S-Acyl and *N*-Acyl Derivatives of Benzothiazole-2-thiol: An Example of Acyl Group Rearrangement

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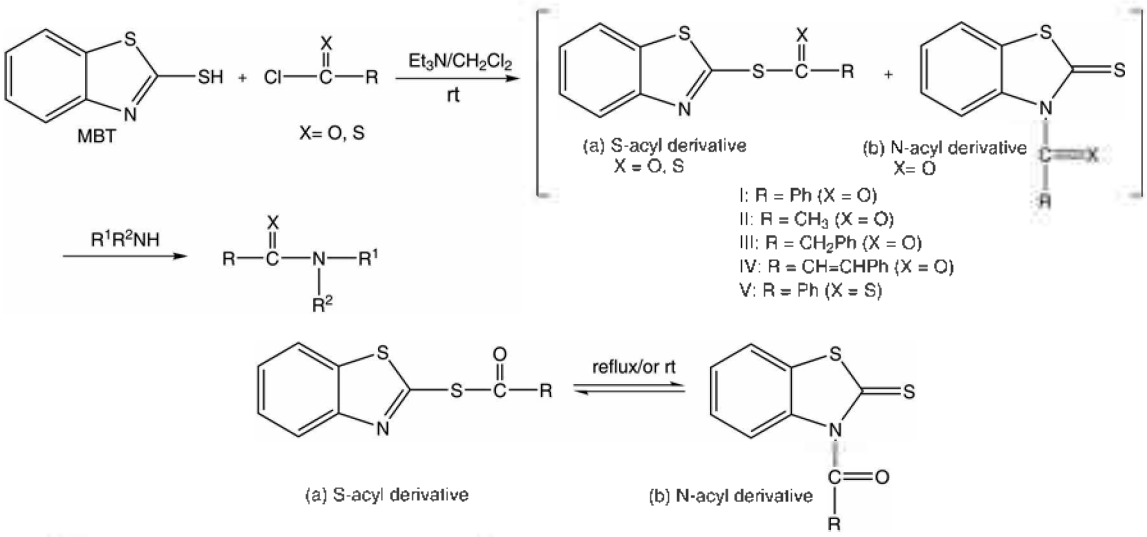
Amides, thioamides and carbamates are versatile intermediates in the synthesis of natural products.[1] Among the most well-known procedures to make amides and thioamides are the reactions between amines and acyl halides, or between amines and thioacyl halides. Acyl halides and thioacyl halides are, however, not easy to handle in general or available in stock most of the time. For instance, thiobenzoyl chloride, a purple liquid collection and purification *via* vaccum distillation, undergoes decomposition very easily in the presence of atmospheric oxygen at 78 °C or above.[2] Thus, effective acylating reagents or acylating intermediates such as acylimidazole,[3] a reaction product of trisdialkylaminoborane and carboxylic acid,[4] acyloxyborane,[5] 1,1'-[carbonyldioxy]dibenzotriazole convertible into 1-acyloxybenzotriazole,[6] and benzotriazole-1-yl diethyl phosphate[7] have been carefully developed for the syntheses of amides. Moreover, the utility of thioacylimide explored by Geordeler,[8] the usage of *N*-thiobenzoylbenztriazole, the reaction between diimidazole sulfide and dithiobenzoic acid reported by Walter,[9] and Lawesson's reagent[10] played a key role for syntheses of thioamides. As for using leaving groups containing sulfur for the preparation of amides, 3-acylthiazolidine-2-thione by Y. Nagao,[11] and utility of 2-mercaptobenzoxazole (MBO) by Ueda have been previously explored.[12]

In a previous paper,[13] we have reported the syntheses for a variety of phenylamides, thiobenzamides and various carbamates by adopting *S*-benzoyl derivative of benzothiazole-2-thiol, so called 2-mercaptobenzothiazole (MBT) as a good leaving group moiety. Here, we wish to report the phenomenon of the acyl group rearrangement between derivatives of MBT, the quantitative isolation of each derivative of MBT, and their chemical properties.[14] Both acyl derivatives of MBT have demonstrated that they can be used in the facile syntheses of other alkylamides (alkyl = methyl, benzyl, cinnamyl) and benzylthioamide.

Although Ueda observed the formation of *S*-acyl derivative and *N*-acyl derivative of MBO as result of the acyl group rearragement during the reaction, there was no mention of the ratio distribution of derivatives or mechanistic details.[12] For a comparison to *S*-acyl/*N*-acyl rearrangement of MBO, Ueda also reported that the acylating reagent, derived from 1,2-benzisothiazol-3-ol and benzoyl chloride, also gives the benzoyl group rearrangement between the *O*-



Scheme 1. The formation of *S*-acyl and *N*-acyl derivatives from the reactions of MBT with acyl chloride or thioacyl chloride and their acyl migrations.

Table 1. Reactions of MBT with acyl chloride RCOCl (CH_2Cl_2/rt)

R	Ratio (*S*-acyl/*N*-acyl)	mp (°C)	Yield (%)
Ph	75/25	*S*-acyl: 130[a], *N*-acyl: 105	99 (2 spots)
CH_3	70/30	*S*-acyl: 75-76, Mixture: 43	95 (2 spots)
$PhCH_2$	70/30	*S*-acyl: 64-65, *N*-acyl: –[b]	99 (2 spots)
PhCH=CH	55/45	*S*-acyl: 139-140, *N*-acyl: 117-118	99 (2 spots)
Ph[c]	100/0	*S*-acyl: 99	99 (1 spot)

[a]See reference 13 (a). [b]The compound is separated as an oil. [c]Thiobenzoyl chloride is used with a reaction media of dimethylether.

derivative. 3-benzoyl-1.2-benzisothiazole and the *N*-derivative. *N*-benzoyl-[1.2-benzisothiazol-3(2*H*)-one].[15] At a same time Ito reported a one-pot method of synthesis for amides through rections of 2,2'-dithiobis[benzothiazole], triphenylphosphine, a carboxylic acid. and an amine.[16] However he did not isolate the intermediates, thioester derivatives.

The reaction of MBT with various acyl chlorides in the presence of Et_3N at room temperature gave the corresponding acylating reagent *S*-acyl-2-benzothiazole thioester (derivative a) along with 3-acylbenzothiazoline-2-thione (derivative b) quantitatively (Scheme 1).

Starting with either form of the MBT acyl derivative (*S*-acyl or *N*-acyl), acyl group rearrangement occurred to achieve a certain ratio of mixture under either reflux conditions or room temperature. In particular, the isolated pure solid *N*-acetyl derivative (IIb) was converted into *S*-acetyl derivative (IIa) even under vacuum storage. Moreover only *S*-acyl derivative with lower yield of 50% was obtained from the reaction in the DMF instead of methylene chloride and no presence of triethyl amine which traps HCl.

In the presence of Et_3N, both derivatives formed quantitatively. Interestingly, the ratio of *S*-acyl and *N*-acyl derivatives was very similar regardless of the R substituent of acyl group except cinnamoyl group. The fact that the *S*-acyl derivative was the dominant species indicates that sulfur containing anion is more stable and stronger nucleophile owing to *d*-orital delocalization of sulphur compared to the nucleophilic properties of the nitrogen containing anion (Table 1).[17]

For example. The spectrum of *S*-benzoyl-2-benzothiazole thioester (**Ia**) shows a signal at 1400-1500 cm^{-1} assigned as the C=N strechand a signal at 1700 cm^{-1} or lower than this assigned to the C=O strech, on the other hand for the corresponding rearrangement compound 3-benzoyl-benzothiazoline-2-thione (Ib). the C=S streching signals and the C=O streching signals are at 1000-1100 cm^{-1} and 1700 cm^{-1} or higher than this. respectively. This is the opposite to the observation made by Halasa.[18] However. ^{1}H NMR pattern for **IIa** and **IIb** is accordance with Halasa's report. Four hydrogens of the *N*-acyl derivative (**IIb**) in the region of heterocyclic ring give rise to one doublet for one hydrogen and three multiplets for three hydrogens and the corresponding *S*-acyl derivative (**IIa**) leads to two doublets for each hydrogen and one multiplet for two hydrogens (Figure 1). Overall the chemical shifts assignable to heterocyclic ring hydrogens in **Ib** appear at higher field than for those in **Ia**. For additional support. in ^{13}C NMR. the 2 position of C [N=C(-S-)-S] of **Ia** has shown at δ 157.8 and that of **Ib** is δ 169.3 attributed to an anistropic effect of the C=S group. In the UV-Vis spectrum compound **Ib** shows a distinct absorption for the dithiocarbamate group [N-C(=S)-S] at 320-325 nm.[19]

Hasala reported that the only *S*-acyl derivative was obtained from the reaction of benzoyl chloride with MBT (*i.e.* **Ia**). and for the use of acetyl chloride, the formation of *N*-acyl derivative was dominant over the *S*-acyl derivative and he explained this observation probably owing to the stabilization of enegy in *N*-acyl derivative. However. we obtained a mixture of *S*-acyl and *N*-acyl derivatives with *S*-acyl derivative being the dominant form when MBT and acyl chlorides were used. Interestingly, when MBT was reacted with thiobenzoyl chloride. unlike acyl chloride case, it formed only the *S*-acyl derivative. *S*-thiobenzoyl-2-benzothiazole thioester (**Va**) which is a red crystalline solid. very stable toward hydrolytic, thermal. air oxidation and long time storable thiobenzoylation reagent. The mechanism of acyl group rearrangement between *N*-acyl and *S*-acyl derivatives can be predicted through the use of Hyper Chem (method:PM3) energy optimization which shows that the the

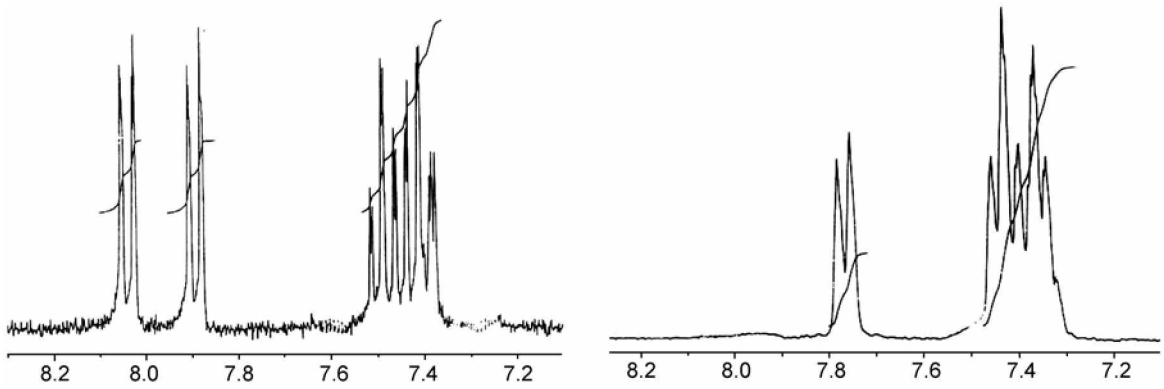
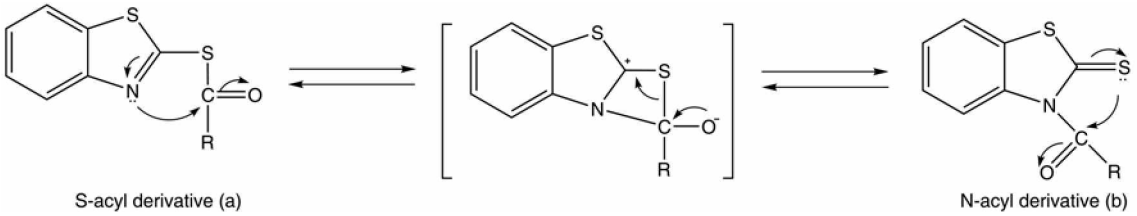


Figure 1. ^{1}H NMR spectra of *S*-acetyl derivative (**IIa**) (left) and the *N*-acetyl derivative (**IIb**) (right). Only the aromatic region reflecting the heterocyclic ring hydrogens is shown.



Scheme 2. The rearrangement of acyl group between *N*-acyl and *S*-acyl derivatives.

lone pair electrons on the N or S are positioned close enough to attack the carbonyl group carbon (Scheme 2).

The mixture of *S*-acyl derivative (**Ia-Va**) and *N*-acyl derivative (**Ib-IVb**) underwent reaction wth various amines to give amides quantitatively in very high yield. We also tried to prepare amides starting with either the pure *S*-acyl derivative or pure *N*-acyl derivative. Each pure derivative gave the same result as when a mixture was used. It is worth noting that *N*-acyl derivative takes more time to react with amines than the *S*-acyl derivative does overall. This may be attributed to the fact that bond energy of C-S (259 kJ/mol) is smaller than that of C-N (292 kJ/mol) and *N*-acyl derivative has double bond character between C and N like that of usual amide bond. In addition, the aminoalcohol, which has a hydroxyl group and amine group within one molecule, reacted with *S*-acyl/*N*-acyl derivatives cleanly, without protection of the OH group, to give the corresponding amide with hydroxyl group intact. Most cases the reaction occured at room temperature, sometimes it needs a reflux condition depending on which amine is used. The MBT was reproduced after compeletion of the reaction and was recovered after it precipitated by acidification of the aqueous solution. Alternatively, it can be easily washed out with basic aqueous solution *via* the isolation of desired product amides without further purification.

Experimental Section

The representative synthesis of *S*-benzoyl-2-benzothiazole thioester (Ia) and 3-benzoylbenzothiazoline-2-thione (Ib). To a 2-neck round bottom flask containing benzothiazole-2-thiol (8.35 g, 0.05 mol) and triethylamine (6.06 g, 0.06 mol) in methylene chloride (40 mL) were added dropwise benzoyl chloride (8.43 g, 0.06 mmol) for 20 min at room temperature. The reaction mixture was stirred for 10 min. The salt was separated under reduced pressure through vacuum filtration. The filtered solution was washed with diluted HCl solution and water (each of 3 times) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (elution solvent: benzene) to give **Ia** as a pale yellow solid (10.15 g, 75%) and **Ib** as a yellow solid (3.38 g, 25%).

Ia: m.p. 130 °C (lit. 129-131 °C), IR (KBr) 3059, 1669, 1581, 1450, 756, 648 cm^{-1}, ^1H NMR ($CDCl_3$, 300 MHz): δ 8.1-8.0 (t, 3H), 7.95 (d, J = 7.03 Hz, 1H), 7.7-7.6 (d, J = 7.40 Hz, 1H), 7.6-7.4 (m, 4H). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 186.97, 157.84, 151.69, 136.09, 135.51, 134.69, 129.14, 127.73, 126.38, 125.59, 123.03, 121.24, Mass: m/e 77, 105, 271 (M^+).

Ib: m.p. 105 °C, IR (KBr) 3057, 1726, 1597, 1454, 1053, 750, 690 cm^{-1}, ^1H NMR ($CDCl_3$, 300 MHz) δ 7.92 (d, J = 7.15 Hz, 2H), 7.75-7.65 (t, J = 7.49 Hz, 1H), 7.6-7.5 (m, 3H), 7.4-7.3 (m, 2H), 7.05-7.1 (m, 1H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 189.11, 169.32, 140.27, 135.56, 131.07, 130.70, 129.40, 129.07, 127.30, 125.39, 121.56, 112.7, Mass: m/e 77, 105, 167, 271 (M^-).

The representative rearrangement of 3-benzoylbenzothiazoline-2-thione (Ib) into *S*-benzoyl-2-benzothiazole thioester (Ia). 3-Benzoyl-benzothiazoline-2-thione (**Ib**) (1.36 g, 0.005 mol) in acetone (10 mL) in a 3-neck round bottom flask was heated at reflux under Ar atmosphere for 1 hr. After being cooled to room temperature, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: benzene) to give **Ia** as a pale yellow solid whose structure is identified by melting point and ^1H NMR spectroscopy (1.23 g, 90%).

The representative rearrangement of *S*-phenylacetyl-2-benzothiazole thioester (IIIa) into 3-phenylacetylbenzothiazoline-2-thione (IIIb). 3-Phenylacetylbenzothiazoline-2-thione (**IIIb**) (1.43 g, 0.005 mol) in toluene (10 mL) in a 3-neck round bottom flask was heated reflux under Ar atmosphere for 2 hr. After being cooled to room temperature, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent:benzene) to give **IIIb** as a yellow oil which is identified by ^1H NMR spectroscopy (0.43 g, 30%).

Synthesis of *S*-thiobenzoyl-2-benzothiazole thioester (Va). To a 2-neck round bottom flask containing 2-mercaptobenzothiazole (16.70 g, 0.1 mol) and triethylamine (12.12 g, 0.12 mol) in ether (70 mL) were added dropwise thiobenzoyl chloride (18.78 g, 0.12) in ether (30 mL). The reaction mixture was stirred for 10 min. The solution was filtered, washed with diluted HCl solution and water (each of 3 times) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by recrystallization from *n*-hexane to give a red solid (14.35 g, 50%).

Va: m.p. 99 °C, IR (KBr) 3060, 1441, 1405, 1246, 1055, 751, 684 cm^{-1}, ^1H NMR ($CDCl_3$, 300 MHz) δ 8.15 (d, J = 7.38 Hz, 1H), 8.05 (d, J = 7.16 Hz, 2H), 7.94 (d, J = 8.62 Hz, 1H), 7.6-7.4 (m, 5H). Mass: m/e 77, 108, 121, 167, 287 (M^-).

General description for the preparation of amide. To a 2-neck round bottom flask containing mixture of *S*-acetyl-2-

benzothiazole thioester (**IIa**) and 3-acethylbenzothiazoline-2-thione (**IIb**) (1.05 g, 0.005 mol) in methylene chloride (10 mL) were added dropwise aniline (0.56 g, 0.006 mmol) in methylene chloride (5 mL) for 5 min at room temperature. The compounds **IIa** and **IIb** were gone by judging from the TLC check after 10 min and 30 min of stirring, respectively. The resulting solution was washed with diluted NaOH solution and water (each of 2 times), and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by recrystallization from methanol to give a white solid, acetanilide (0.98 g, 99%). m.p.: 115 °C (lit. 115-117 °C). IR (KBr): 3295, 3061, 2928, 1664, 1556, 694 cm^{-1}.

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