# Convenient Synthesis of Amides, Esters, and Thioesters Using 2,2′-Oxalyldi(2,3-dihydro-3-oxobenzisosulfonazole)

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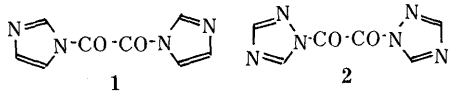
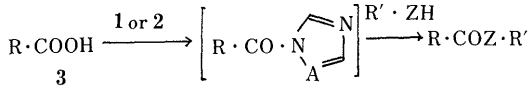
**Potassium salts (22) of various carboxylic acids readily react with 2,2′-oxalyldi(2,3-dihydro-3-oxobenzisosulfonazole) (17) to form the corresponding 2-acyl-2,3-dihydro-3-oxobenzisosulfonazoles (24) as intermediates, which undergo aminolysis, alcoholysis, and thioalcoholysis to afforded amides (5), esters (6), and thioesters (7), respectively. These findings show that 17 can be conveniently used as a condensing agent for the synthesis of carboxylic acid derivatives (5, 6 or 7).**

**Keywords** oxalyl derivative; condensing reagent; amidation; saccharin; 2-acylsaccharin; aminolysis; esterification; carboxylic acid; oxalyl derivative

As a continuation of our studies on oxalyl derivatives with interesting reactivity in synthetic organic chemistry, we have found that 1,1′-oxalyldiimidazole (**1**) and 1,1′-oxalyldi(1,2,4-triazole) (**2**) can be used as efficient and convenient reagents for the conversions of carboxylic acids (**3**) into the corresponding amides (**5**), esters (**6**), and thioesters (**7**), as shown in Chart 1.[1] Recently, Inomata *et al.* have shown that reaction of Z–Ile·OH (**9**) with Gly·OEt (**10**) using diethyl 2-(3-oxo-2,3-dihydro-1,2-benzisosulfonazolyl)phosphonate (**8**) led to the Z–Ile–Gly·OEt (**11**) in 85% yield.[2] Separately, Tokutake *et al.* later observed that treatment of Z–Phe·OH (**13**) with Gly·OEt (**10**) in the presence of 3-(succinimidoxy)-1,2-benzoisothiazole-1,1-dioxide (**12**) afforded a 75% yield of the corresponding dipeptide (**14**)[3] (Chart 2). As the result of the successful application of the 2,3-dihydro-3-oxobenzisosulfonazolyl group as a leaving group in peptide synthesis, our interest in oxalyl derivatives led us to examine the possibility that 2,2′-oxalyldi(2,3-dihydro-3-oxobenzisosulfonazole)(2,2′-oxalyldisaccharin) (**17**) may be generally effective as a condensing reagent.



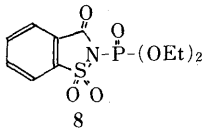
**1** **2**



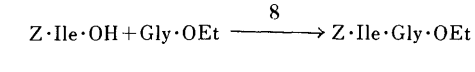
**3** **4a** : A=CH, **4b** : A=N

**5** : Z=NH, **6** : Z=O, **7** : Z=S

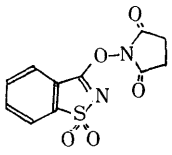
Chart 1



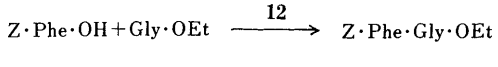
**8**



**9** **10** **11**



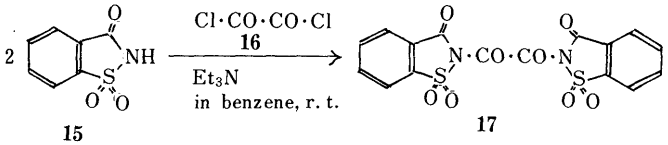
**12**



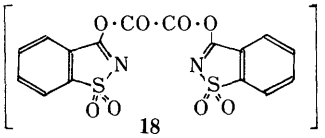
**13** **10** **14**

Chart 2

The present paper reports that the synthetically useful conversions of potassium carboxylates (**22**) into the corresponding amides (**5**), esters (**6**), and thioesters (**7**) were successfully carried out under mild conditions by using **17**. First of all, it was fortunately found that the critical reagent (**17**) could be easily prepared on a laboratory scale by the reaction of 2,3-dihydro-3-oxobenzisosulfonazole(saccharin) (**15**) in benzene with oxalyl chloride (**16**) in the presence of triethylamine at room temperature (Chart 3). Concerning the structure of the oxalyl derivative produced from the reaction of saccharin (**15**) with **16** mentioned above, we anticipated that the thermodynamically preferred *N*-isomer (**17**) and/or the kinetically controlled *O*-isomer (**18**) would be formed.[4a] The infrared (IR) spectrum of the oxalyl derivative showed characteristic carbonyl absorption bands at 1760, 1740, and 1720 $cm^{-1}$. These IR data are consistent with the spectral properties that have been thus far determined for the thermodynamically stable *N*-acyl product,[4b] and the structure of the oxalyl derivative formed from **15** with **16** was confirmed as **17** rather than **18**,



**15** **17**



**18**

Chart 3

accordingly.

Next, the synthetic utility of **17** as a condensing reagent for the preparation of amides (**5**) was studied. In our initial experiments, the reaction of benzoic acid (**3a**) in acetonitrile with 2,2′-oxalyldisaccharin (**17**) in the presence of triethylamine as a base followed by aminolysis with aniline (**25a**) gave benzanilide (**5a**) directly in 45% yield. In the course of the treatment of **3a** with **17** described above, thin layer chromatographic (TLC) monitoring revealed the presence of benzoic acid anhydride (**19**). As shown in Chart 4, a possible explanation for the unexpectedly poor yield of benzanilide (**5a**) lies in the speculation that the *N*-benzoylsaccharin (**24a**) formed from the reaction of **3a** with **17** is not accumulated in the acetonitrile solution at step 1 but is subjected to attack of unreacted benzoic acid (**3a**) as soon as **24a** is formed as a transient intermediate, to give benzoic acid anhydride (**19**), which undergoes aminolysis to form benzanilide (**5a**) in an unsatisfactory yield. Therefore, we were forced to make some alteration in the above experimental conditions. The change from the combination of benzoic acid (**3a**) and triethylamine as a base in acetonitrile to that of sodium benzoate (**21a**) in dimethylformamide (DMF), for instance, was fairly good, giving a 68% yield of **5a**. In view of encouraging results obtained with sodium benzoate (**21a**), the relative effectiveness of lithium benzoate (**20a**) and potassium benzoate (**22a**) was examined in DMF. As the result, treatment of lithium benzoate (**20a**) with aniline (**25a**) using **17** gave benzanilide (**5a**) in 63% yield. Similarly, in the case of potassium benzoate (**22a**), **5a** was afforded in 97% yield. Judging from the yields of benzanilide (**5a**), these results show that the potassium salt (**22a**) of benzoic acid is the most effective to prepare benzanilide (**5a**). Thus, the remaining condensation reaction was performed using potassium salts of carboxylic acids to give the corresponding amides (**5**). The reaction of a heteroaromatic compound, potassium furancarboxylate (**22i**), with aniline (**25a**) gave the desired amide (**5i**) in 80% yield. Moreover, we found that potassium salts (**22**) of

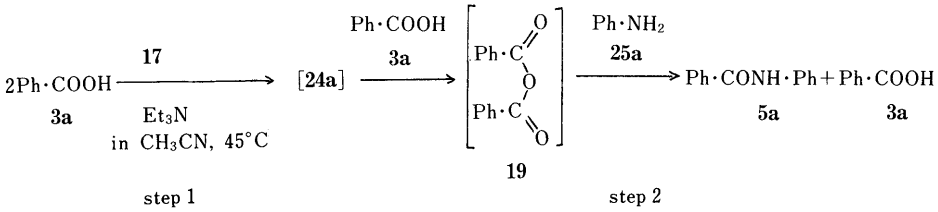



Chart 4

TABLE I. Preparation of Amides (**5**), Esters (**6**), and Thioesters (**7**) Using 2,2′-Oxalyldisaccharin (**17**)

$$\underset{\mathbf{22}}{R\cdot COOK} + \underset{\mathbf{25\text{—}27}}{HZ\cdot R'} \xrightarrow{\mathbf{17}} \underset{\mathbf{5\text{—}7}}{R\cdot CO\cdot Z\cdot R'}$$

| No. | R | Z | R′ | Yield (%) | mp (°C) (bp/mmHg)[c] Found | mp (°C) (bp/mmHg)[c] Reported | Lit. |
|---|---|---|---|---|---|---|---|
| **5a** | Ph | NH | Ph | 97<br>68[a]<br>63[b] | 160—162 | 162—163 | 5) |
| **5b** | *p*-Cl·Ph | NH | Ph | 90 | 192—193 | 193 | 6) |
| **5c** | *p*-$O_2N$·Ph | NH | Ph | 78 | 214 | 214 | 7) |
| **5d** | *p*-$CH_3$·Ph | NH | Ph | 83 | 143—145 | 145—146 | 8) |
| **5e** | *p*-$CH_3O$·Ph | NH | Ph | 84 | 172—174 | 173 | 9) |
| **5f** |  | NH | Ph | 78 | 175—177 | 178 | 10) |
| **5g** |  | NH | Ph | 81 | 130—132 | 131—132 | 11) |
| **5h** | $CH_3(CH_2)_{12}$– | NH | Ph | 95 | 86—87 | 85—86 | 12) |
| **5i** |  | NH | Ph | 80 | 122—124 | 124 | 13) |
| **6a** | Ph | O | Me | 72 | (90—93/21) | (195—199) | 14) |
| **6i** |  | O | Me | 65 | (72—75/15) | 181.3 | 15) |
| **7a** | Ph | S | 2-Pyridyl | 80 | 49—51 | 50—51 | 16) |
| **7d** | Cyclohexyl | S | 2-Pyridyl | 81 | 89—90 | 88—90 | 17) |
| **7g** |  | S | 2-Pyridyl | 73 | (110—115/0.25) | | |
| **7i** |  | S | 2-Pyridyl | 84 | 42—45 | | |

*a*) Yield when sodium benzoate was used. *b*) Yield when lithium benzoate was used. *c*) Temperature of the oil bath.

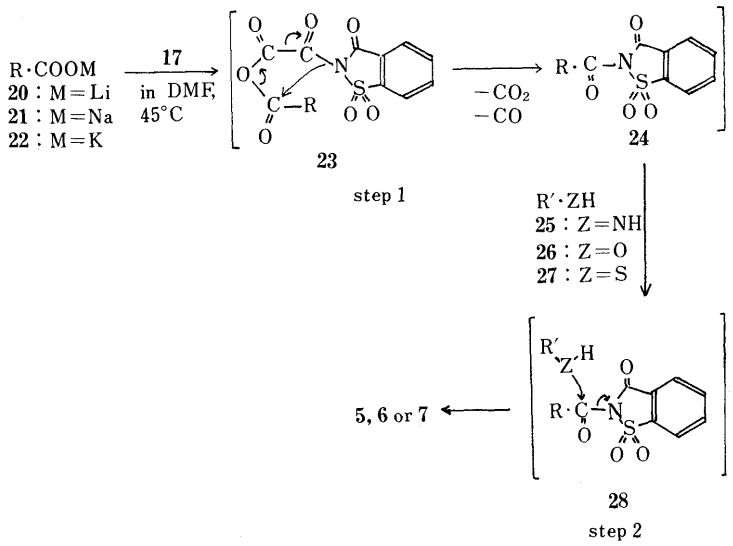



Chart 5

sterically hindered carboxylic acids, for examples, potassium 2,6-dichlorobenzoate (**22f**) and potassium 2,2-dimethylpropioate (**22g**), readily react with aniline (**25a**) using **17**, but at a higher temperature (70 °C rather than 45 °C), to provide the corresponding anilides (**5f** and **5g**) in 78% and 81% yields, respectively.

The successful application of 2,2′-oxalyldisaccharin (**17**) as a condensing agent led us to investigate briefly its usefulness in the preparation of esters (**6**) and thioesters (**7**). Thus, reaction of potassium benzoate (**22a**) with methanol (**26a**) afforded the desired methylester (**6a**) in 72% yield. 2-Mercaptopyridine (**27a**) can be used as a nucleophile for thioesterification. The reaction of potassium furancarboxylate (**20b**) in DMF with **17** was carried out for 1 h at 45 °C to give 2-furoylsaccharin (**24i**) as an intermediate, which was subsequently treated with 2-mercaptopyridine (**27a**) for 1 h at 45 °C to afford *S*-2-pyridyl furancarbothioate (**7i**) in 84% yield. Similarly, conversion of potassium 2,2-dimethylpropioate (**22g**) to the corresponding *S*-2-pyridyl thioate (**7g**) was accomplished without difficulty in an acceptable yield (73%). The results obtained with a number of additional carboxylic acids chosen to demonstrate the effectiveness of this method are summarized in Table I.

The condensation reactions described herein were carried out basically as a two-step, one-pot procedure, as shown in Chart 5. Step 1, involves the formation of active 2-acylsaccharins (**24**) from the reaction of potassium carboxylates (**22**) with 2,2′-oxalyldisaccharin (**17**) for 1 h at 45 °C in DMF accompanied with liberation of carbon dioxide and carbon monoxide, and step 2, the activated 2-acylsaccharins (**24**) react subsequently with nucleophiles such as amines (**25**), alcohols (**26**) or thioalcohols (**27**) to give the corresponding carboxylic acid derivatives (**5**, **6**, and **7**) as the final products.

In conclusion, preliminary experiments have shown that compound **17** can be conveniently used as a condensing reagent for the conversion of the potassium carboxylates (**22**), including sterically hindered ones, into amides (**5**), esters (**6**), and thioesters (**7**), respectively, under mild reaction conditions with gentle heating.

## Experimental

Melting points were taken on a Yanagimoto melting point apparatus. All melting and boiling points are uncorrected. Nuclear magnetic resonance (NMR) spectra were measured on a Bruker AM-400 spectrometer (400 MHz) using tetramethylsilane as an internal reference, and chemical shifts were recorded as $\delta$-values.

**Synthesis of 2,2′-Oxalyldi(2,3-dihydro-3-oxobenzisosulfonazole) (17)** A solution of oxalyl chloride (**16**) (12.7 g, 0.1 mol) in benzene (50 ml) was added dropwise to a solution of 2,3-dihydro-3-oxobenzisosulfonazole (**15**) (36.6 g, 0.2 mol) and triethylamine (20.2 g, 0.2 mol) in benzene (500 ml) under vigorous stirring at room temperature. After 3 h, the precipitate was collected by filtration and washed with water. The crystalline mass obtained was recrystallized from acetonitrile to give 34.5 g (82%) of **17**; colorless prisms, mp 254—257 °C (dec.). *Anal.* Calcd for $C_{16}H_8N_2O_8S_2$: C, 45.71; H, 1.90; N, 6.66. Found: C, 45.65; H, 1.88; N, 6.71. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1760, 1740, 1720 (C=O), 1330, 1310 ($SO_2$). NMR (DMSO-$d_6$) $\delta$: 7.60—8.10 (m, 8H, aromatic).

**Preparation of Potassium Carboxylates (22)** General Procedure: Carboxylic acid (0.1 mol) was added in a single portion to a solution of potassium hydroxide (0.1 mol) in methanol (300 ml) under stirring at room temperature. After 15 min, methanol was evaporated off under reduced pressure to give the corresponding potassium carboxylate (**22**), which was used without further purification. Lithium and sodium salts (**20a** and **21a**) of benzoic acid were also prepared according to the procedure described above.

**Synthesis of Amides (5)** General Procedure: **17** (2.1 g, 5 mmol) was added rapidly in a single portion to a stirred solution of a potassium carboxylate (**22**) (5 mmol) in DMF (10 ml). The mixture was stirred at room temperature for 15 min, heated for 1 h at 45 °C, and then cooled to room temperature. A solution of aniline (**25a**) (0.46 g, 5 mmol) in DMF (1 ml) was added dropwise. The resultant mixture was heated again for 1 h at 70 °C. After it had cooled to room temperature, the reaction mixture was poured into a mixture of ethyl acetate and ice. The organic layer was washed with 5% $NaHCO_3$, 2% HCl, and water, and then dried over anhydrous $Na_2SO_4$. The organic solvent was evaporated off *in vacuo* to give the crude amide (**5**), which was purified by recrystallization.

**2,6-Dichloro-*N*-phenylbenzamide (5f)** **17** (2.1 g, 5 mmol) was added rapidly in a single portion to a stirred solution of potassium 2,6-dichlorobenzoate (**22f**) (1.1 g, 5 mmol) in DMF (10 ml). The mixture was heated for 1 h at 70 °C, and then cooled to room temperature. A solution of aniline (**25a**) (0.46 g, 5 mmol) in DMF (1 ml) was added dropwise. The resultant mixture was heated again for 1 h at 70 °C. After the mixture had cooled to room temperature, it was poured into a mixture of ethyl acetate and ice. The organic layer was washed with 5% $NaHCO_3$. 2% HCl, and water, and then dried over anhydrous $Na_2SO_4$. The organic solvent was evaporated off *in vacuo* to give the crude **5f**, which was purified by recrystallization from benzene.

**2,2-Dimethyl-*N*-phenylbenzamide (5g)** **5g** was prepared according to the procedure for **5f** described above.

**Synthesis of Esters (6) and Thioesters (7)** General Procedure: **17** (1.5 g, 3.6 mmol) was added rapidly in a single portion to a stirred solution of a potassium carboxylate (**22**) (3.6 mmol) in DMF (10 ml). The mixture was stirred for 15 min at room temperature, heated for 1 h at 45 °C, and then

cooled to room temperature. A solution of methanol (**26a**) (3.6 mmol) or 2-mercaptopyridine (**27a**) (3.6 mmol) in DMF (1 ml) was added dropwise. The resulting mixture was heated again for 1 h at 45 °C. After the reaction mixture had cooled to room temperature, it was poured into a mixture of ethyl acetate and ice. The organic layer was washed with 5% $NaHCO_3$, 2% HCl, and water, and then dried over anhydrous $Na_2SO_4$. The organic solvent was evaporated off *in vacuo* to give the crude esters (**6**) or thioesters (**7**), which were purified by distillation or recrystallization.

***S*-2-Pyridyl Furancarbothioate (7i)** **7i** was prepared in 84% yield by the above general procedure. Crude **7i** was recrystallized from a mixture of petroleum ether and ether. mp 42—45 °C. *Anal.* Calcd for $C_{10}H_7NO_2S$: C, 58.54; H, 3.44; N, 6.83. Found: C, 58.56; H, 3.31; N, 6.78. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1670 (C=O). NMR ($CDCl_3$) $\delta$: 8.65, 7.77, 7.72, 7.32 (each 1H, each m, pyridine 3-, 4-, 5-, and 6-H).

***S*-2′-Pyridyl 2,2-Dimethylpropanthioate (7g)** **17** (5.0 g, 12 mmol) was added rapidly in a single portion to a stirred solution of potassium 2,2-dimethylpropanoate (**22i**) (1.6 g, 12 mmol) in DMF (10 ml). The mixture was heated for 1 h at 70 °C, and then cooled to room temperature. 2-Mercaptopyridine (**27a**) (1.4 g, 12 mmol) was added, and the resulting mixture was heated again for 1 h at 70 °C. The homogeneous reaction mixture was cooled to room temperature, and diluted with 50 ml of ethyl acetate. The mixture was filtered to remove some crystalline material and the filtrate was washed with 5% $NaHCO_3$, 2% HCl, and water, and then dried over anhydrous $Na_2SO_4$. Removal of the solvent under reduced pressure afforded the crude product (**7g**), which was fractionally distilled to give 1.7 g (73%) of **7g**, bp 110—115 °C (oil bath)/0.25 mmHg. *Anal.* Calcd for $C_{10}H_{13}NOS$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.48; H, 6.95; N, 7.03. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1690 (C=O). NMR ($CDCl_3$) $\delta$: 1.33 (s, 9H, $-CH_3$), 8.63, 7.73, 7.56, 7.28 (each 1H, each m, pyridine 3-, 4-, 5-, and 6-H).

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