1,1′-[Carbonyldioxy]dibenzotriazole: A New, Reactive Condensing Agent for the Synthesis of Amides, Esters, and Dipeptides

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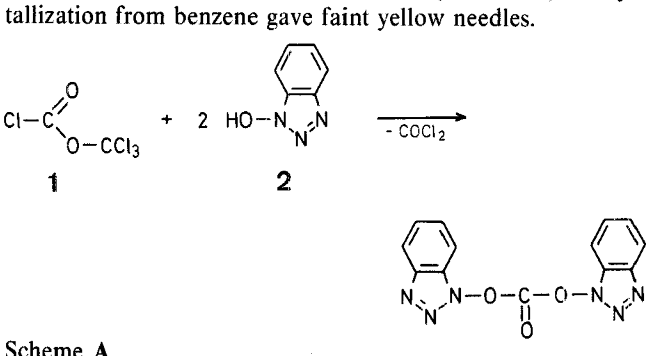
As a part of a continuing research program on the preparation of amides, esters, and polyamides under mild conditions, we have recently initiated the synthesis of new active condensing agents[1,2]. One requirement for an improved condensing agent is that the conversion of carboxylic acids to the active intermediates should be occur readily under mild conditions. We now report that 1,1′-[carbonyldioxy]dibenzotriazole (**3**) is a new reactive condensing agent for the synthesis of amides, esters, and dipeptides.

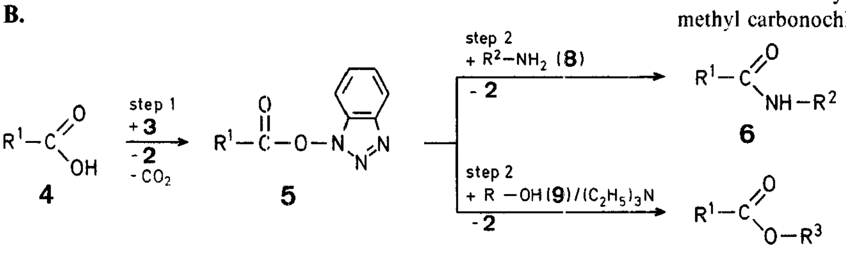
The new condensing agent **3** was conveniently prepared from trichloromethyl carbonochloridate (**1**) and 1-hydroxybenzotriazole (**2**) in 1:2 molar ratio in benzene (Scheme **A**). Recrystallization from benzene gave faint yellow needles.



Scheme **A**

In order to clarify the reaction path, the condensing agent **3** was treated with benzoic acid (**4a**) in *N*-methyl-2-pyrrolidone at room temperature for 1 h in the presence of pyridine. The reaction proceeded smoothly with liberation of carbon dioxide, to give 1-benzoyloxybenzotriazole (**5a**) in good yield. The active ester **5a** has been characterized by its high reactivity toward the nucleophiles[3,4].

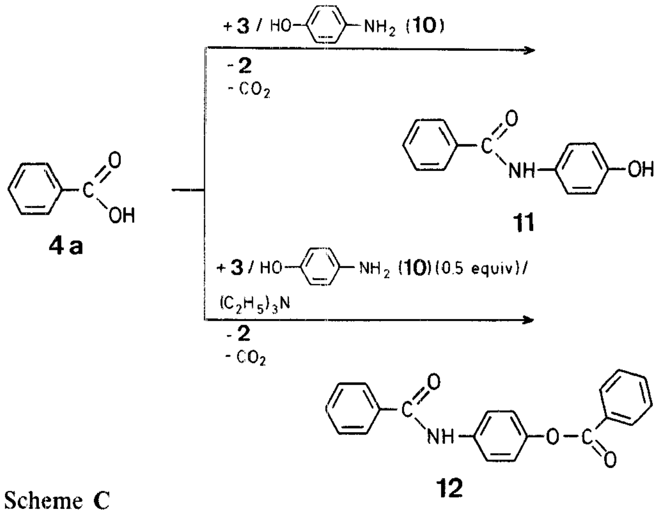
The conversions of carboxylic acids **4** into amides **6** or esters **7** using the condensing agent **3** were carried out by a one-pot procedure at room temperature in the presence of pyridine. Equimolar amounts of **4**, nucleophile, and the condensing agent **3** were used. This efficient procedure consists essentially of two reactions: formation of the active ester **5** from carboxylic acids as described above, and subsequent aminolysis or alcoholysis of the active ester **5** as shown in Scheme **B**.



Scheme **B**

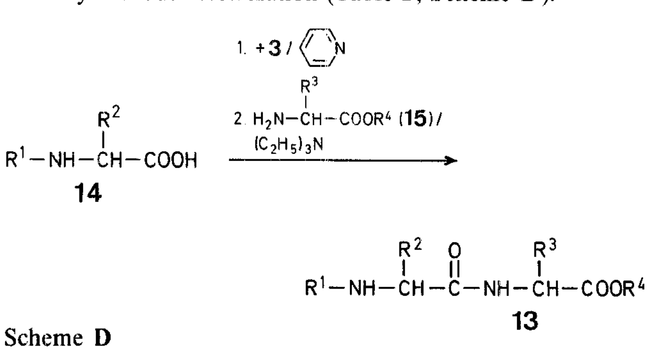
The reactions proceeded smoothly to give the corresponding amides **6** and esters **7** in moderate yields. The alcoholysis required the presence of an equimolar amount of triethylamine in step 2.

Having noticed this different reactivity of **5a** towards amines and alcohols we then studied the selective *N*-acylation and *N,O*-diacylation of *p*-aminophenol (**10**) either in the absence or the presence of triethylamine, respectively. The corresponding amide **11** and amide-ester **12** were obtained in good yields (Scheme **C**; Table 1).



Scheme **C**

Furthermore, the present reaction was found to be applicable to the preparation of dipeptides **13**. Thus, the reaction of an *N*-protected α-amino acid **14** with an α-amino acid ester hydrochloride **15** was carried out in the presence of pyridine. *N*-protected dipeptide esters **13** were prepared in good yields virtually without racemization (Table 2; Scheme **D**).



Scheme **D**

The new condensing agent **3** is a crystalline solid having good hydrolytic stability and therefore it is handled more easily than conventional agents. Furthermore, 1-hydroxybenzotriazole (**2**), as leaving group, is readily removed from the reaction products by washing the reaction mixture with cold 1% aqueous sodium hydrogen carbonate.

1,1′-[Carbonyldioxy]dibenzotriazole (3):

A mixture of 1-hydroxybenzotriazole (**2**; 41 g, 0.3 mol) and trichloromethyl carbonochloridate (**1**; 18 ml, 0.15 mol) in benzene (200 ml) is refluxed with stirring for 2 h. The precipitate is filtered, washed with benzene, and dried; yield: 31 g (70%); m.p. 150°C (dec.; from benzene).

$C_{13}H_8N_6O_5$	calc.	C 52.71	H 2.72	N 28.37
(296.2)	found	53.0	2.6	28.5

I.R. (KBr): ν = 1800 cm^{-1} (C=O).

Table 1. Preparation of Amides **6** and Esters **7** using Condensing Agent **3** (Schemes **B** and **C**)

Carboxylic Acid 4 (R^1)	Amine **8** (R^2) or Alcohol **9** (R^3)	Reaction Time	Product	Yield [%]	m.p. [°C]	
					found	reported
C_6H_5	**8** (C_6H_5)	2 h	**6a**	85	163-164°	163-164°[1]
C_6H_5	**8** ($C_6H_5CH_2$)	2 h	**6b**	75	105-106°	105-106°[1]
C_6H_5	**8** (C_6H_{11})	2 h	**6c**	80	150-151°	148-149°[6]
n-C_5H_{11}	**8** (C_6H_5)	2 h	**6d**	66	97-98°	97-98°[1]
n-C_5H_{11}	**8** ($C_6H_5CH_2$)	2 h	**6e**	64	54-55°	54-55°[1]
C_6H_5	**9** (C_6H_5)	2 d	**7a**	73	70-71°	70-71°[1]
C_6H_5	**9** (4-O_2N—C_6H_4)	2 d	**7b**	73	79-80°	81°[7]
C_6H_5	**9** (4-O_2N—C_6H_4—CH_2)	3 d	**7c**	65	90-91°	90-91°[1]
C_6H_5	**10**	2 h	**11**	94	219-221°	219-221°[1]
C_6H_5	**10** + $(C_2H_5)_3N$	2 h/2 d	**12**	84	242-243°	242-243°[1]

Table 2. Preparation of Protected Dipeptide Esters **13** using Condensing Agent **3** (Scheme **D**)

Protected Amino Acid	Amino Acid Ester	Product	Yield [%]	m.p. [°C]		$[\alpha]_D$ (temperature [°C], c, solvent)	
				found	reported	found	reported
Z-Val	Gly-OC_2H_5	Z-Val-Gly-OC_2H_5	75	170-171°	170-171°[1]	−32.9 (22°, 0.85, dioxan)	−32.4 (20°, 1.85, dioxan)[1]
Z-Val	Val-OCH_3	Z-Val-Val-OCH_3	70	114-116°	116°[8]	−24.4 (22°, 2.40, CH_3OH)	−24.3 (25°, 0.3, CH_3OH)[8]
Z-Ala	Gly-OC_2H_5	Z-Ala-Gly-OC_2H_5	78	100-101°	99-100°[9]	−22.0 (22°, 2.71, C_2H_5OH)	−22.3 (—, 3.65, C_2H_5OH)[9]
Boc-Leu	Leu-OCH_3	Boc-Leu-Leu-OCH_3	70	140-141°	141-142°[9]	−50.3 (22°, 0.73, CH_3OH)	−50.0 (—, 0.39, CH_3OH)[9]
Boc-Phe	Val-OCH_3	Boc-Phe-Val-OCH_3	92	116-117°	117-118°[9]	−10.8 (22°, 2.07, DMF)	−11.0 (—, 1.89, DMF)[9]

1-Benzoyloxybenzotriazole (5a):

To a stirred solution of **4a** (0.306 g, 2.5 mmol) and pyridine (0.20 ml, 2.5 mmol) in N-methyl-2-pyrrolidone (5 ml) is added **3** (0.741 g, 2.5 mmol), followed by stirring at room temperature for 1 h. The mixture is then poured into water (100 ml). The precipitate formed is collected by filtration, washed with water, and dried; yield: 0.47 g (80%); m.p. 80-81°C (from n-hexane); (Lit.[5], m.p. 77°C).

I.R. (KBr): $\nu = 1770\ cm^{-1}$ (C=O).

Amides 6; General Procedure:

Reagent **3** (0.741 g, 2.5 mmol) is added with stirring to a solution of the carboxylic acid **4** (2.5 mmol) and pyridine (2.5 mmol) in N-methyl-2-pyrrolidone (4 ml) at room temperature. After 1 h, the amine **8** (2.5 mmol) is added. Stirring is continued for 2 h. The mixture is poured into 1% aqueous sodium hydrogen carbonate (100 ml). The precipitate is collected and dried (Table 1).

Esters 7; General Procedure:

A solution of **3** (0.741 g, 2.5 mmol), benzoic acid (2.5 mmol), and pyridine (2.5 mmol) in N-methyl-2-pyrrolidone (4 ml) is stirred at room temperature for 1 h. Then the alcohol **9** (2.5 mmol) and triethylamine (2.5 mmol) are added. Stirring is continued two or three days. The reaction mixture is worked up as described above (Table 1).

Amide Ester 12:

A solution of **3** (0.741 g, 2.5 mmol), benzoic acid (2.5 mmol), and pyridine (2.5 mmol) in N-methyl-2-pyrrolidone (4 ml) is stirred at room temperature for 1 h. To this solution, p-aminophenol (**10**; 2.5 mmol) is added. After stirring for 2 h, triethylamine (2.5 mmol) is added and the reaction mixture is stirred for 2 days, and worked up described above (Table 1).

Hydroxy-amide **11** is obtained when triethylamine is omitted (Table 1).

Protected Dipeptide Esters 13; General Procedure:

To a solution of the N-protected α-amino acid **14** (1 mmol) and pyridine (1 mmol) in dichloromethane (2 ml), **3** (0.30 g, 1 mmol) is added under nitrogen. The solution is stirred for 1 h at 0°C, then the α-amino acid ester hydrochloride **15** (1 mmol) and triethylamine (1 mmol) are added. The solution is stirred for 3 h at room temperature. After removal of the solvent in vacuo, the residue is dissolved in ethyl acetate (100 ml) and the organic solution is washed successively with 1 normal hydrochloric acid (100 ml), 5% aqueous sodium hydrogen carbonate (100 ml), and saturated brine (100 ml), and then dried with anhydrous sodium sulfate. After evaporation of ethyl acetate, the dipeptide ester is purified by recrystallization (Table 2).

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