A New Synthesis of Monothiodiacylamines

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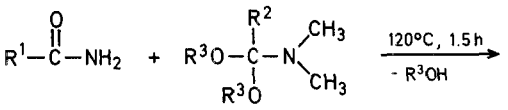
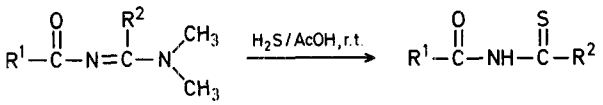
Recently, we reported the reaction of N^2-acyl-N^1,N^1-dimethylamidines **3** with nucleophiles such as water[1], ethyl carbazate[2], hydroxylamine[2], and hydrazines[2] in acetic acid. We now report the extension of it to a new synthesis of monothiodiacylamines.

N^2-Acyl-N^1,N^1-dimethylamidines **3** were prepared in excellent yields by reactions of amides **1** with *N*,*N*-dimethylformamide dimethyl acetal (**2**; $R^2 = H$, $R^3 = CH_3$), *N*,*N*-dimethylacetamide dimethyl acetal (**2**; $R^2 = R^3 = CH_3$) or *N*,*N*-dimethylbenzamide diethyl acetal[3] (**2**; $R^2 = C_6H_5$, $R^3 = C_2H_5$). The acylamidines **3** then reacted with hydrogen sulfide in acetic acid to give monothiodiacylamines **4** in almost quantitative yield (Table).



1 **2**



3 **4**

Four methods for the synthesis of monothiodiacylamines **4** have been reported in the literature. They are respectively: (A) acylation of thioamides[4-7]; (B) addition of a Grignard reagent to benzoyl isothiocyanate[4]; (C) reaction of benzoyl isothiocyanate with benzene, toluene or *p*-xylene in the presence of aluminum chloride[5]; (D) reaction of a thioamide with the corresponding nitrile in the presence of hydrogen chloride, followed by hydrolysis of the resulting thioacylamidine[4]. Of these methods, Method A which provides monothiodialkanoylamines and monothioalkanoylaroylamines in

Table. Monothiodiacylamines **4a–k** prepared

Product No.	R^1	R^2	(R^3)	Yield [%] this work	Yield [%] reported	m.p. [°C]	Molecular Formula[a] or Lit. m.p. [°C]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
4a	C_6H_5	H	(CH_3)	90	–	122–124°	C_8H_7NOS (165.2)	7.3–7.8 (m, 3H); 8.0–8.3 (m, 2H); 10.45 (d, J = 11 Hz, 1H); 12.75 (br. s, 1H)[b]
4b	4-H_3CO—C_6H_4	H	(CH_3)	95	–	139–140°	$C_9H_9NO_2S$ (195.2)	3.91 (s, 3H); 7.05 (d, J = 9 Hz, 2H); 7.95 (d, J = 9 Hz, 2H); 10.39 (s, 1H); 12.54 (s, 1H)
4c	4-Br—C_6H_4	H	(CH_3)	97	–	180–182°	C_8H_6BrNOS (244.1)	7.65 (d, J = 9 Hz, 2H); 8.05 (d, J = 9 Hz, 2H); 10.45 (d, J = 11 Hz, 1H); 12.45 (br. s, 1H)[b]
4d	C_6H_5	CH_3	(CH_3)	90	20 (A)[4], 31 (B)[4]	81–78°[4]	76–78°[4]	3.10 (s, 3H); 7.3–7.6 (m, 3H); 7.7–8.0 (m, 2H); 10.05 (br. s, 1H)
4e	4-H_3CO—C_6H_4	CH_3	(CH_3)	97	–	128–130°	$C_{10}H_{11}NO_2S$ (209.3)	3.10 (s, 3H); 3.91 (s, 3H); 7.00 (d, J = 9 Hz, 2H); 7.88 (d, J = 9 Hz, 2H); 10.04 (br. s, 1H)
4f	4-Cl—C_6H_4	CH_3	(CH_3)	93	27 (A)[7]	101–103°	100.5°[7]	2.95 (s, 3H); 7.62 (d, J = 9 Hz, 2H); 7.97 (d, J = 9 Hz, 2H); 12.42 (br. s, 1H)[c]
4g	t-C_4H_9	CH_3	(CH_3)	73	52 (A)[4]	55–57°	60–71°[4]	1.27 (s, 9H); 3.00 (s, 3H); 9.50 (br. s, 1H)
4h	C_6H_5	C_6H_5	(C_2H_5)	91	45 (C)[5], 71 (D)[4]	99–100°	117.5–118.5°[5], 117–119°[4]	7.1–8.3 (m, 10H); 9.85 (br. s, 1H)
4i	4-H_3CO—C_6H_4	C_6H_5	(C_2H_5)	91	0 (A)[5]	138–140°	136–137°[5]	3.88 (s, 3H); 7.00 (d, J = 9 Hz, 2H); 7.2–7.8 (m, 5H); 7.90 (d, J = 9 Hz, 2H); 9.90 (br. s, 1H)
4j	4-Cl—C_6H_5	C_6H_5	(C_2H_5)	93	18 (A)[5]	160–161°	157–158.5°[5]	7.2–8.0 (m, 9H); 9.90 (br. s, 1H)
4k	CH_3	C_6H_5	(C_2H_5)	90	38 (A)[4]	103–105°	104–106°[4]	2.50 (s, 3H); 7.1–7.9 (m, 5H); 9.78 (br. s, 1H)

[a] The microanalyses were in satisfactory agreement with the calculated values: (C ±0.4, H ±0.3, N ±0.3, S ±0.3, Hal ±0.3).
[b] $CDCl_3$/DMSO-d_6 solution.
[c] DMSO-d_6 solution.

good yields (21–97%)[4–7], is most frequently employed. However, it gives monothiodiaroylamines in poor yields (0–32%)[5,8], particularly the one from the reaction of thiobenzamide with *p*-anisoyl chloride. As is evident from the Table, our method provides a most general and efficient synthesis of monothiodiacylamines, which are useful as reaction intermediates[9,10].

4-Bromo-*N*-(thioxomethyl)-benzamide (4c); Typical Procedure for 4a–g:

A solution of 4-bromobenzamide (10.0 g, 0.050 mol) in *N,N*-dimethylformamide dimethyl acetal (20 ml, 0.15 mol) is stirred at 120 °C for 1.5 h, during which time some methanol is formed and collected through a reflux condenser. After cooling, the solution deposits *4-bromo-*N*-(dimethylaminomethylene)-benzamide* as colourless crystals; yield: 11.2 g (88%); m.p. 105–107 °C.

Hydrogen sulfide is bubbled into acetic acid (100 ml) at 20 °C for 5 min. To the hydrogen sulfide solution in acetic acid is added 4-bromo-*N*-(dimethylaminomethylene)-benzamide (11.2 g). The mixture is stirred and the introduction of hydrogen sulfide is continued for another 10 min. After standing at room temperature for another 10 min and being diluted with water (100 ml), the solution deposits **4c** as yellow crystals; yield: 10.5 g (97%); m.p. 180–182 °C. Analytical and spectral data are given in the Table.

***N*-[(Phenylthioxo)-methyl]benzamide (4k); Typical Procedure for 4h–4k:**

A suspension of benzamide (3.63 g, 0.030 mol) in *N,N*-dimethylbenzamide diethyl acetal[3] (7.36 g, 0.033 mol) is stirred at 120 °C for 1 h, during which time some ethanol is formed and collected through a reflux condenser. After removal of the volatile materials at 120 °C under reduced pressure, *N-[(dimethylamino)-phenylmethylene]benzamide* is obtained as a yellow oil; yield: 7.76 g (103%).

Hydrogen sulfide is bubbled into acetic acid (80 ml) at 20 °C for 5 min. The hydrogen sulfide solution is then poured into the round-bottomed flask containing *N*-[(dimethylamino)-phenylmethylene]benzamide (7.76 g). The mixture is stirred and the introduction of hydrogen sulfide is continued for another 10 min. After standing at room temperature for another 20 min and being diluted with water (300 ml), the solution deposites **4h** as bright orange crystals; yield: 6.6 g (91%); m.p. 98–100 °C. The product may be recrystallized from a mixture of chloroform and cyclohexane. Spectral data are given in the Table.

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