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DMF·HCl as a versatile and straightforward *N*- and *O*-formylating agent

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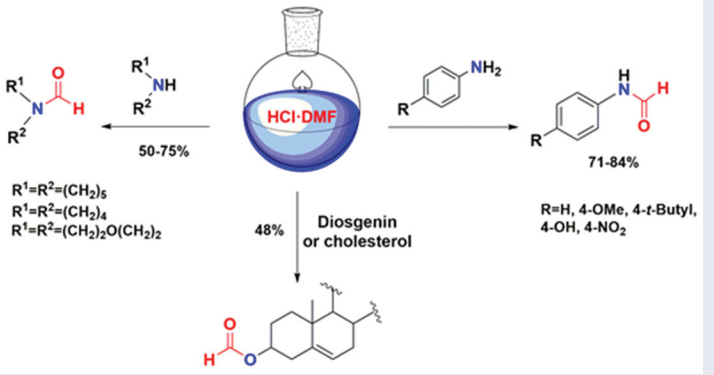
ABSTRACT

Inspired by the serendipitous isolation of *N*-formylpiperazines when we attempted the synthesis of a series of piperazines, we have developed a straightforward methodology for the *N*- and *O*- formylation of secondary cyclic amines, anilines and steroids, respectively. Such approach is based on the hitherto non-reported use of DMF·HCl complex, as a versatile and easily-available formylating system that can be stored without apparent loss of activity.

GRAPHICAL ABSTRACT



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KEYWORDS
N-Formylation; DMF·HCl complex; *O*-Formylation; cyclic amines; anilines

Introduction

N,*N*-Dimethylformamide (DMF), is an organic compound widely used in Organic Chemistry as a versatile solvent with polar aprotic and hydrophilic properties, for example with great efficiency in S_N2 reactions.[1] Furthermore, this compound has found many other applications such as stabilizer of metal nanoclusters and nanoparticles,[2] ligand[3], catalyst,[4] or as a reagent in organic synthesis,[5] among other uses. As a reagent, DMF is well known as a source of the formyl moiety to obtain formamides in aromatic, heteroaromatic and non-aromatic systems in the Vilsmeier-Haack reaction.[6] The Vilsmeier-Haack reagent ($POCl_3$-DMF) has also been used to convert

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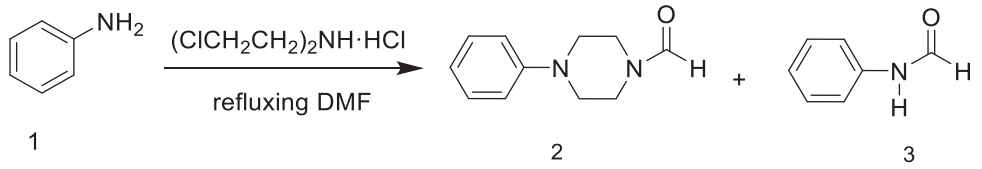


Scheme 1. Obtention of phenylpiperazine and phenylformamide from aniline.

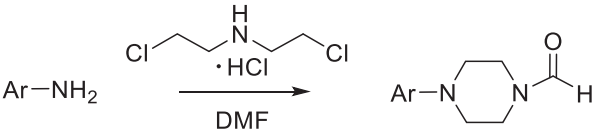
O-silyl protected carbohydrates[7] and phenol into their corresponding formats.[8] More recently, formylation of the hydroxyl group at C-3 and C-17 positions of some sterols was achieved using a combination of $POCl_3$-DMF.[9] Formylation reactions frequently include transition metals or complex reagents to catalyze the reaction.[10] Most of these protocols are expensive and sometimes require long reaction times and high temperatures. Protic acids and DMF have been used to a lesser extent for *N*-formylation and to our knowledge, there are no reports for *O*-formylation. In 1973, Kraus reported the slow formylation of alkyl amines with refluxing DMF and showed that the addition of concentrated sulfuric acid greatly enhanced the rate of the reaction and improved the yields.[11] Later, Takahashi et al., reported[12] a protocol of transamidation of carboxamides using catalytic amounts of silica-supported H_2SO_4 under solvent-free conditions which was applied to the formylation of aromatic/heteroaromatic amines and some alkyl amines, as well. Chen and co-workers[13] described the preparation of some formamides including a two-step route, first, a C–N bond formation of *β*-keto amides and then a different C–N cleavage in the presence of a HCl (0.2 equiv)-DMF solution in a Schlenk tube at 120° C; similar conditions were used by Zhang (36.5% HCl solution/DMF at 100 °C) for the synthesis of aryl formamides.[14] More recently, acid-promoted *N*-formylation of 2-aminophenol was studied with different acids, camphorsulfonic acid being found to be the best catalyst for this purpose.[15]

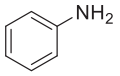
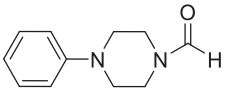
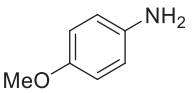
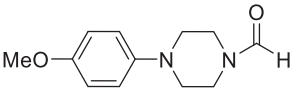
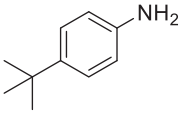
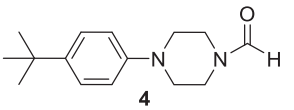
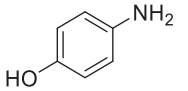
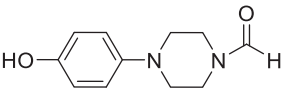
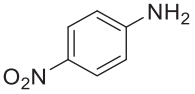
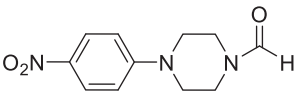
We herein report a new methodology for the *N* or *O*-formylation of aromatic or alkyl amines and two sterols (diosgenin and cholesterol), respectively, using a stable DMF·HCl complex as a versatile formylating agent under metal-free conditions. This method is inexpensive and the complex can be prepared and stored under no special conditions.

Results and discussion

Access to the DMF·HCl complex as a formylating agent occurred in a total serendipitous fashion. We attempted to prepare a phenylpiperazine derivative from aniline in the presence of bis(2-chloroethyl)amine hydrochloride, and a base (K_2CO_3) in refluxing ethylene glycol. However, we did not obtain the expected compound. In order to favor the nucleophilic reaction with a polar non-protic solvent, we used DMF instead of ethylene glycol. After the work-up and the chromatographic purification, we isolated 4-phenylpiperazine-1-carboxaldehyde (**2**) and *N*-phenylformamide (**3**) (Scheme 1). The same result was observed in the absence of K_2CO_3 what can be explained by the low solubility of K_2CO_3 in DMF. In previous reports, this protocol was carried out to obtain phenylpiperazine derivatives; however, the yields were poor and the formylated products were not detected.[16]

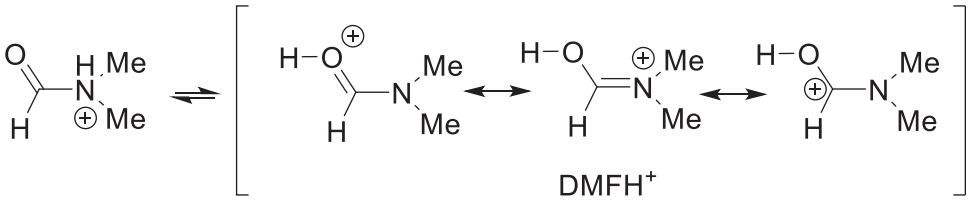
Table 1. Synthesis of *N*-formyl piperazines.



Entry	Ar–NH_2	Product	Yield (%)
1		 **2**	58
2		 **3**	71
3		 **4**	62
4		 **5**	48
5		 **6**	48

On the basis that DMF can be a source of the formyl moiety in presence of protic or Lewis acids, we deduced that the HCl formed during the S_N2 reaction between the aniline and bis(2-chloroethyl)amine hydrochloride could catalyze the formylation of the aniline and phenyl piperazine initially obtained in the reaction. In order to analyze the scope and limitations of this approach, different anilines bearing both, electron-withdrawing and electron-donating groups were studied (Table 1, entries 1–5). In general, moderate yields were obtained; the highest yield was observed in the reaction of *p*-methoxyaniline (entry 2, 71%). It is worth mentioning that *N*-formylpiperazines are important scaffolds for the synthesis of more complex compounds such as explosives[17] and bioactive derivatives.[18,19]

To confirm the hypothesis that HCl formed during the reaction could be catalyzing the formylation, HCl (g) was produced by the reaction of H_2SO_4 and NaCl and then it was bubbled into a flask containing DMF during 3 h. The HCl concentration was determined by titration using a 0.1 M NaOH solution, and it turned out to be



Scheme 2. DMF·HCl resonance hybrids

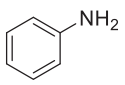
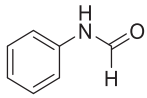
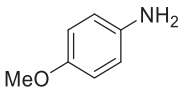
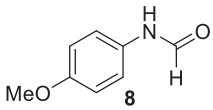
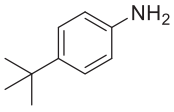
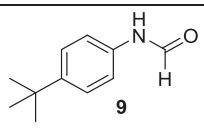
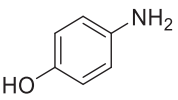
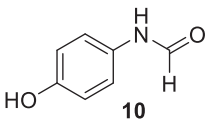
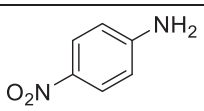
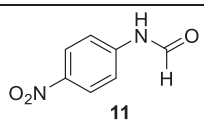
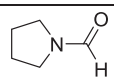
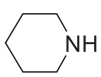
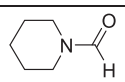
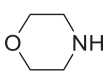
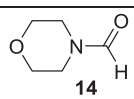
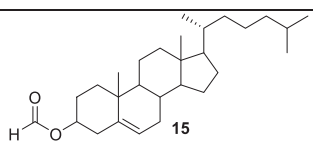
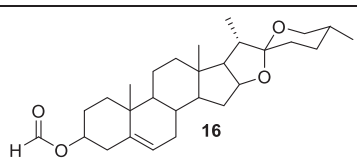
3.2 M. It is known that when an amide is treated with an acid, the protonation occurs more easily at the carbonyl oxygen rather than at the nitrogen, because of the resonance stabilization of the corresponding cation (Scheme 2). The DMF·HCl system was characterized by NMR. Concerning the ^{1}H-NMR spectrum, an additional signal at 15.10 ppm was observed, attributed to the proton of the oxonium ion in the resonance hybrid $DMFH^{+}$ (Scheme 2). The same peak was detected by Deng et al.,[20] in the complex prepared with DMF and trifluoroacetic or tetrafluoroboric acids (15.39 ppm in DMSO-d_6). A small change of 2.2 ppm was observed in the ^{13}C-NMR spectrum (160.8 ppm *vs* 163.0 ppm). It is worthy to mention that the system HCl·DMF was stored and after a month it was titrated, exhibiting the same concentration.

The DMF·HCl was used without further purification to formylate a series of anilines and secondary amines (Table 2, entries 1–5). The methodology consisted of the addition of DMF·HCl solution (5 mL) to the corresponding amine (4.5 mmol) and refluxing with continuous stirring for 3 h. After work-up and chromatographic purification, a series of formyl derivatives were obtained in good yields. The anilines tested contained either no substitution on the aromatic ring (entry 1), electron-donating groups (entries 2–4), or a strong electron-withdrawing group (entry 5); in all cases, the yields ranged from good to excellent (70–84%). This protocol showed to be efficient also for cyclic secondary amines (entries 6–8) and for the *O*-formylation of two steroids, cholesterol and diosgenin (entries 9–10), in the latter example, the reaction proceeded at 50–55 °C. Formate esters are used as intermediates in organic synthesis,[21] mainly as protecting groups of alcohols.[22] Several methodologies for formylation reported in the literature involve strong reaction conditions[23] and can affect other functional groups. In this regard, the protocol depicted herein represents an alternative and inexpensive method with good yields.

Experimental

Reagents were used as received from Sigma-Aldrich without further purification. NMR spectra were recorded on a VARIAN Mercury spectrometer (400 MHz for ^{1}H, 100.6 MHz for ^{13}C) or on a 80 MHz Spinsolve 80 NMR spectrometer (80 MHz for ^{1}H, 20 MHz for ^{13}C). IR spectra were acquired on FTIR Perkin Elmer Spectrum 100 (range: 4000–600 cm^{-1}). High resolution mass spectra (HRMS) were obtained by direct infusion in a Synapt G2-Si Q-TOF system (Waters) equipped with an electrospray (ESI) probe, and the following parameters were used: flow rate, 10 µL/min; ionization mode, positive; capillary voltage, 3000 V; cone voltage, 40 V; capillary temperature, 100 °C; nitrogen was used as desolvation gas at 200 °C; and a flow rate of 800 L/h, cone gas, 50 L/h;

Table 2. *N*-formylation of anilines, secondary amines and sterols using the system HCl·DMF.

Entry	Ar–NH_2	Product	Yield (%)
1		 **7**	71
2		 **8**	75
3		 **9**	84
4		 **10**	70
5		 **11**	73
6		 **12**	50
7		 **13**	60
8		 **14**	75
9	Cholesterol	 **15**	48
10	Diosgenin	 **16**	48

Nebulizer pressure; 6 bar. Mass spectrometer was calibrated with sodium formate and spectra were corrected by simultaneous infusion of the compound Leucine Enkephaline (556.2771). Data analysis was conducted using MassLynx software version 4.1 (Waters). Analytical TLC was performed on silica gel ALUGRAM® SIL G/UV254 plates, and chromatographic columns were carried out on Davisil^{TM} grade 633 silica gel (200–425 mesh).

Typical experimental procedure for preparation of the DMF·HCl complex

H_2SO_4 (10 mL) was slowly dropped into a stirred flask containing NaCl (10 g, 171.11 mmol) in order to produce $HCl_{(g)}$. The liberated $HCl_{(g)}$ was bubbled into a two-neck flask containing DMF (50 mL) during 3 h. A 10% NaOH solution trap was attached to the second neck. The concentration of HCl of the complex was determined by titration with a 0.1 M NaOH solution, being 3.2 M. ^{1}H NMR (80 MHz, DMSO-d_6) δ 15.10 (s, 0.3H), 8.00 (s, 1H), 2.89 (s, 3H), 2.70 (s, 3H).

Typical experimental procedure for the preparation of N-formylanilines

The DMF·HCl solution (5 mL) was added to the corresponding aniline (4.5 mmol) and refluxed for 3 h. Then, a saturated aqueous $NaHCO_3$ solution (10 mL) was added and the resulting mixture was extracted with EtOAc (3 × 20 mL) and washed with brine (3 × 20 mL). The organic layer was dried over Na_2SO_4, filtrated, and the filtrate was removed under reduced pressure. The residue was purified as indicated in each case.

Typical experimental procedure for the synthesis of O-formylated species

DMF·HCl complex (10 mL) was added to the corresponding alcohol (1.20 mmol) keeping the temperature between 50 and 55 °C for 2 h. Then, an aqueous $NaHCO_3$ solution (10 mL) was added and the resulting mixture was extracted with AcOEt (3 × 20 mL) and washed with brine (3 × 20 mL). The solvent was removed under reduced pressure. The residue was purified as indicated below.

Full experimental details, characterization data and isolated yields for *N*-formyl-4-arylpiperazines, *N*-formylanilines, cyclic amides and *O*-formylated species can be found through the "Supplementary Content" section of this article's webpage.

Conclusions

In conclusion, based on the results obtained in the reaction between aniline and bis(2-chloroethyl)amine hydrochloride, we envisioned the possibility that $HCl_{(g)}$ could catalyze the formylation of aniline and phenyl piperazine. These observations let us to develop a new straightforward methodology for the simple *N*-formylation of aniline derivatives using a stable DMF·HCl complex as an easily-handled catalyst, and extended the scope of this process to secondary cyclic amines and to the *O*-formylation of two steroids (diosgenin and cholesterol). DMF·HCl complex is easy to prepare and that can be stored for more than one month without the apparent loss of activity.

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