S- and *N*-Acyl Derivatives of 2-Mercaptobenzoxazole; New, Highly Reactive Acylating Agents for Synthesis of Amides and Esters

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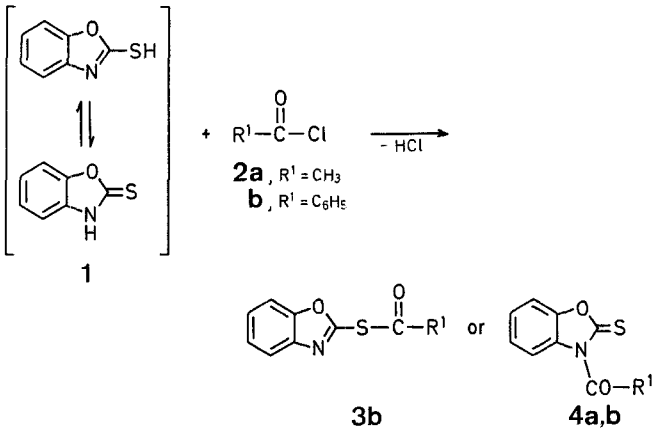
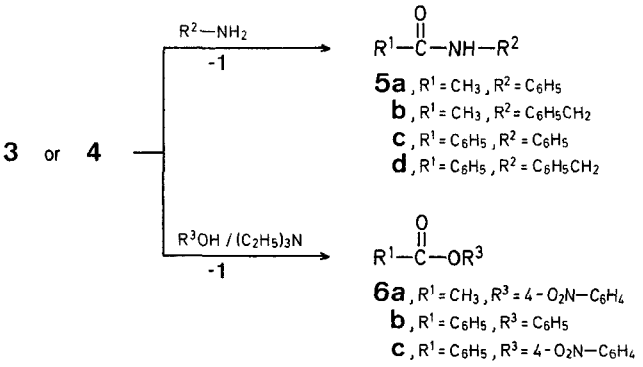
Recently, new, highly reactive acylating agents[1-6] have been extensively exploited for the synthesis of amides and esters. We have previously reported that *S*-(2-benzothiazolyl) thioesters react very rapidly with various amines to give excellent yields of the corresponding amides[7]. This result prompted us to develop further new acylating agents for the synthesis of various types of amides and esters. In this communication, we now report that the *N*- and *S*-acyl derivatives (**4** and **3**) of 2-mercaptobenzoxazole (**1**) are new, highly reactive acylating agents for amines and alcohols. Acylation of **1** might be expected to yield the *S*-(2-benzoxazolyl) thioester (**3**, *S*-acyl derivative) or the 3-acylbenzoxazoline-2-thione (**4**, *N*-acyl derivative), because of the tautomerism of **1**, as shown in Scheme **A**.



Scheme **A**

The thermodynamically more stable isomer **4**[8,9,10] was readily obtained under a variety of reaction conditions. With a careful control of the reaction conditions, we have successfully synthesized the new compound **3b** in tetrahydrofuran. The structure of **3b** was assigned on the basis of I.R. and microanalysis. The I.R. spectrum exhibited a strong thiolester carbonyl absorption at 1695 cm^{-1}, and no trace of a C=S stretching absorption was detected. Additional proof for the structure of **3b** was obtained through the thermal rearrangement of **3b** at 90 °C to the isomeric **4b**, quantitatively.

The reactions of **3** or **4** with amines were carried out in tetrahydrofuran (THF) or 1-methyl-2-pyrrolidone (NMP) at room temperature. Both **3** and **4** reacted with benzylamine and aniline to give excellent yields of the corresponding benzamides **5a–d** within 10 min. On the other hand, acylation of alcohols required the presence of a tertiary amine such as triethylamine, and the reactions with phenol in NMP proceeded to completion in 10 h at room temperature (Scheme **B**, Table 1).

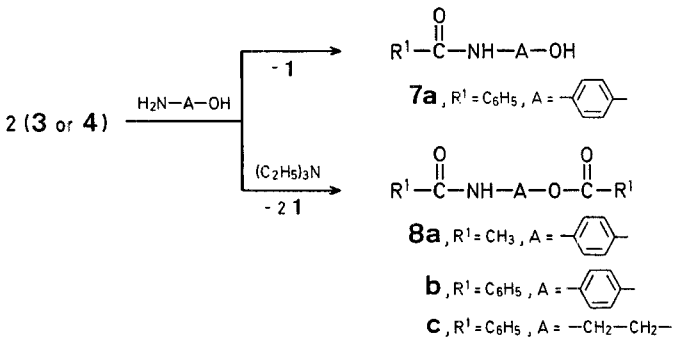


Scheme **B**

Both selective *N*-acylation and *N,O*-diacylation of amino alcohols were carried out at room temperature in the absence or presence of triethylamine (Scheme **C**, Table 2).

The high reactivity of **3** is connected with the pseudoaromatic character of benzoxazole and the electron withdrawal by the heterocyclic ring. The high reactivity of **4** is associated with the amide nitrogen electron pair and the pseudoaromaticity of the ring; the result is polarization towards nitrogen in the *N*-

0039-7881/81/1232-0991 $ 03.00



Scheme C

(COR) bond. Furthermore, the enhanced aminolysis may be explained by anchimeric assistance (intramolecular general-base catalysis). It is advantageous that compounds **3** and **4** are crystalline solids having excellent hydrolytic stability and, therefore, are handled more easily than acyl chlorides.

***S*-(2-Benzoxazolyl) Thiobenzoate (3b):**
To a cold solution (−30 °C) of 2-mercaptobenzoxazole (**1**; 15.1 g, 0.1 mol) and triethylamine (14 ml) in tetrahydrofuran (300 ml) is added dropwise a solution of benzoyl chloride (**2b**; 14 g, 0.1 mol) in tetrahydrofuran (30 ml). The solution is stirred at a temperature lower than −20 °C for 20 min and poured into ice/water (1000 ml). The precipitate is collected by filtration and dried in vacuo; yield: 23 g (90%); m.p. 83–85 °C (from cyclohexane).

$C_{14}H_9NO_2S$	calc.	C 65.87	H 3.55	N 5.48
(255.3)	found	66.0	3.8	5.5

I.R. (KBr): ν = 1695 cm^{-1} (C=O).

3-Acetylbenzoxazoline-2-thione (4a):
Compound **4a** is prepared as described above at 15 °C for 30 min; yield: 90%; m.p. 120–121 °C (from cyclohexane); (Lit.[8], m.p. 118 °C).

I.R. (KBr): ν = 1720 (C=O), 1340 cm^{-1} (C=S).

3-Benzoylbenzoxazoline-2-thione (4b):
Compound **4b** is prepared as described above using acetone as a solvent at 15 °C for 30 min; yield: 93%; m.p. 117–118 °C (from ethanol); (Lit.[8], m.p. 117 °C).

$C_{14}H_9NO_2S$	calc.	C 65.87	H 3.55	N 5.48
(255.3)	found	65.8	3.8	5.7

I.R. (KBr): ν = 1695 (C=O), 1340 cm^{-1} (C=S).

Amides 5; General Procedure:
The amine (2.5 mmol) is added to a solution of **3b** or **4** (2.5 mmol) in the solvent (5 ml). The solution is stirred at 15 °C for 10 min, and then poured into 1% aqueous sodium hydrogen carbonate (100 ml). The precipitate formed is collected and dried (Table 1).

Esters 6; General Procedure:
A solution of **3b** or **4** (2.5 mmol), the alcohol (2.5 mmol), and triethylamine (2.5 mmol) in the solvent (5 ml) is stirred at 15 °C for 24 h. The product is isolated by pouring the solution into 1% cold aqueous so-

Table 1. Reaction of **3** or **4** with Amines or Alcohols (Scheme **B**)

Acylating Agent	Amine or Alcohol	Conditions: Solvent	Acid Acceptor	Time	Product	Yield [%]	m.p. [°C] found	m.p. [°C] reported
3b	C_6H_5—NH_2	THF	—	10 min	**5c**	95	163–164°	162° [11]
3b	$C_6H_5CH_2$—NH_2	THF	—	10 min	**5d**	81	105–106°	105° [12]
4a	C_6H_5—NH_2	THF	—	10 min	**5a**	98	115–117°	115–116° [13]
4a	$C_6H_5CH_2$—NH_2	THF	—	10 min	**5b**	95	61–62°	61° [14]
4b	C_6H_5—NH_2	THF	—	10 min	**5c**	92		
4b	$C_6H_5CH_2$—NH_2	THF	—	10 min	**5d**	82		
3b	C_6H_5—OH	THF	$(C_2H_5)_3N$	24 h	**6b**	93	70–71°	70° [15]
3b	C_6H_5—OH	NMP	$(C_2H_5)_3N$	10 h	**6b**	82		
4b	C_6H_5—OH	THF	$(C_2H_5)_3N$	24 h	**6b**	98		
4b	C_6H_5—OH	NMP	$(C_2H_5)_3N$	10 h	**6b**	86		
4a	*p*-O_2N—C_6H_4—OH	NMP	$(C_2H_5)_3N$	2 d	**6a**	82	79–80°	81° [16]
3b	*p*-O_2N—$C_6H_4CH_2$—OH	NMP	$(C_2H_5)_3N$	3 d	**6c**	95	90–91°	89° [17]
4b	*p*-O_2N—$C_6H_4CH_2$—OH	NMP	$(C_2H_5)_3N$	3 d	**6c**	94		

Table 2. Reactions of **3** or **4** with Amino Alcohols (Scheme **C**)

Acylating Agent	Amino Alcohol	Solvent	Acid Acceptor	Time	Product	Yield [%]	m.p. [°C] found	m.p. [°C] reported
3b	*p*-H_2N—C_6H_4—OH	THF	—	20 min	**7a**	88	219–221°	216–217° [18]
3b	*p*-H_2N—C_6H_4—OH	NMP	—	20 min	**7a**	95		
4b	*p*-H_2N—C_6H_4—OH	THF	—	20 min	**7a**	86		
4b	*p*-H_2N—C_6H_4—OH	NMP	—	20 min	**7a**	97		
3b	H_2N—$(CH_2)_2$—OH	NMP	$(C_2H_5)_3N$	3 d	**8c**	87	91–92°	88° [19]
4b	H_2N—$(CH_2)_2$—OH	NMP	$(C_2H_5)_3N$	3 d	**8c**	85		
3b	*p*-H_2N—C_6H_4—OH	THF	$(C_2H_5)_3N$	24 h	**8b**[a]	86	242–243°	235° [20]
3b	*p*-H_2N—C_6H_4—OH	NMP	$(C_2H_5)_3N$	10 h	**8b**	84		
4a	*p*-H_2N—C_6H_4—OH	THF	$(C_2H_5)_3N$	24 h	**8a**	80	150–151°	152° [21]
4b	*p*-H_2N—C_6H_4—OH	THF	$(C_2H_5)_3N$	24 h	**8b**	92		
4b	*p*-H_2N—C_6H_4—OH	NMP	$(C_2H_5)_3N$	10 h	**8b**	84		

[a] $C_{20}H_{15}NO$ (317.3): calc. C 75.69, H 4.76, N 4.41; found 75.7, 4.9, 4.4

dium hydrogen carbonate (100 ml). The precipitate is collected and dried (Table 1).

Amide Esters 8; General Procedure:
A mixture of **3b** or **4** (5 mmol) and the amino alcohol (2.5 mmol) in the solvent (5 ml) is stirred at 15 °C for 10 min and then triethylamine (2.5 mmol) is added. Stirring is continued for 24 h. The reaction mixture is worked up as described above (Table 2). Hydroxyamide **7a** is obtained when triethylamine is omitted.

Received: March 20, 1981
(Revised form: June 1, 1981)

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0039-7881/81/1232-0993 $ 03.00