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N,N'-Carbonyldi[1,2-benzisoxazol-3(2*H*)-one]: New, Reactive Condensing Agent

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A new condensing agent, *N,N'*-carbonyldi[1,2-benzisoxazol-3(2*H*)-one] (**6**), was readily prepared by the reaction of 1,2-benzisoxazol-3-ol and trichloromethyl chloroformate in toluene. The condensing agent **6** was shown to be very useful for the preparation of amides, esters, and dipeptides under mild conditions. A successful polyamide synthesis by one-pot polycondensation of isophthalic acid with diamines using **6** was also described.

Condensations among the most important and fundamental reactions in organic synthesis and many reagents for promoting condensations by one-pot procedures have been reported.[1-4] In particular, their full potential has been realized in conversions of carboxylic acids into amides and esters. Most such condensing agents first react with the carboxylic acids to give the intermediates, active esters or amides, which undergo subsequent nucleophilic attack by the amino or hydroxyl group. Therefore, a primary factor in determining whether or not the condensing agents are effective is their ability to activate carboxylic acids.

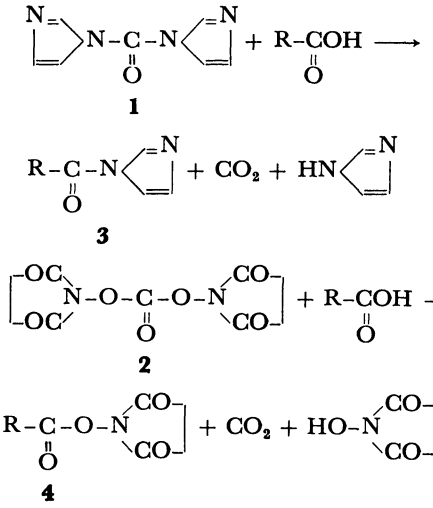
It is well recognized that increased reactivity of carboxylic acid derivatives toward nucleophiles may be roughly correlated with greater stability of the leaving group anions, that is, pK_a of the leaving groups. From this point of view, we previously exploited a series of good leaving groups in the syntheses of active esters and amides, demonstrating that the active ester and amide methods are useful in the preparation of high molecular weight polyamides under mild conditions.[5]

Based on the success of those studies, we continued to investigate new active condensing agents for the synthesis of amides, esters and polyamides. One requirement for improved condensing agents 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-(2-benzothiazolythio)-1,2-benzisothiazole 1,1-dioxide and 3-(2-benzoxazolylthio)-1,2-benzisothiazole 1,1-dioxide were new reactive condensing agents for the synthesis of amides and esters.[6]

We now report that amides, esters, peptides, and polyamides can be easily obtained from carboxylic acids and nucleophiles by a one-pot procedure using the new condensing agent, *N,N'*-carbonyldi[1,2-benzisoxazol-3(2*H*)-one] (**6**).

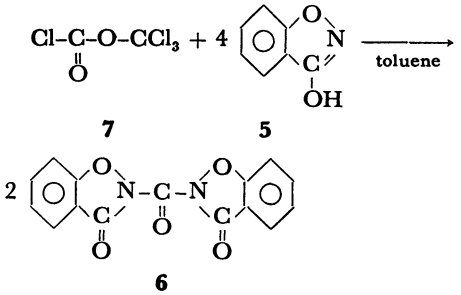
Results and Discussion

Synthesis of N,N'-*Carbonyldi[1,2-benzisoxazol-3*(2H)*-one]* (*6*). The widely used condensing agents derived from phosgene, such as *N,N'*-carbonyldiimidazole (**1**) and *N,N'*-(carbonyldioxy)disuccinimide (**2**) have been reviewed.[7,8] The reaction of carboxylic acids with **1** and **2** lead to the intermediate imidazolides (**3**) and *N*-hydroxysuccinimide ester (**4**) respectively, both of which have been characterized by their very high reactivity in nucleophilic reactions.

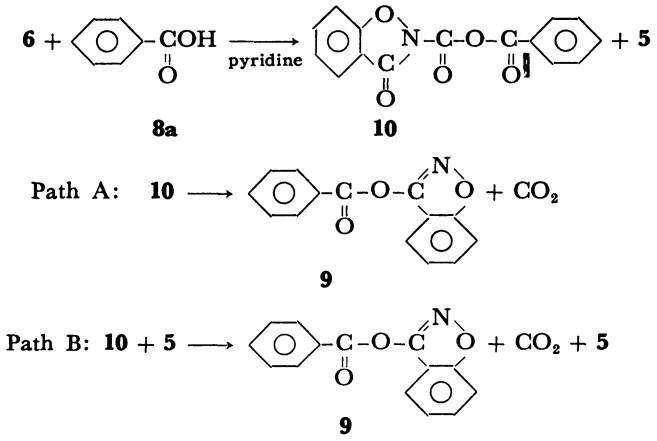


Recently, we found that the *N*- or *O*-acyl products from the acylation of 1,2-benzisoxazol-3-ol (**5**) were susceptible to aminolysis under mild conditions and the corresponding amides were produced in quantitative yields.[5i] This finding led to the synthesis of *N,N'*-carbonyldi[1,2-benzisoxazol-3(2*H*)-one] (**6**) which was expected to serve as new condensing agent with a wide range of preparative applications.

The condensing agent **6** was readily prepared in high yield by reacting **5** with trichloromethyl chloroformate (**7**) in a 4 : 1 molar ratio in toluene (Scheme 1). Recrystallization from toluene gave white needles melting point at 205—206 °C. Acylation of **5** may involve reaction at either oxygen or nitrogen. Acylations reported earlier gave *N*- or *O*-acyl products, depending on the reaction conditions employed and acylating agent used.[9] The reaction of **5** with **7** in toluene under reflux conditions gave preferentially the more thermo-



Scheme 1.



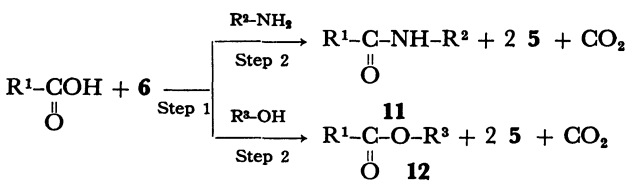
Scheme 2.

dynamically stable *N*-acyl product **6**. The structure of **6** was characterized by elemental analysis and IR spectroscopy. The IR spectrum showed carbonyl absorption bands at 1780, 1765, and 1750 cm^{-1}.

Reaction of ***6*** *with Benzoic Acid* (***8a***). To get a better picture of the course of the reaction, **6** was treated with benzoic acid (**8a**) in *N*-methyl-2-pyrrolidone (NMP) at 50 °C for 1 h in the presence of pyridine. The condensing agent **6** reacted rapidly with **8a** with liberation of CO_2, to give 3-benzoyloxy-1,2-benzisoxazole (**9**). The formation of benzoic anhydride was not observed. The intermediate **9** has been characterized by its high reactivity toward aminolysis.[5i] Consequently, the reaction pathway suggested for the formation of **9** is shown in Scheme 2.

Initially, the attack of the benzoate anion at the carbonyl carbon of **6** gives the mixed anhydride (**10**). Two pathway are possible for the further reaction of **10**. The mixed anhydride (**10**) loses CO_2 to form the intermediate **9** (Path A). Alternatively, **5** liberated in the first step of the reaction attacks the carbonyl carbon of **10**, giving the intermediate **9** (Path B). A similar mechanism has been proposed to account for the formation of imidazolide (**3**) by the reaction of **1** with carboxylic acids.[10]

Synthesis of Amides (***11***) *and Esters* (***12***). The syntheses of amides (**11**) and esters (**12**), using our new activating reagent **6**, were carried out by a one-pot procedure. This efficient procedure consists essentially of two reactions: formation of the active ester (**9**) from carboxylic acids as described above, and subsequent aminolysis or alcoholysis of the active ester (**9**) as shown in Scheme 3. The aminolysis and alcoholysis of the active ester (**9**) proceeded smoothly at room temperature to give the corresponding amides (**11**) and esters (**12**). The alcoholysis required an equimolar amount of triethylamine (TEA).



Scheme 3.

Next, the selective *N*-acylation and the *N,O*-diacylation of *p*-aminophenol (**13**) were performed in either the absence or the presence of TEA, respectively. The corresponding amide (**14**) or amide ester (**15**) were obtained in good yields (Scheme 4). These results are summarized in Table 1.

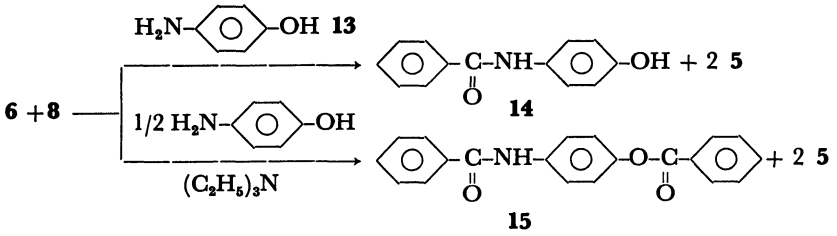
Synthesis of Dipeptides (***18***). In order to further demonstrate the preparative utility of our method, it was applied to the synthesis of dipeptides. Thus the reaction of an *N*-protected amino acid (**16**) with an amino acid ester hydrochloride (**17**) was carried out in the presence of pyridine. The *N*-protected amino acid (**16**) was reacted with equimolar amount of **6** in dichloromethane in the presence of pyridine at room temperature. After several hours, the amino acid ester hydrochloride (**17**) and TEA as an acid acceptor were added. The dipeptide product **18** was isolated in the normal manner. *N*-Protected dipeptide ester (**18**) were prepared in good yields virtually without racemization (Table 2), (Scheme 5).

Synthesis of Polyamides (***19***). Our method can be extended to the synthesis of polyamides (**19**) and it provides a novel approach to direct polycondensation. The one-pot polycondensation of isophthalic acid was carried out in solution at low temperature using three diamines (**20**): 4,4′-oxydianiline, 4,4′-methylenedianiline, and 1,6-hexanediamine. The polar aprotic solvents, NMP, hexamethylphosphoric triamide

TABLE 1. PREPARATION OF AMIDES **11** AND ESTERS **12** USING CONDENSING AGENT **6**[a]

Carboxylic acid R-COOH, **8** R-	Amine or Alcohol	Reaction time (Step 2)	Product	Yield[b] %
C_6H_5	Aniline	15 h	Benzanilide	94
C_6H_5	Benzylamine	1 h	*N*-Benzylbenzamide	80
C_6H_5	Phenol	2 d	Phenyl benzoate	86
C_6H_5	*p*-Nitrophenol	1 d	*p*-Nitrophenyl benzoate	74
C_6H_5	*p*-Nitrobenzyl alcohol	3 d	*p*-Nitrobenzyl benzoate	68
C_6H_5	*p*-Aminophenol	1 d	4′-Hydroxybenzanilide	90
C_6H_5	1/2 *p*-Aminophenol	1 d/2 d	4′-Benzoyloxybenzanilide	86
n-C_5H_{11}	Aniline	1 d	*N*-Phenylhexanamide	85
n-C_5H_{11}	Benzylamine	1 d	*N*-Benzylhexanamide	61

a) Reaction was carried out with 2 mmol of the reactants in 4 ml of NMP. Reaction temperature: Step 1, 50 °C; Step 2, room temperature. b) Isolated yields.



Scheme 4.

TABLE 2. PREPARATION OF DIPEPTIDE EATERS **18** USING CONDENSING AGENT **6**[a)]

N-Protected α-amino acid	α-Amino acid ester	Reaction time/h		Product	Yield %	Mp θ_m/°C (Found reported)		$[\alpha]_D$/° (temp, *c*, solv) (reported)
		Step 1	Step 2					
Z-Val	Gly-OEt	12	24	Z-Val-Gly-OEt	87	170—171	170—171	−31.4 (22°, 1.75, dioxane) −32.4 (20°, 1.85, dioxane)[6)]
Z-Val	Val-OMe	3	19	Z-Val-Val-OMe	75	115	116	−24.4 (22°, 1.08, MeOH) −24.3 (25°, 0.3, MeOH)[12)]
Z-Ala	Gly-OEt	5	24	Z-Val-Gly-OEt	84	101	99—100	−22.3 (22°, 2.70, EtOH) −22.3 (3.67, EtOH)[13)]
Boc-Leu	Leu-OMe	6	17	Boc-Leu-Leu-OMe	84	138—139	141—142	−49.1 (22°, 1.75, MeOH) −50.0 (0.39, MeOH)[13)]
Boc-Phe	Val-OMe	3	24	Boc-Phe-Val-OMe	80	118	117—118	−11.5 (22°, 3.42, DMF) −11.0 (1.89, DMF)[13)]

a) Reaction was carried out with 1 mmol of the reactants in 5 ml of dichloromethane at room temperature.
b) Isolated yields.

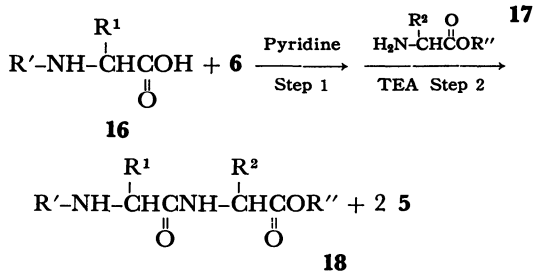
TABLE 3. SYNTHESIS OF POLYAMIDES **19** BY A ONE-POT POLYCONDENSATION OF ISOPHTHALIC ACID WITH DIAMINES **20** USING THE CONDENSING AGENT **6**[a)]

	Diamine H_2N-R-NH_2 R	Reaction conditions			Polymer		
		Base	Solvent	Time/min Step 1	Type	Yield %	η_{inh}[b)] dl·g^{-1}
20a	-C_6H_4-O-C_6H_4-	Pyridine	NMP	70	**19a**	98	0.12
20a	-C_6H_4-O-C_6H_4-	TEA	NMP	2	**19a**	99	0.10
20a	-C_6H_4-O-C_6H_4-	TEA	NMP	30	**19a**	99	0.12
20a	-C_6H_4-O-C_6H_4-	Pyridine	HMPA	70	**19a**	99	0.10
20a	-C_6H_4-O-C_6H_4-	Imidazole	HMPA	5	**19a**	99	0.17
20a	-C_6H_4-O-C_6H_4-	TEA	HMPA	5	**19a**	99	0.25
20a	-C_6H_4-O-C_6H_4-	*N*-Ethyl piperidine	HMPA	3	**19a**	99	0.18
20b	-C_6H_4-CH_2-C_6H_4-	TEA	NMP	3	**19b**	61	0.12
20b	-C_6H_4-CH_2-C_6H_4-	TEA	DMAc	3	**19b**	97	0.15
20b	-C_6H_4-CH_2-C_6H_4-	TEA	HMPA	3	**19b**	79	0.15
20b	-C_6H_4-CH_2-C_6H_4-	Pyridine	HMPA	60	**19b**	72	0.10
20c	-$(CH_2)_6$-	TEA	NMP	2	**19c**	99	0.14
20c	-$(CH_2)_6$-	TEA	DMAc	2	**19c**	99	0.18
20c	-$(CH_2)_6$-	TEA	HMPA	2	**19c**	99	0.23
20c	-$(CH_2)_6$-	Pyridine	HMPA	2	**19c**	99	0.18
20c	-$(CH_2)_6$-	Imidazole	HMPA	15	**19c**	98	0.10

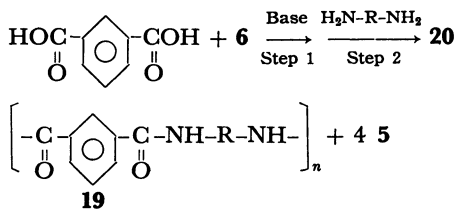
a) Polymerzation was carried out with 1 mmol of the monomers using the condensing agent **6** (2 mmol) in the solvent.
b) Measured at a concentration of 0.5 g/dl in concentrated sulfuric acid at 30 °C.

(HMPA), and *N*,*N*′-dimethylacetamide (DMAc) were used as polymerization media (Scheme 6). Polycondensations in the NMP and DMAc proceeded heterogeneously which impeded the increase in molecular weight. Various tertiary amines with different base strength were also tested in these polymerizations in order to elucidate the influence of bases. TEA, with its high basicity, was found to be good base. The results are summarized in Table 3. The polyamides were produced in quantitative yields with inherent viscosities of 0.1 to 0.25 dl·g^{-1}. The polymers were identified as polyamides by comparison of their IR spectra with those of the authentic polyamides. Although this one-pot syntheses of polyamides was successful, the viscosities of polyamides were relatively low. Thus, studies of the polycondensation conditions must be continued.

In summary, our studies indicate that **6** is a very useful reagent for the formation of amides, esters and



Scheme 5.



Scheme 6.

peptides. The new condensing agent **6** is a crystalline solid having excellent hydrolytic stability and therefore it is handled more easily than conventional agents. Furthermore, 1,2-benzisoxazol-3-ol (**5**), a reaction byproduct, is readily removed from the reaction products by washing the reaction mixture with 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 triamide and *N*,*N*-dimethylacetamide were purified by vacuum distillation and stored over 4-Å Molecular Sieves. *N*-Protected amino acids and amino acid ester hydrochlorides were prepared by usual procedures. The other reagents were used without further purification.

1,2-Benzisoxazol-3-ol (5). This compound was prepared by the modified method reported by Böshangen.[11] To a ice-cold suspention of salcilohydroxamic acid (15.3 g 0.1 mol) in tetrahydrofuran (45 ml), thionyl chloride (10 ml) was added dropwise over 1 h. Then excess thionyl chloride and the solvent were removed *in vacuo* to give a white paste, which was dissolved in dioxane (10 ml). This solution was added dropwise over 1 h to a solution of triethylamine (42 ml) in dioxane (35 ml). The temperature was kept below 10 °C. The yellow mixture was poured into water (300 ml) and then was acidified with 10% HCl. The solution was allowed to crystallize overnight at 0—10 °C. The product was collected by filtration, washed with water, and dried to give 9 g of **5**. Recrystallization from 25% aqueous ethanol solution produced faint yellow needles. Mp 145—146 °C (lit,[11] 144 °C).

N,N′-*Carbonyldi*[*1,2-benzisoxazol-3(2H)-one*] *(6).* A mixture of (**5**) (4.3 g, 0.032 mol) and trichloromethyl chloroformate (0.96 ml, 0.008 mol) in toluene (30 ml) was refluxed with stirring for 1 d, then cooled. The precipitate was isolated by filtration and washed with toluene, and dried. Yield was 3.5 g (73%). Purification by recrystallization from toluene to give a white needles. Mp 205—206 °C; IR (KBr), 1780, 1765, and 1750 cm^{-1}.

Found: C, 60.8; H, 2.9; N, 9.3%. Calcd for $C_{15}H_8N_2O_5$: C, 60.82; H, 2.72; N, 9.46%.

3-Benzoyloxy-1,2-benzisoxazole (9). To a stirred solution of benzoic acid (0.244 g, 2.0 mmol), pyridine (0.16 ml, 2.0 mmol) in NMP (4 ml) was added **6** (0.592 g, 2.0 mmol), followed by stirring at 50 °C for 1 h. The reaction mixture was poured into water (100 ml). The precipitate formed was collected filtration, washed with water and dried *in vacuo*. Yield: 0.400 g (98%). Recrystallization from hexane produced white needles, mp 65—66 °C (lit,[9] 64 °C).

Amide (11). *General Procedure*: The condensing agent **6** (0.592 g, 2 mmol) was added to a stirred solution of the carboxylic acid (2 mmol) and pyridine (2 mmol) in NMP (4 ml) at 50 °C. After 1 h, the amine (2 mmol) was added. Stirring was continued for several hours. The mixture was poured into 1% aqueous sodium hydrogencarbonate. The precipitate was filtered and washed with water and dried.

Ester (12). *General Procedure*: A mixture of **6** (2 mmol), benzoic acid (2 mmol) and pyridine (2 mmol) in NMP (4 ml) was stirred at 50 °C for 1 h. To this mixture the alcohol (2 mmol) and triethylamine (2 mmol) were added. Stirring was continued for several hours. The reaction mixture was worked up as described above.

Amide Esrer (15). The condensing agent **6** (2 mmol) was added with stirring to a solution of benzoic acid (2 mmol) and pyridine (2 mmol) in NMP (4 ml) at 50 °C. After 1 h, *p*-aminophenol (**13**) (1 mmol) was added to this mixture. After stirring 1 d, triethylamine (2 mmol) was added, the mixture was stirred for 2 d and worked up as described. The compound **14** was obtained when triethylamine was omitted.

Protected Dipeptide Ester (18). *General Procedure*: To a solution of the *N*-protected α-amino acid (1 mmol) and pyridine (1 mmol) in dichloromethane (5 ml), **6** (1 mmol) was added under nitrogen. The solution was stirred for several hours at room temperature, then the α-amino acid ester hydrochloride (1 mmol) was added. The solution was stirred for 1 d at room temperature. After removal of the solvent *in vacuo*, the residue was dissolved in ethyl acetate, and the organic solution was washed 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 crystallization.

Polyamide (19). *General Procedure*: The condensing agent **6** was added to a stirred solution of isophthalic acid (1 mmol) and pyridine (2 mmol) in NMP (2 ml). The mixture was stirred for a defined time, then diamine (1 mmol) was added at room temperature. Stirring was continued for 2 d. 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. Inherent viscosity was measured at a concentration of 0.5 $g \cdot dl^{-1}$ in concentrated sulfuric acid at 30 °C.

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