with water (5 ml) and dried over anhydrous sodium sulphate. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography (ethyl acetate-methanol 10:0 to 30:1) to yield **3e** (47%).

Formylation of compound 1e with formic acetic anhydride generated *in situ*.

Acetic anhydride (5 mmol) was added dropwise and with stirring to an ice cold solution of **1e** (5 mmol) in 98% formic acid (10 mmol) during 10 minutes. The acid solution was diluted with water and made alkaline with 10% aqueous sodium hydroxide in an ice bath. The mixture was extracted with chloroform (2 x 20 ml), and the organic layer was washed with water (5 ml) and dried over anhydrous sodium sulphate. The crude product was purified by flash column chromatography (ethyl acetate-methanol 10:0 to 30:1), to afford 24 % of **2e**, 5% of **3e** and 41% of another compound which was identified as *N*-acetyl-*N'*-(*p*-methoxyphenyl)-1,3-diaminopropane; MS: m/z 222 ($M^{+\cdot}$); ^{1}H NMR: δ=6.78 (2H, dd, 2 ortho H), 6.60 (2H, dd, 2 meta H), 5.82 (1H, bs, ex., NHCO), 3.74 (3H, s, $ArOCH_3$), 3.36 (2H, q, CH_2NHCO), 3.13 (2H, t, CH_2NHAr), 1.97 (3H, s, $COCH_3$), 1.78 (2H, m, $CH_2CH_2CH_2$).

Anal. calcd. for $C_{12}H_{18}N_2O_2$: C 64.84, H 8.16, N 12.60; found: C 64.93, H 8.21, N 12.47.

Formylation of compounds 1a-g with formic acid. General procedure.

A solution of the corresponding *N*-(3-propylamino)arylamine (5 mmol) in excess formic acid (5 ml) was heated under reflux for 6 hours. The solution was cooled (0°C), extracted with chloroform (1 ml) and then made alkaline (pH=12) with 10% aqueous sodium hydroxide solution in an ice bath. The resulting mixture was extracted with methylene chloride (2 x 20 ml). The organic layer was washed with water (5 ml) and dried over anhydrous sodium sulphate. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography (ethyl acetate-methanol 10:0 to 10:1). Yields of *N*-aryl-*N'*-formyl-1,3-diaminopropanes **2a-c,e-f** obtained by this method were as follows: **2a** 51%, **2b** 53%, **2c** 58%, **2e** 55%, **2f** 54% and **2g** 53%.

N-Acetyl-N'-(p-chlorophenyl)-1,3-diaminopropane (**2h**).

Acetic acid anhydride (5 mmol) was added to a chloroform solution of *N*-(3-aminopropyl)-*p*-chloroaniline **1b** (5 mmol) in an ice/salt bath, followed by 4% aqueous sodium hydroxide solution (5 ml). The mixture was vigorously shaken during 10 minutes, after which the organic layer was separated. The aqueous solution was extracted with chloroform (2 x 5 ml). The organic layers were pooled, washed with water (5 ml) and dried over anhydrous sodium sulphate. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography (ethyl acetate), to yield **2h** (84%), mp and mixed mp with an authentic sample[2b] 91-93°C.

N-Benzoyl-N'-(p-chlorophenyl)-1,3-diaminopropane (**2i**).

Benzoic acid anhydride (6 mmol) was added to a chloroform solution of *N*-(3-aminopropyl)-*p*-chloroaniline **1b** (5 mmol), followed by 4% aqueous sodium hydroxide solution (5 ml). The mixture was shaken during 20 minutes at room temperature, after which the organic layer was separated. The aqueous solution was extracted with chloroform (2 x 5 ml). The organic layers were pooled, washed with water (5 ml) and dried over anhydrous sodium sulphate. The solvent

was removed *in vacuo*, and the residue purified by flash column chromatography (chloroform-ethyl acetate 1:1), to yield **2i** (87%), mp and mixed mp with an authentic sample[1b] 117°C.

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