S,S-Bis[4,6-dimethyl-2-pyrimidinyl] Dithiocarbonate. A New Reactive Coupling Agent for the Direct Esterification of Carboxylic Acids

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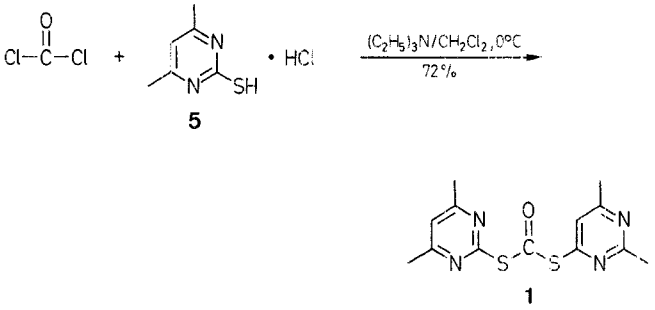
S,S-Bis[4,6-dimethyl-2-pyrimidinyl] dithiocarbonate, prepared from 4,6-dimethyl-2-pyrimidinethiol hydrochloride and phosgene in the presence of triethylamine in dichloromethane/toluene, is a new reactive coupling agent for the direct esterification of carboxylic acids with alcohols.

As part of our work on new esterification methods[1-4], we report here that *S,S*-bis[4,6-dimethyl-2-pyrimidinyl] dithiocarbonate **(1)** is a new reactive coupling agent for the direct esterification of carboxylic acids **(2)** with alcohols **(3)**.

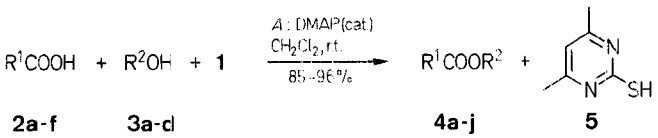
Reagent **1** was conveniently prepared in 72% yield by treatment of 4,6-dimethyl-2-pyrimidinethiol **(5)** hydrochloride with phosgene in the presence of triethylamine in dichloromethane/toluene at 0°C. It is a stable yellow crystalline solid and shows no sign of decomposition when kept at room temperature for one month.

Esterification of carboxylic acids **(2)** with equimolecular amounts of alcohols **(3)** and reagent **1** in the absence of a base or in the presence of a base such as pyridine or triethylamine in dichloromethane did not proceed to an observable extent.



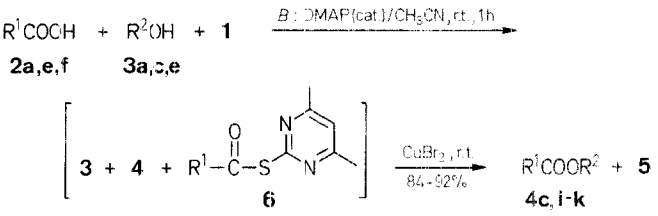
However, it was found that combination of reagent **1** with 4-dimethylaminopyridine (DMAP)[5] as catalyst was highly effective in the direct esterification of acids **2**. The reaction of caprylic acid with equimolecular amounts of benzyl alcohol and reagent **1** in the presence of 0.02 equiv and 0.1 equiv. of DMAP in dichloromethane at room temperature gave benzyl caprylate in essentially quantitative yields within 2 h and 0.3 h, respectively, indicating that reagent **1** is much more reactive than the recently developed di-2-pyridyl carbonate[3].

In general, the esterification was carried out with equimolar amounts of acids **2**, alcohols **3**, and reagent **1** using 0.1 equiv of DMAP in dichloromethane at room temperature (Method A).



DMAP = 4-dimethylaminopyridine

Method A works well with primary and secondary aliphatic acids and primary and secondary alcohols. However, with the sterically hindered pivalic acid (**2**, $R^1 = t\text{-}C_4H_9$) or with *t*-butyl alcohol (**3**, $R^2 = t\text{-}C_4H_9$), only the *S*-(2-pyrimidinyl) thiocarboxylates **6** are obtained whereas with benzoic acid a mixture of compounds **4** and **6** is obtained in a ratio of 3:1, as determined by ^{1}H-NMR analysis. The *S*-(4,6-dimethyl-2-pyrimidinyl)-thiocarboxylates **6** obtained from pivalic and caprylic acid were characterized by their IR and ^{1}H-NMR-spectral data; chromatographic purification of these products was difficult due to their instability on silica gel columns.



For the above mentioned esters derived from pivalic or benzoic acid or from *t*-butyl alcohol we therefore modified the preparative procedure to a two-step, one-pot procedure which is based on our previous report[2]. Treatment of acids **2** with equimolecular amounts of alcohols **3** and reagent **1** in the presence of 0.1 equiv. of DMAP in acetonitrile at room temperature for 1 h, followed by the addition of copper(II) bromide and subsequent stirring at room temperature (Method B) gave the mentioned esters **4** in high yields.

Noteworthy features of the present method as compared with the conventional methods[6-12] are: the esterification proceeds under very mild conditions; Method A is a one-step procedure and requires only a catalytic amount of DMAP; Method B works well with sterically hindered acids and alcohols and thus complements Method A.

S,S-Bis[4,6-dimethyl-2-pyrimidinyl] Dithiocarbonate (1):
Phosgene (10 ml of a 2.5 molar solution in toluene) is added to dichloromethane (40 ml). This solution is stirred at 0°C and a solution of 4,6-dimethyl-2-pyrimidinethiol hydrochloride (**5**; 8.823 g, 50 mmol) and triethylamine (17.4 ml, 125 mmol) in dichloromethane is added dropwise. Stirring is continued for 1 h at 0°C.

Table. Esterification of Carboxylic Acids **2** with Alcohols **3** using Reagent **1**

Acid		Alcohol		Method[a]	Reaction Time	Ester		m.p. [°C] or b.p. [°C]/torr	
2	R^1	**3**	R^2		[h]	**4**	Yield [%][b]	found	reported
a	$CH_3(CH_2)_6$	**a**	$C_6H_5CH_2$	A	0.3	**a**	85	b.p. 109–112°/0.7	148°/3[13]
a		**b**	CCl_3CH_2	A	0.2	**b**	86	b.p. 89–92°/2.5	78–82°/1.65[14]
a		**c**	$(CH_3)_3C$	A	15	**c**	(87)[c]		
				B	0.5[e]	**c**	88	b.p. 55–58°/2.4	91.5°/13[18]
b	$C_6H_5CH_2$	**a**	$C_6H_5CH_2$	A	2	**d**	96	b.p. 139–142°/2	155–157°/4[15]
c	$(CH_3)_2CH$	**d**	C_2H_5	A	1.5	**e**	91	b.p. 109°/760	111°/760[16]
c		**a**	$C_6H_5CH_2$	A	2	**f**	90	b.p. 80–83°/3	76–80°/2.5[14]
d	$(C_6H_5)_2CH$	**d**	C_2H_5	A	3	**g**	85	m.p. 58°	59°[16]
d		**a**	$C_6H_5CH_2$	A	2.5	**h**	87	b.p. 196–199°/0.9	203–205°/1[17]
e	C_6H_5	**a**	$C_6H_5CH_2$	A	15	**i**	f		
				B	7[e]	**i**	84	b.p. 150–154°/2.6	323°/760[16]
f	$(CH_3)_3C$	**a**	$C_6H_5CH_2$	A	15	**j**	(87)[d]		
				B	0.3[e]	**j**	89	b.p. 73–76°/1.5	60.5°/1[19]
f		**c**	*c*-C_6H_{11}	B	0.4[e]	**k**	92	b.p. 50–52°/2.1	45–48°/1.3[2]

[a] See experimental procedures.
[b] The numbers in parentheses indicate the yields of isolated *S*-(4,6-dimethyl-2-pyrimidinyl)thiocarboxylate **6**.
[c] IR (film): $\nu = 1720\ cm^{-1}$.
^{1}H-NMR (CCl_4): $\delta = 0.94$–1.94 (m, 13H); 2.40 (s, 6H); 2.65 (t, 2H, $J = 7$ Hz); 6.90 ppm (s, 1H).
[d] IR (film): $\nu = 1720\ cm^{-1}$.
^{1}H-NMR (CCl_4): $\delta = 1.35$ (s, 9H); 2.41 (s, 6H); 6.90 ppm (s, 1H).
[e] Reaction times **6** → **4**.
[f] A 3:1 mixture of **4** and **6** was obtained according to ^{1}H-NMR analysis.

The mixture is then diluted with dichloromethane (100 ml), washed with cold 5% sodium hydrogen carbonate solution (150 ml) and with cold saturated sodium chloride solution (100 ml), and dried with magnesium sulfate. The solvent is evaporated under reduced pressure and the remaining crude product is recrystallized from petroleum ether/dichloromethane; yield: 5.51 g (72%); m.p. 95–96°C.

$C_{13}H_{14}OS_2$	calc.	C 50.96	H 4.60	N 18.29
(306.4)	found	50.66	4.35	18.03

IR (KBr): $\nu = 1730\ cm^{-1}$ (C=O).

^{1}H-NMR ($CDCl_3$): $\delta = 2.6$ (s, 12H); 7.1 ppm (s, 2H).

Alkyl Carboxylates (4); General Procedures:

Method A: *S,S*-Bis[4,6-dimethyl-2-pyrimidinyl] dithiocarbonate (**1**; 1.532 g, 5 mmol) is added to a stirred solution of the carboxylic acid **2** (5 mmol), the alcohol **3** (5 mmol), and 4-dimethylamino-pyridine (61 mg, ~0.5 mmol) in dichloromethane (15 ml) at room temperature, and stirring is continued for the time given in the Table. The mixture is then diluted with dichloromethane (30 ml), washed with 5% aqueous hydrochloric acid (20 ml), saturated sodium carbonate solution (20 ml), and saturated sodium chloride solution (20 ml), dried with magnesium sulfate, and evaporated to dryness under reduced pressure. The crude product is purified by distillation or crystallization.

Method B: *S,S*-Bis[4,6-dimethyl-2-pyrimidinyl] dithiocarbonate (**1**; 1.532 g, 5 mmol) is added to a stirred solution of the carboxylic acid **2** (5 mmol), the alcohol **3** (5 mmol), and 4-dimethylamino-pyridine (61 mg, ~0.5 mmol) in acetonitrile (15 ml) at room temperature and stirring is continued for 1 h at room temperature. Then, copper(II) bromide (1.117 g, 5 mmol) is added and stirring is continued for the time given in the Table. The mixture is then diluted with dichloromethane (40 ml), washed with saturated ammonium chloride solution (30 ml), 5% hydrochloric acid (30 ml), saturated sodium carbonate solution (50 ml), and saturated sodium chloride solution (30 ml), dried with magnesium sulfate, and evaporated to dryness under reduced pressure. The crude product is purified by distillation.

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