An Extension of the Willgerodt-Kindler Reaction

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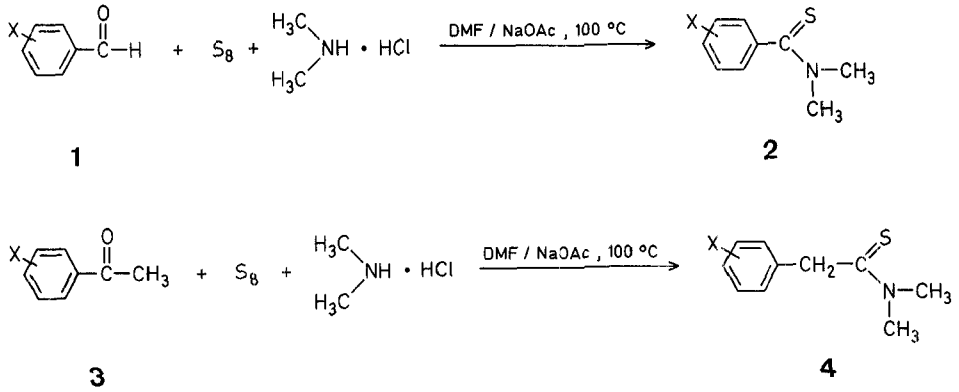
The most useful methods for the preparation of thiocarboxamides[1] are

(a) the reaction of amides with phosphorus pentasulfide[2] or Lawesson reagent[11];
(b) the Willgerodt-Kindler reaction[3];
(c) the reaction of acyl chlorides with hydrogen sulfide[4].

Method (a) is easily carried out; however, product isolation may be tedious and the reaction of primary amides may mainly afford nitriles. Method (b) involves the reaction of aldehydes, ketones, or other carbonyl compounds with equimolecular amounts of sulfur and a dry amine. While the reaction with high-boiling amines can be performed in conventional glass equipment, autoclaves or sealed tubes[6] have to be used in the case of volatile dimethylamine. To avoid these latter inconveniences, I have developed a modification of the Willgerodt-Kindler reaction by which *N,N*-dimethylthiocarboxamides of the types **2** or **4** can be prepared in good yields by reaction of aldehydes (**1**) or ketones (**3**), respectively, with dimethylammonium chloride (in place of volatile dimethylamine), sulfur, and anhydrous sodium acetate in dimethylformamide at 100 °C (steam or oil bath).



1 **2** **3** **4**

Good yields of thiocarboxamides (**2, 4**) may also be obtained using dimethyl sulfoxide or pyridine as solvents. However, dimethylformamide is preferred as solvent because it is cheaper and less toxic and can be used at considerably lower temperatures.

The sodium salts present in the reaction mixture, unreacted amine hydrochloride, and dimethylformamide (or dimethyl sulfoxide) are soluble in water and are removed when the product thiocarboxamide (**2, 4**) is filtered off. Unreacted sulfur remains with the product on the filter and is removed by crystallization of the crude product from ethanol or ethanol/water.

Of the many useful conversions of thiocarboxamides only the reaction with alkyl halides be mentioned as an example; it leads to 1-alkylthioalkaniminium salts which are valuable synthetic intermediates[5].

***N,N*-Dimethylthiocarboxamides (2, 4); General Procedure:**

The aldehyde (**1**; 0.1 mol) or ketone (**3**; 0.1 mol), dimethylamine hydrochloride (12.24 g, 0.15 mol), anhydrous sodium acetate (12.3 g, 0.15 mol), sulfur (4.8 g, 0.15 mol), and dimethylformamide (40 ml) are placed in a flask fitted with an air-cooled reflux condenser, drying tube, and stirrer. The mixture is gradually (over 30 min) heated to 100 °C (steam or oil bath) and kept at this temperature for 3 h. The dark-brown mixture is then poured into water (300 ml) and this mixture cooled in ice with stirring. The oil solidifies. The solid product is isolated by suction, washed with water, and recrystallized from ethanol to remove unreacted sulfur. Further purification (if necessary) can be achieved by recrystallization from petroleum ether.

Table. *N,N*-Dimethylthiobenzamides (**2**) and *N,N*-Dimethyl(aryl)thioacetamides (**4**) from Benzaldehydes (**1**) and Acetophenones (**3**), respectively

Educt	X	Product	Yield [%]	m.p. [°C]	Molecular formula[a] or m.p. [°C] reported
1a	H	**2a**	82	67–68°	67°[7,8]
1b	4-Cl	**2b**	92	79–80°	$C_9H_{10}ClNS$ (199.6)
1c	4-Br	**2c**	86	120–121°	$C_9H_{10}BrNS$ (244.1)
1d	4-OCH_3	**2d**	91	68–69°	68–68.5°[7]
1e	4-NO_2	**2e**	83	145–146°	145.5–146.5°[10]
1f	4-$N(CH_3)_2$	**2f**	54	106–107°	105–106°[9]
3a	H	**4a**	87	78–80°	80–81°[7,8]
3b	4-Cl	**4b**	72	69–71°	$C_{10}H_{12}ClNS$ (213.7)

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.2; H, ±0.2; N, ±0.1.

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