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Surprising formylations with methylformamidopyridines and oxalyl chloride

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Abstract

4-*N*-(Methylformamido)pyridine with $(COCl)_2$ gives the corresponding Vilsmeier reagent which reacts with 4-substituted dimethylanilines to produce 5-substituted-*N*-methylisatins. The corresponding 2-*N*-(methylformamido)pyridine under the same conditions generates benzo[2,3]pyrido[6,7-*b*][1,5]diazocines.
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Recently, we have demonstrated[1] that Vilsmeier reagents (hereinafter referred to as VRs; $R_2N^+{=}CHCl\ Cl^-$) are readily transformed into carbenes by the action of bases such as pyridine. These nucleophilic carbenes react with the unchanged VR to give an ethene ($R_2NCCl{=}CClNR_2$) which can be isolated or further formylated to give products such as isatins, quindolines and 2,2-biindoles. In other work,[2] we have shown that when the base utilised to react with the VR is a 4-substituted dimethylaniline, a dibenzo[1,5]diazocine results (Scheme 1). We herein examine the reactions of 2- and 4-methylformamidopyridines (MFPs) in Vilsmeier formylations, since they combine the presence both of an electrophilic formylating group and a basic centre, thereby hopefully enabling Vilsmeier→carbene transformations.

It is surprising that no work has been reported on utilising MFPs in Vilsmeier reactions. Indeed, while the 2-isomer is commercially available,[3] the 4-isomer is previously unreported, but easily made by NaH/MeI methylation of 4-formamidopyridine, itself made by HCO_2H/Ac_2O formylation of 4-aminopyridine. Both isomers are readily and efficiently converted into solid VRs with oxalyl chloride.

Treatment of the VR of 4-MFP with various 4-substituted dimethylanilines proved most interesting. While under a nitrogen atmosphere no definable product could be isolated, the interaction in air produced, to our surprise, the corresponding *N*-methylisatin **1**. Yields of the isatins from a 1:1 ratio of the two reactants were moderate (30–52%) but perhaps this is not surprising in the light of our suggested mechanism (Scheme 2). This envisages a formylation as in Scheme 1 followed by an aerial oxidation

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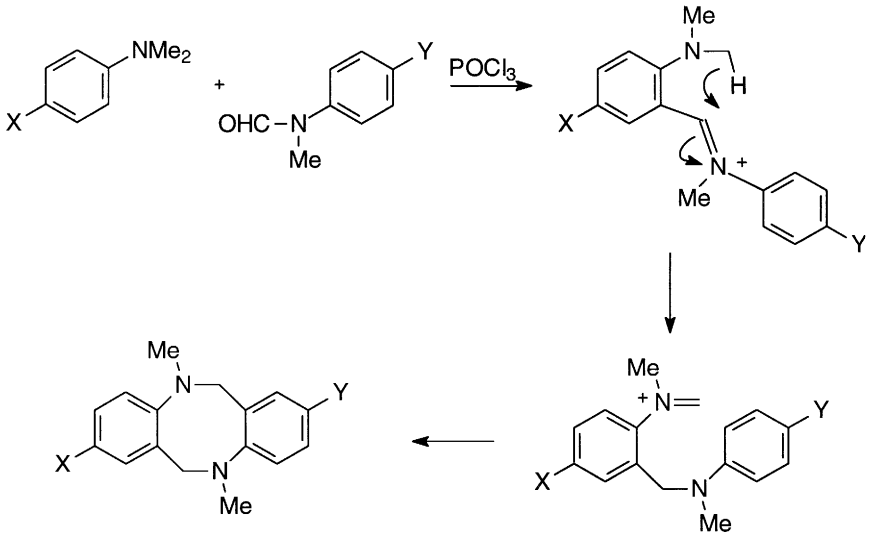
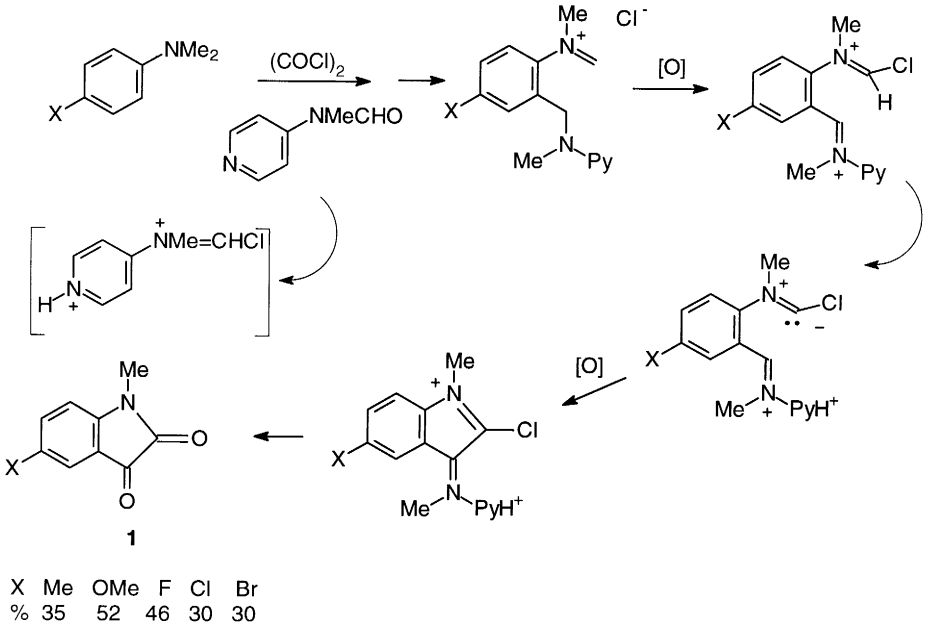


Scheme 1.

of the intermediate to an intermediate carbene which then cyclises. It is possible the the VR acts as an intermolecular hydride abstractor but this is not borne out by attempts to abstract hydride from *N*,*N*-dimethylbenzylamine (which remains unchanged). The simplicity of the reaction even with these yields makes the method worthy of further optimisation, towards important, but presently not easily made, isatins. In the formation of **1**, X=Me, the yield increased to 41% if oxygen was slowly bubbled into the reaction mixture during the interaction. We are currently examining other oxidants.

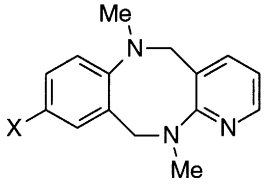


X	Me	OMe	F	Cl	Br
%	35	52	46	30	30

Scheme 2.

The corresponding 2-MFP behaved quite differently when treated with the same dimethylanilines in the same manner. Again we were surprised, since despite the possibly deactivated pyridine ring,

benzo[2,3]pyrido[6,7-*b*][1,5]diazocines **2**, members of a new and interesting system,[4] were isolated in yields of 56–58%, no doubt exactly as depicted in Scheme 1.



X	Me	F	Cl	Br
%	57	58	57	56

2

It would appear that the 2-MFP VR is not significantly protonated on the ring nitrogen due to the proximate (quaternised?) group, thus allowing cyclisation, while the more nucleophilic 4-isomer (cf. DMAP) is protonated significantly, thus deactivating the system to diazocine formation. Clearly, these two VRs are of some interest and deserve a fuller study to clarify their other potentials. Illustrative examples of the above reactions are given below:

– Isatin **1** formation utilising 4-MFP: To 4-(methylformamido)pyridine (1.36 g, 0.01 M) was added oxalyl chloride (2 mL) with stirring in an ice-bath, with gas evolution evident. The resulting red mixture was stirred at room temperature for 30 min and the excess of oxalyl chloride was removed in vacuo. Under ice-bath cooling, a solution of the dimethylaniline (0.01 M) in dry chloroform (30 mL) was added dropwise. The resulting red solution was refluxed for 18 h and the solvent was removed, the residue basified and then extracted with chloroform. The chloroform layer was dried, evaporated and the residue purified by silica gel chromatography.[5]

– Diazocine **2** formation utilising 2-MFP: To 2-(methylformamido)pyridine (1.36 g, 0.01 M) was added oxalyl chloride (2 mL) with stirring in an ice-bath, with gas evolution evident. The resulting yellow mixture was stirred at room temperature for 30 min and the excess of oxalyl chloride was removed in vacuo. Under ice-bath cooling, a solution of the dimethylaniline (0.01 M) in dry chloroform (30 mL) was added dropwise. The resulting red solution was refluxed for 10 h and the solvent was removed. The residue was basified and extracted with chloroform and the chloroform layer dried, evaporated and the residue purified by silica gel chromatography.[6]

In conclusion, we have shown that the VR derived from 2-(methylformamido)pyridine and oxalyl chloride formylates 4-substituted dimethylanilines to give benzopyrido[1,5]diazocines, while the 4-isomer under the same conditions yields 5-substituted *N*-methylisatins.

Acknowledgements

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2. (a) Meth-Cohn, O.; Taylor, D. L. *J. Chem. Soc., Chem. Commun.* **1995**, 1463–1464; (b) Cheng, Y.; Meth-Cohn, O. *Tetrahedron Lett.* **1996**, *37*, 2679–2682; (c) Meth-Cohn, O. *Adv Het. Chem.* **1996**, *65*, 1–39; (d) Cheng, Y.; Meth-Cohn, O.; Taylor, D. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1257–1262.
3. From Aldrich; compound 23654-3.

4. The corresponding dipyrido[2,3-*b*;2′,3′-*j*][1,5]diazocine is known as its 5,11-dione. See: Seide, K. *Chem. Ber.* **1924**, *57*, 1807–1812, and references cited therein.
5. The isatins are all known and mps together with ^{1}H and ^{13}C NMR spectroscopy are in accord with our own previous data; see Ref. 1c.
6. All the products gave correct CHN analysis data. Some properties of the diazocines **2** are: Mps: **2**, X=Me, 107–109°C; X=F, 115–117°C; X=Cl, 125–127°C; X=Br, 124–126°C. ^{1}H NMR ($CDCl_3$): **2**, X=Me: 8.11 (1H, dd, *J*=4.8 and 1.8), 7.31 (1H, dd, *J*=7.2 and 1.8), 7.02 (1H, dd, *J*=8.0 and 2.0), 6.96 (1H, d, *J*=2.0), 6.76 (1H, d, *J*=8.0), 6.60 (1H, dd, *J*=7.0 and 4.8), 3.90–4.50 (4H, br, 2×NCH_2), 3.03 (3H, s, NMe), 2.77 (3H, s, NMe), 2.29 (3H, s, ArMe). ^{13}C NMR ($CDCl_3$): **2**, X=Me: 159.6, 147.9, 146.1, 138.9, 132.1, 128.7, 127.2, 125.6, 119.6, 115,4, 112.5, 58.1, 56.6, 38.9, 37.1, 20.1. MS **2**, X=Me: *m/z* 253 (100%, M^+), 238 (87%). ^{1}H NMR ($CDCl_3$): **2**, X=F: 8.11 (1H, dd, *J*=4.8 and 1.6), 7.32 (1H, dd, *J*=7.0 and 1.6), 6.73–6.94 (3H, m), 6.62 (1H, dd, *J*=7.4 and 5.2), 4.36 (2H, s, NCH_2), 4.25 (2H, s, NCH_2), 3.04 (3H, s, NMe), 2.74 (3H, s, NMe). ^{13}C NMR ($CDCl_3$): **2**, X=F: 159.8, 157.6, 154.1, 146.7, 146.4, 139.2, 127.5, 119.5, 118.0, 117.6, 114.6, 114.3, 113.0, 58.2, 56.5, 39.3, 37.2. MS **2**, X=F: *m/z* 257 (100%, M^+), 242 (80%). ^{1}H NMR ($CDCl_3$): **2**, X=Cl: 8.11 (1H, dd, *J*=5.0 and 1.8), 7.31 (1H, dd, *J*=7.4 and 1.8), 7.08–7.16 (2H, m), 6.74 (1H, d, *J*=8.6), 6.61 (1H, dd, *J*=7.0 and 4.8), 4.10–4.50 (4H, br, 2×NCH_2), 3.02 (3H, s, NMe), 2.76 (3H, s, NMe). ^{13}C NMR ($CDCl_3$): **2**, X=Cl: 159.6, 148.8, 146.1, 139.2, 131.2, 128.0, 127.2, 122.6, 119.0, 112.9, 58.0, 56.4, 38.9, 37.1. MS **2**, X=Cl: *m/z* 273/275 (100%, M^+), 258/260 (80%). ^{1}H NMR ($CDCl_3$): **2**, X=Br: 8.10 (1H, dd, *J*=4.8 and 1.6), 7.23–7.32 (3H, m), 6.68 (1H, d, *J*=8.2), 6.60 (1H, dd, *J*=7.4 and 4.6), 4.10–4.50 (4H, br, 2×NCH_2), 3.02 (3H, s, NMe), 2.75 (3H, s, NMe). ^{13}C NMR ($CDCl_3$): **2**, X=Br: 159.6, 149.2, 146.5, 139.2, 134.0, 131.0, 127.6, 119.0, 116.8, 112.9, 109.8, 58.0, 56.4, 38.9, 37.2. MS **2**, X=Br: *m/z* 317/319 (70%, M^+), 302/304 (47%).