Heterocycles; CCI. A Novel Synthesis of Heterocyclic Thioformylamines

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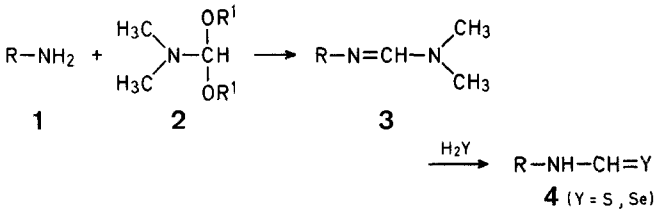
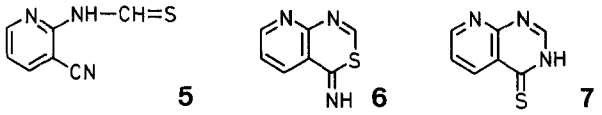
N-Formyl derivatives of amines, in general, are well known and easily prepared. Their sulfur analogs, thioformylamines, are much less known, although the high reactivity of the thioformyl group[1] is diminished when it is attached to a neighbouring heteroatom as, for example, in a thioformylamino function. The greater stability is mainly due to increased polarization of the thiocarbonyl group and delocalization of the charge to the neighbouring heteroatom.

So far, several methods exist for the preparation of substituted thioformylamines, one among them from amines, chloroform, and hydrogen sulfide in the presence of alkali. Here, apparently a dichlorocarbene is involved as intermediate[2]. Thiocarboxylic acids react with isocyanides to give *N*-thioformyl-*N*-acylamines and, with esters of phosphorus dithioacids, *N*-thioformyl-*N*-phosphoramides are formed in a similar manner[3]. Some other examples involve reaction between the corresponding formylamino compound and phosphorus pentasulfide[4,5] or the dimer of *p*-methoxyphenylthionophosphine sulfide[6], the reaction between the corresponding isocyanide and hydrogen sulfide[7], or reaction between thioformic acid *O*-esters and amines[8]. Since thioformylamines are useful as efficient thiocarbamoylation reagents[8,9] and since heterocyclic thioformylamines can be employed as useful synthons, an efficient synthetic procedure was desirable.

We now report a simple synthesis of thioformylamines and their selenium analogs **4**. The corresponding *N,N*-dimethylaminomethylenamino compounds **3**, obtained from the corresponding amine **1** and dimethylformamide dialkyl acetals[10-13] (**2**), react smoothly in aqueous alcohol or acetone solution with hydrogen sulfide or selenide to give the desired products **4** (Table).



In non-aqueous solvents, the yields were rather low or some isocyanides were formed and, from *N,N*-dimethylaminomethylenaniline (**3**; R = C_6H_5), aniline was generated. 2-(*N,N*-Dimethylaminomethylenamino)-3-cyanopyridine afforded, on reaction with hydrogen sulfide, a product which gave a molecular ion peak in the mass spectrum at *m/e* = 163 for which theoretically three structures can be written, i.e. **5**, **6**, or **7**.



Since compounds of the type **6** easily rearrange to **7**[14], structure **6** is the least probable. The I.R. spectrum of the product showed a typical CN absorption band and, on the other hand, compound **7** could be prepared from the starting compound and hydrogen sulfide in alkaline solution and was identical with an authentic specimen[15]. In this manner, in the absence of a base, compound **5** is formed, but, in the presence of alkali, the cyclic product **7** is obtained after treatment with hydrogen sulfide.

The thioformylamino can be converted into a hydroxyiminomethylenamino group with hydroxylamine. For example, 2-thioformylaminopyridine reacted at room temperature with an aqueous solution of hydroxylamine hydrochloride to give 2-hydroxyiminomethylenaminopyridine[16] in 66% yield.

Although there are several existing methods for the preparation of thioamides and the recently reported use of the dimer of *p*-methoxyphenylthionophosphine sulfide as sulfurization reagent gives the products in high yield[6], our method possesses several attractive features in addition to its simplicity and convenience. Previously, we have shown that sulfurization of heterocycles may give, in addition to the anticipated thioamides, also products of cyclization or sulfurization of the heterocycle[17]. The new method has the advantage that it can be easily applied to compounds containing additional, sensitive functional groups (CO, CN, etc.), as shown in the case of selective formation of compound **5**, and is in particular suitable in the heterocyclic series. It can be performed under mild conditions in short times and can be used for the preparation of the selenium analogs.

N,N-Dimethylaminomethylenaminoarenes or -heteroarenes 3 (R = aryl or heteroaryl):

The starting formamidines **3** were obtained either as described in the literature[10-13] or as follows.

A mixture of amine **1** (0.01–0.02 mol), dimethylformamide dimethyl acetal (**2**; R' = CH_3; 10% excess), and toluene or dimethylformamide (5–10 ml) is heated under reflux for 3 h. Upon cooling, the separated product is filtered or, alternatively, the reaction mixture is evaporated in vacuo and the residue crystallized or distilled in vacuo.

Compound **3** (R = 4,6-dimethyl-2-pyrimidyl); yield: 56%; m.p. 71 °C (distilled at 140 °C/1.5 torr and then crystallized from hexane).

$C_9H_{14}N_4$	calc.	C 60.65	H 7.92	N 31.44
(178.2)	found	60.84	7.99	31.66

M.S.: *m/e* = 178 (M^+).

Compound **3** (R = C_6H_5); yield: 92%; b.p. 87 °C/1.5 torr (*Lit.*[18], b.p. 75–76 °C/0.2 torr).

$C_9H_{12}N_2$	calc.	C 72.94	H 8.16	N 18.90
(148.2)	found	72.83	8.30	19.12

0039-7881/81/0432-0299 $ 03.00

Table. Thio- and Selenoformylaminoarenes and -heteroarenes **4**

Product No.	R	Y	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a] or Lit. m.p. [°C]	M.S *m/e* (M^+)
4a	C_6H_5	S	88[b]	139–141° (water)	138°[7]	137
4b	4-O_2N—C_6H_4	S	90	225° (ethanol/water)	$C_7H_6N_2O_2$ (182.1)	182
4c	2-pyridyl	S	86[c]	168–169° (ethanol/water)	164–165°[5]	138
4d	2-pyrimidyl	S	84	229° (ethanol/water)	$C_5H_5N_3S$ (139.1)	139
4e	1,2,4-triazin-2-yl	S	80	145° (DME/*n*-hexane)	$C_4H_4N_4S$ (140.1)	140
4f	4,6-dimethyl-2-pyrimidyl	S	79	135–137° (ethanol/water)	$C_7H_9N_3S$ (167.2)	167
4g	1,2,4-triazol-3-yl	S	37	295° (dec) (ethanol/water)	$C_3H_4N_4S$ (128.1)	128
4h	benzothiazol-2-yl	S	34	212–215° (ethanol/water)	$C_8H_6N_2S_2$ (194.1)	194
4i	C_6H_5	Se	38	133° (*n*-heptane)	C_7H_7NSe (184.1)	184
4j	2-pyridyl	Se	55	135° (*n*-heptane)	$C_6H_6N_2Se$ (185.1)	185
4k	3-cyano-2-pyridyl	Se	12	197° (ethanol/water)	$C_7H_5N_3Se$ (210.1)	210
4l	4,6-dimethyl-2-pyrimidyl	Se	79	181° (*n*-heptane)	$C_7H_9N_3Se$ (214.1)	214
5	3-cyano-2-pyridyl	S	76	125–126° (*n*-propanol)	$C_7H_5N_3S$ (163.1)	163

[a] Satisfactory microanalyses obtained: C ±0.27, H ±0.28, N ±0.28.
[b] Previously obtained[7] in 10% yield from phenyl isocyanide and hydrogen sulfide.
[c] Previously obtained[5] in 17% yield from the formylamino derivative and phosphorus pentasulfide.

Thio- or Selenoformylaminoarenes or -heteroarenes 4 (R = aryl or heteroaryl, Y = S or Se); General Procedure:

Into a solution of the *N,N*-dimethylaminomethylenamino derivative **3** (0.01–0.02 mol) in 60% aqueous ethanol or acetone (5–10 ml; the latter is used exclusively for the synthesis of seleno analogs) hydrogen sulfide or selenide is introduced. The precipitated product is filtered and crystallized from an appropriate solvent (Table).

2-Hydroxyiminomethylenaminopyridine:

A solution of 2-thioformylaminopyridine (**4**; R = 2-pyridyl, Y = S; 0.276 g) and hydroxylamine hydrochloride (0.24 g) in methanol (5 ml) is left at room temperature for 3 h. The reaction mixture is evaporated in vacuo to dryness, the residue is dissolved in water (3 ml), the solution is neutralized with sodium carbonate solution, and extracted with chloroform (2 × 10 ml). The solvent is evaporated in vacuo, the residue is dissolved in ethyl acetate (~5 ml), and the product precipitated by addition of hexane (10 ml); yield: 0.14 g (51%). It is crystallized from aqueous ethanol; m.p. 141 °C (Lit.[16], m.p. 140–141 °C); m.m.p. with authentic sample[16]: 141 °C.

Received: August 29, 1980
(Revised form: November 21, 1980)

[1] E. Campaigne, *Chem. Rev.* **39**, 1 (1946).
[2] W. Walter, G. Maerten, *Justus Liebigs Ann. Chem.* **669**, 66 (1963).
[3] J. P. Chupp, K. L. Leschinsky, *J. Org. Chem.* **40**, 66 (1975).
[4] A. W. Hofmann, *Ber. Dtsch. Chem. Ges.* **11**, 338 (1878).
[5] W. L. F. Armarego, *J. Chem. Soc.* **1965**, 2778.
[6] S. Scheibye, B. S. Pedersen, S. O. Lawesson, *Bull. Soc. Chim. Belg.* **87**, 229 (1978).
[7] A. W. Hofmann, *Ber. Dtsch. Chem. Ges.* **10**, 1095 (1877).
[8] D. Seebach, W. Lubosch, D. Enders, *Chem. Ber.* **109**, 1309 (1979).
[9] D. Seebach, W. Lubosch, *Angew. Chem.* **88**, 339 (1976); *Angew. Chem. Int. Ed. Engl.* **15**, 313 (1976).
[10] M. Zupan, V. Pirc, A. Pollak, B. Stanovnik, M. Tišler, *J. Heterocycl. Chem.* **11**, 525 (1974).
[11] M. Drobnič-Košorok, S. Polanc, B. Stanovnik, M. Tišler, B. Verček, *J. Heterocycl. Chem.* **15**, 1105 (1978).
[12] H. Bredereck, F. Effenberger, A. Hofmann, *Chem. Ber.* **97**, 61 (1964).
[13] R. Richter, H. Ulrich, *Chem. Ber.* **103**, 3525 (1970).
[14] E. C. Taylor, S. Vromen, A. McKillop, R. V. Ravindranathan, *Angew. Chem.* **78**, 332 (1966); *Angew. Chem. Int. Ed. Engl.* **5**, 308 (1966).
[15] R. K. Robins, G. H. Hitchings, *J. Am. Chem. Soc.* **77**, 2256 (1955).
[16] S. Polanc, B. Verček, B. Šek, B. Stanovnik, M. Tišler, *J. Org. Chem.* **39**, 2143 (1974).
[17] L. Kramberger, P. Lorenčak, S. Polanc, B. Verček, B. Stanovnik, M. Tišler, F. Považanec, *J. Heterocycl. Chem.* **12**, 337 (1975).
[18] N. Steiger, *U. S. Patent* 3135755 (1961), Hoffmann-La Roche; *C. A.* **65**, 7094 (1966).