N,N'-Carbonyldi[2(3*H*)-benzoxazolethione]: New, Reactive Condensing Agent for the Synthesis of Amides, Esters, Peptides, and Polyamides

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A new condensing agent, *N,N'*-carbonyldi[2(3*H*)-benzoxazolethione] (**3**), was readily prepared by the reaction of 2-benzoxazolethiol and trichloromethyl chloroformate in benzene. The condensing agent **3** is shown to be useful for the preparation of amides, esters, and dipeptides under mild conditions. A successful polyamide synthesis by the polycondensation of isophthalic acid with diamines using **3** is also described.

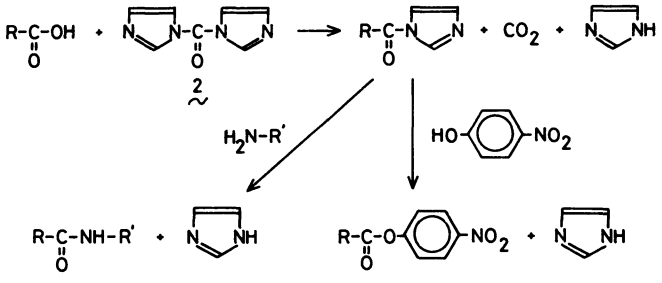
Dicyclohexylcarbodiimide (DCC) (**1**) and *N,N'*-carbonyldiimidazole (**2**) are useful and popular condensing agents. However, they have some disadvantages in acylation reactions; **1** is accompanied by the formation of *N*-acylurea which causes a purification problem as well as reducing the yield, and **2** is very sensitive to moisture, and must be handled with care. To overcome these problems, many condensing agents have been reported.[1]

As a part of our continuing research program on the preparation of amides, esters, and polyamides under mild conditions,[2] our group has recently initiated the synthesis of new active condensing agents. One requirement for an improved condensing agent is that the conversion of carboxylic acids to the active intermediates should occur readily under mild conditions. In the preceding paper, we showed that 3-substituted 1,2-benzisothiazole 1,1-dioxides and *N,N'*-carbonyldi[1,2-benzisoxazol-3(2*H*)-one] are new reactive condensing agents for the synthesis of amides and esters.[3,4]

We now report that amides, esters, dipeptides, and polyamides can be easily obtained from carboxylic acids and nucleophiles by a one-pot procedure using the new condensing agent, *N,N'*-carbonyldi[2(3*H*)-benzoxazolethione] (**3**).

Results and Discussion

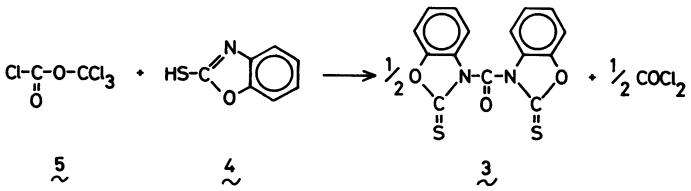
Synthesis of N,N'-*Carbonyldi[2(3H)-benzoxazolethione] (3).* *N*-Acyl derivatives of imidazoles, pyrazoles, and triazoles are highly reactive acylating agent which are involved in numerous condensing methods.[5] For example, carbonyldiimidazole (**2**) has been used for direct condensing method as in Scheme 1. The actual acylating agent is an *N*-acyl imidazole.



Scheme 1.

Recently we reported that *N*- or *S*-acyl derivatives of 2-benzoxazolethiol (**4**) is a new highly reactive acylating agent for amines and alcohols.[6] This finding prompted us to develop further new condensing agent, *N,N'*-carbonyldi[2(3*H*)-benzoxazolethione] (**3**) for the synthesis of amides and esters *via* *N*- or *S*-acyl derivatives of **4** as an active intermediate.

The condensing agent **3** was conveniently prepared from trichloromethyl chloroformate (**5**) and **4** in a 1:1 molar ratio in benzene (Scheme 2). Recrystallization from cyclohexane gave white needles melting point at 160—161 °C. It is stable even if exposed to atmospheric moisture for a long time. Acylation of **4** might be expected to yield the *S*- or *N*-acyl prod-



Scheme 2.

uct, because of the tautomerism of **4**. The more thermodynamically stable isomers (*N*-acyl products) were obtained under a variety of reaction conditions,[7] but *S*-acyl products were obtained with a careful control of the reaction conditions.[6] The reaction of **4** and **5** in benzene under reflux conditions gave preferentially the more thermodynamically stable *N*-acyl product **3**. The structure of **3** was assigned on the basis of IR spectroscopy and elemental analysis. The IR spectrum exhibited a strong carbonyl absorptin at 1680 cm^{-1} and a C=S stretching absorption at 1350 cm^{-1}.

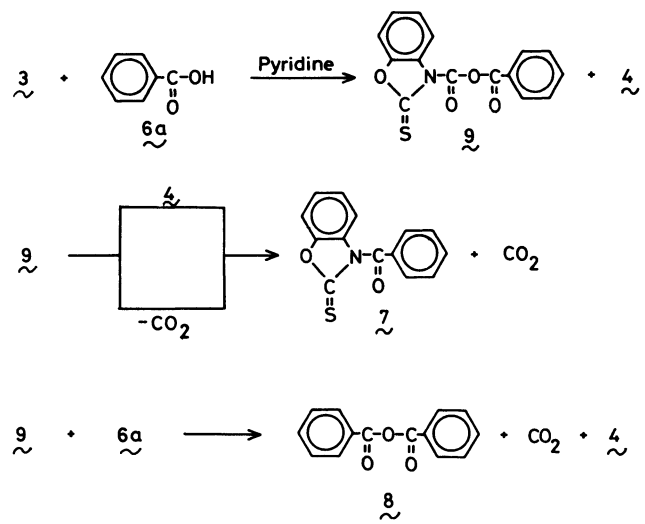
Reaction of 3 with Benzoic Acid (6a). In order to clarify the reaction pathway, the reaction of **3** with benzoic acid (**6a**) was carried out in *N*-methyl-2-pyrrolidone (NMP) at room temperature for 2 h in the presence of pyridine as a tertiary base. **3** reacted rapidly with **6a** with liberation of CO_2, and gave 3-benzoyl-2(3*H*)-benzoxazolethione (**7**) together with a

Table 1. Preparation of amides **10** and esters **11** using condensing agent **3**[a]

Carboxylic acid R-COOH, **6** R-	Amine or Alcohol	Reaction time (Step 2)	Product	Yield[b] %
C_6H_5	Aniline	1 h	Benzanilide	83[c]
C_6H_5	Aniline	1 h	Benzanilide	95
C_6H_5	Benzylamine	1 h	*N*-Benzylbenzamide	91
C_5H_{11}	Aniline	1 h	*N*-Phenylhexanamide	85
C_5H_{11}	Benzylamine	1 h	*N*-Benzylhexanamide	84
C_6H_5	Phenol	1 d	Phenyl benzoate	90
C_6H_5	Benzyl alcohol	4 d	Benzyl benzoate	80
C_6H_5	*p*-Nitrophenol	1 d	*p*-Nitrophenyl benzoate	98
C_6H_5	*p*-Aminophenol	1 h	4′-Hydroxybenzanilide	88
C_6H_5	1/2 *p*-Aminophenol	1 h/1 d	4′-Benzoyloxybenzanilide	88

a) Reaction was carried out with 2 mmol of the reactants in 4 ml of NMP at room temperature. Pyridine was used as a tertiary base at step 1. Reaction time: Step 1, 2 h. b) Isolated yields. c) Triethylamine as a tertiary base was used at the step 1.

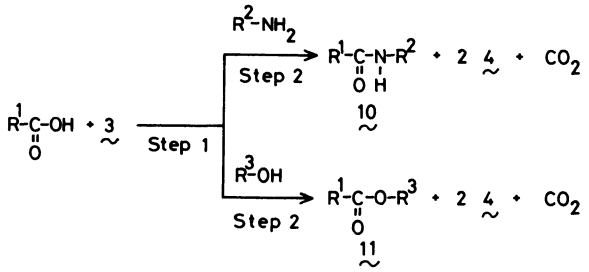
small amount of benzoic anhydride (**8**). The intermediate **7** has been characterized by high reactivity toward aminolysis. The above observations point to the following pathway (Scheme 3). **3** reacts first with



Scheme 3.

6a to form the mixed anhydride **9**, a highly activated acylating agent. The product **9** was less stable and it's enhanced reactivity causes it to react more rapidly with available nucleophiles, **4** and **6a**. These reactions yield the active intermediates **7** and **8**.

Synthesis of Amides (10) and Esters (11). The conversions of carboxylic acids into amides **10** or esters **11** using new condensing agent **3** were carried out by a one-pot procedure at room temperature in the presence of a tertiary base. Equimolar amounts of carboxylic acids, nucleophiles, and the condensing agent **3** are used. This efficient procedure involves two separate steps; (1) "activation" of the carbonyl component, *i.e.* generation of active intermediate **7** and **8** described above; and (2) "condensing" with the nucleophilic reagent (Scheme 4). The rections proceeded smoothly to give the corresponding amides **10**



Scheme 4.

and esters **11** in good yields. Pyridine as a base was more favorable than triethylamine (TEA) in step 1. The alcoholysis required an equimolar amount of TEA at step 2.

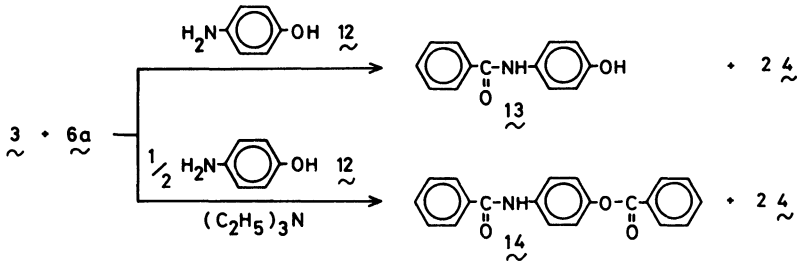
The amines, as expected from their generally greater reactivity in nucleophilic reactions, react more rapidly than the alcohols with the active intermediates **7** and **8**. With this different reactivity cited above between the reactions of the active intermediates with amines and alcohols, next, the selective *N*-acylation and *N,O*-diacylation of *p*-aminophenol (**12**) were performed either in the absence or in the presence of TEA, respectively. The corresponding amide **13** or amide ester **14** were obtained in good yields (Scheme 5). These results are summarized in Table 1.

Synthesis of Dipeptides (15). Futher it was found that the present reaction was applicable to the preparation of dipeptides **15**. Thus, the reaction of an *N*-protected α-amino acid (**16**) with an α-amino acid ester hydrochloride (**17**) was carried out with **3** in the presence of TEA. The *N*-protected α-amino acid **16** reacted with an equimolar amount of **3** in dichloromethane in the presence of TEA at room temperature. After several hours, the α-amino acid ester hydrochloride **17** and TEA, an acid acceptor, were added. The dipeptide product **15** was isolated in the ordinary manner. The optical purity of the dipeptides was estimated by comparison with the specific rotation of the reported values. *N*-Protected dipeptide esters **15** were prepared in good yields with the suppressed racemization (Table 2), (Scheme 6).

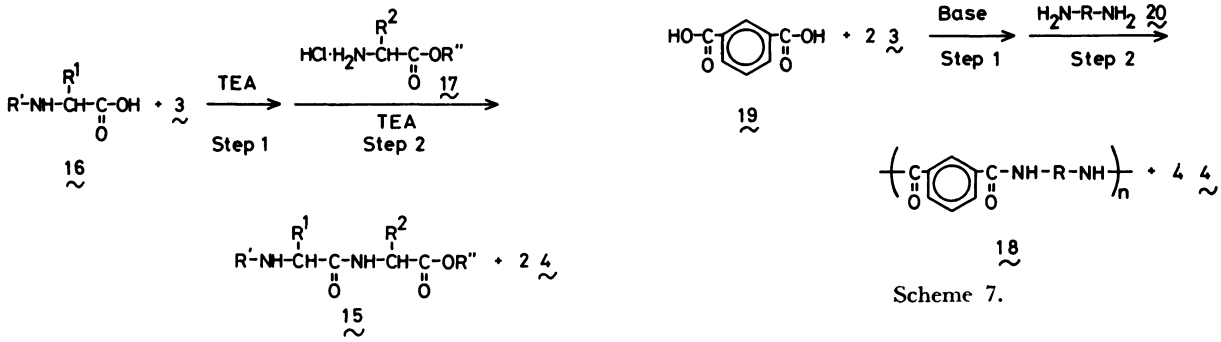
Table 2. Preparation of dipeptide esters **15** using condensing agent **3**[a]

N-Protected α-amino acid	α-Amino acid ester	Product	Yield[b] %	Mp θ_m/°C Found	Mp θ_m/°C Reported	$[\alpha]_D$/°(Temp/°C, *c*, Solv.) (Reported)
Z-Ala	Gly-OEt	Z-Ala-Gly-OEt	81	99—100	99—100	−21.0(22, 3.33, EtOH) −22.3(3.65, EtOH)[8]
Z-Val	Gly-OEt	Z-Val-Gly-OEt	91	169—170	170—171	−30.0(22, 3.33, Dioxane) −32.4(20, 1.85, Dioxane)[3]
Boc-Leu	Leu-OMe	Boc-Leu-Leu-OMe	77	129—131	131—132	−49.4(22, 2.33, MeOH) −50.0(22, 0.39, MeOH)[9]
Boc-Phe	Val-OMe	Boc-Phe-Val-OMe	82	115—117	117—118	−10.7(20, 3.00, DMF) −11.0(1.89, DMF)[8]
Z-Val	Val-OMe	Z-Val-Val-OMe	81	114—116	116	−23.0(22, 1.52, MeOH) −24.3(25, 0.3, MeOH)[10]

a) Reaction was carried out with 1 mmol of the reactants in 5 ml of dichloromethane. Reaction time: Step 1, 3 h, Step 2, 12 h. b) Isolated yields.



Scheme 5.

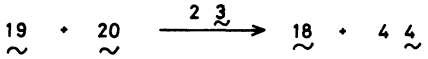


Scheme 6.

Scheme 7.

Synthesis of Polyamides (18). The direct polycondensation of diamines with dicarboxylic acids to form polyamides under mild conditions has received considerable attention. Most of them are based on phosphorylation reactions. Facile one-pot amide synthesis using the condensing agent **3** provides a promising route to polyamides. The polycondensation of isophthalic acid (**19**) with aromatic diamines (**20**) using **3** was investigated by the two methods, the one-pot polycondensation and the direct polycondensation. The one-pot polycondensation was carried out in solution at low temperature using 4,4′-oxydianiline and 4,4′-methylenedianiline as diamines **20**. The polar aprotic solvents, NMP and hexamethylphosphoric triamide (HMPA), were used as polymerization media (Scheme 7). The activation of isophthalic acid **19** (step 1) was carried out by the addition of the condensing agent **3** to a cold solution of **19** in a polar solvent in the presence of tertiary base. After several hours, the diamine was added. The solution was stirred at room temperature for a specified time. Although the polymers were isolated in excellent yields the molecular weights remained low. In order to determine the influence of base strength in these polymerizations, tertiary amines with a wide range of pK_a values were tested. But, there is no correlation between base strength and the resulting viscosity of the polymer. These results are summarized in Table 3.

To prevent the formation of a small amount of anhydride, the direct polycondensation of **19** with **20** was carried out at temperatures of 0—25 °C in the presence of the condensing agent **3** (Scheme 8). As



Scheme 8.

Table 3. Synthesis of polyamides **18** by the one-pot polycondensation of isophthalic acid with diamines **20** using the condensing agents **3**[a)]

Diamine H_2N-R-NH_2	Reaction conditions				Polymer		
	Base	Solvent	Time/h		Type	Yield %	η_{inh}[b)] dl g^{-1}
			Step 1	Step 2			
20a -C_6H_4-O-C_6H_4-	TEA	NMP	3	24	**18a**	99	0.10
20a -C_6H_4-O-C_6H_4-	TEA	NMP	24	48	**18a**	99	0.15
20a -C_6H_4-O-C_6H_4-	Pyridine	NMP	3	1	**18a**	99	0.20
20a -C_6H_4-O-C_6H_4-	2-Ethyl pyridine	NMP	15	3	**18a**	99	0.13
20a -C_6H_4-O-C_6H_4-	2-Ethyl pyridine	NMP	48	6	**18a**	99	0.12
20a -C_6H_4-O-C_6H_4-	2,4,6-Trimethyl pyridine	NMP	0.5	24	**18a**	90	0.14
20a -C_6H_4-O-C_6H_4-	Imidazole	NMP	3	16	**18a**	99	0.16
20a -C_6H_4-O-C_6H_4-	Quinoline	NMP	1	12	**18a**	99	0.15
20a -C_6H_4-O-C_6H_4-	Tributyl amine	HMPA	24	24	**18a**	99	0.18
20a -C_6H_4-O-C_6H_4-	*N*-Ethyl piperidine	HMPA	1	24	**18a**	99	0.15
20b -C_6H_4-CH_2-C_6H_4-	Pyridine	HMPA	3	24	**18b**	92	0.10
20b -C_6H_4-CH_2-C_6H_4-	TEA	HMPA	3	24	**18b**	90	0.10

a) Polymerization was carried out with 1 mmol of the monomers using the condensing agent **3** (2 mmol) in the solvent at room temperature. b) Measured at a concentration of 0.5 g dl^{-1} in concentrated sulfuric acid at 30 °C.

Table 4. Synthesis of polyamides **18** by the direct polycondensation of isophthalic acid with diamines **20** using the condensing agent **3**[a)]

Diamine H_2N-R-NH_2	Reaction conditions		Polymer		
	Time h	Temperature °C	Type	Yield %	η_{inh}[b)] dl g^{-1}
20a -C_6H_4-O-C_6H_4-	24	r. t	**18a**	99	0.37
20a -C_6H_4-O-C_6H_4-	48	r. t	**18a**	98	0.35
20a -C_6H_4-O-C_6H_4-	24	0—r. t	**18a**	99	0.50
20a -C_6H_4-O-C_6H_4-	24	40	**18a**	92	0.27
20b -C_6H_4-CH_2-C_6H_4-	15	r. t	**18b**	98	0.23

a) Polymerization was carried out with 1 mmol of the monomers using the condensing agent **3** (2 mmol) in HMPA (2 ml). b) Measured at a concentration of 0.5 g dl^{-1} in concentrated sulfuric acid at 30 °C.

can be seen from the inherent viscosities in Table 4, the polymers were produced in quantitative yields with inherent viscosities up to 0.5 dl g^{-1}. The polymers were identified as polyamides by comparison of their IR spectra with those of the authentic polyamides.

In summary, our studies indicate that the condensing agent **3** is very useful reagent for the formation of amides, esters, peptides, and polyamides. The new condensing agent **3** is a crystalline solid having excellent hydrolytic stability and therefore it is handled more easily than conventional agents. Futhermore 2-benzoxazolethiol **4**, a leaving group, is readily removed from the reaction products by washing the reaction mixture with cold 1% aqueous sodium hydrogencarbonate.

Experimental

Melting points were uncorrected. Infrared spectra were obtained using potassium bromide pellets with a JASCO IRA-1 spectrophotometer. 4,4′-Oxydianiline, and 4,4′-methylenedianiline were recrystallized from tetrahydrofuran and benzene respectively. *N*-Methyl-2-pyrrolidone (supplied by Mitsubishi Chemical Industries Ltd.), hexamethylphosphoric triamides were purified by vacuum distillation and stored 4-Å Molecular Sieves. *N*-Protected α-amino acids and α-amino acid ester hydrochlorides were prepared by usual procedures. Trichloromethyl chloroformate was purchased from Hodogaya Chemical Industries Ltd. The other reagents were used without futher purification.

N,N′-Carbonyldi[2(3H)-benzoxazolethione] (3). A mixture of **4** (15 g, 0.1 mol) and trichloromethyl chloroformate (**5**) (12 ml, 0.1 mol) in benzene (100 ml) was refluxed with stirring for 3 h. Then the solvent was removed *in vacuo*, and the residue was allowed to stand overnight. Purification by recrystallization from cyclohexane gave white needles. Yield: 7.4 g (45%). Mp 160—161 °C; IR (KBr), 1680 and 1350 cm^{-1}.

Found: C, 55.0; H, 2.7; N, 8.6%. Calcd for $C_{15}H_8O_3N_2S_2$: C, 54.87; H, 2.46; N, 8.53.

Reaction of 3 with Benzoic Acid (6a). To a stirred solution of **6a** (0.244 g, 2.0 mmol), pyridine (0.18 ml, 2.0 mmol) in NMP (4 ml) was added **3** (0.657 g, 2.0 mmol), followed by stirring at room temperature for 2 h. The reaction mixture was poured into water (100 ml). The precipitate formed was collected by filtration, washed with water,

and dried *in vacuo*. 3-Benzoyl-2(3*H*)-benzoxazolethione (**7**) was the major product, and a small amount of benzoic anhydride (less than 5%) was formed. The crude product was recrystallized from ethanol to give yellow needles (**7**). Yield: 0.45 g (88%), mp 117—118 °C (lit,[6] 117 °C); IR (KBr), 1695 and 1340 cm^{-1}.

Amide (10). *General Procedure*: The condensing agent **3** (2 mmol) was added to a stirred solution of the carboxylic acid (2 mmol) and pyridine (2 mmol) in NMP (4 ml) at room temperature. After 2 or 3 h, the amine (2 mmol) was added. Stirring was continued for 1 h. The mixture was poured into 1% aqueous sodium hydrogencarbonate. The precipitate was filtered and washed with water and dried.

Ester (11). *General Procedure*: A mixture of **3** (2 mmol), benzoic acid (2 mmol), and pyridine (2 mmol) in NMP (4 ml) was stirred at room temperature for 2 h. To this mixture, the alcohol (2 mmol) and TEA (2 mmol) were added. Stirring was continued for several hours. The reaction mixture was worked up as described above.

Amide Ester (14). The condensing agent **3** (2 mmol) was added with stirring to a solution of benzoic acid (2 mmol) and pyridine (2 mmol) in NMP (4 ml) at room temperature. After 2 h, *p*-aminophenol (**12**) (1 mmol) was added to this mixture. After stirring 2 h, TEA (1 mmol) was added, the mixture was stirred for 4 d, and worked up as described. The compound (**13**) was obtained when TEA was omitted.

N-Protected Dipepide Ester (15). *General Procedure*: To a solution of the *N*-protected α-amino acid (1 mmol) and TEA (1 mmol) in dichloromethane (5 ml), **3** (1 mmol) was added under nitrogen. The solution was stirred for 3 h at 0 °C, then the α-amino acid ester hydrochloride (1 mmol) and TEA (1 mmol) were added. The solution was stirred for 12 h at room temperature. After removal of the solvent *in vacuo*, the residue was dissolved in ethyl acetate, and the organic solution was successively with 5% aqueous sodium hydrogencarbonate, 1 M hydrochloric acid and saturated brine, and then dried ($MgSO_4$). After evaporation of ethyl acetate, the dipeptide ester was purified by recrystallization.

Polyamide (18). *One-pot Polycondensation*: The condensing agent **3** was added to a stirred solution of isophthalic acid (**19**) (1 mmol) and pyridine (2 mmol) in NMP (2 ml). The mixture was stirred for a defined time at room temperature, then diamine (1 mmol) was added at room temperature. Stirring was continued for several hours. The resulting solution was poured into 1% aqueous sodium hydrogencarbonate (200 ml) and the precipitated polymer was collected and dried *in vacuo* at 60 °C for 2 d. The inherent viscosity was measured at a concentration of 0.5 g dl^{-1} in concentrated sulfuric acid at 30 °C.

Direct Polycondensation. To a solution of **19** (1 mmol) and diamine (1 mmol) in HMPA (2 ml), the condensing agent **3** (2 mmol) was added at 0 °C. The mixture was stirred for 10 h at 0 °C, and then for 14 h at room temperature. The polymer solution was worked up as described above.

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