1,1′-Bis[6-(trifluoromethyl)benzotriazolyl] Oxalate (BTBO): A New Reactive Coupling Reagent for the Synthesis of Dipeptides, Esters, and Thio Esters[1]

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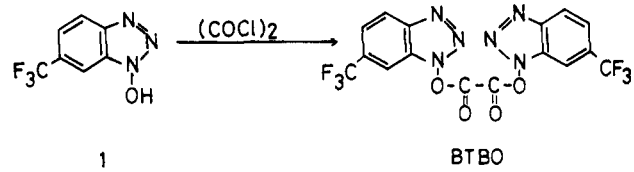
Preparation of amides, esters, and thio esters by coupling reactions is very important in organic synthesis, and many reagents for promoting coupling reactions by one-pot procedures have been reported.[2] In most cases, these coupling reactions are used to convert carboxylic acids into amides, esters, or thio esters. Most of the coupling reagents first react with the carboxylic acids to give activated intermediates which undergo subsequent nucleophilic attack by amino, hydroxy, or sulfhydryl groups. Therefore, the reactivity of the carboxyl is the most important factor in the coupling reaction. 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.[3] Activated esters are frequently prepared from *N*-hydroxy imides[2b,c] or 1-hydroxybenzotriazole[2b,c,4] with *N,N′*-dicyclohexylcarbodiimide (DCC). However, DCC causes side reactions such as formation of *N*-acylurea and Lossen rearrangement for *N*-hydroxysuccinimide.[5] We have therefore studied the behavior of activated esters and methods of activating carboxylic acids without a coupling reagent such as DCC.

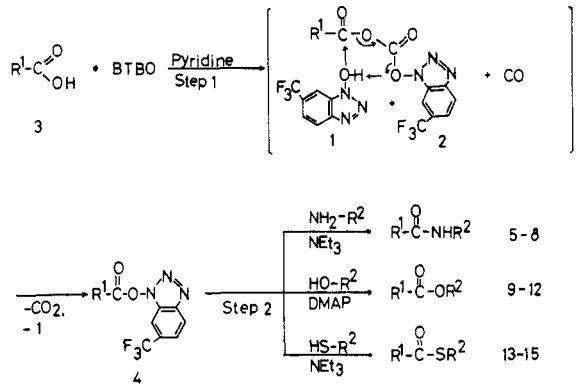
Recently, we have reported *N,N′*-disuccinimidyl carbonate (DSC),[6] *N*-succinimidyl diphenyl phosphate (SDPP),[7] *N,N′*-disuccinimidyl oxalate (DSO),[8] 1,1′-bis(benzotriazolyl) oxalate (BBTO),[8] 1,1′-bis(6-chlorobenzotriazolyl) oxalate (BCTO),[8] *N,N′*-bis(norbornenylsuccinimidyl oxalate (BNO),[8] and *N,N′*-diphthalimido oxalate (DPO)[8] as useful reagents for making activated esters and peptide synthesis without a coupling reagent such as DCC. Three other reagents, 6-chloro-1-[[(*p*-chlorophenyl)sulfonyl]-oxy]benzotriazole,[9,12,13] *O*-benzotriazolyl-*N,N′*-tetramethyluronium hexafluorophosphate,[10] and 1,1′-(carbonyldioxy)dibenzotriazole,[11] have also been reported as effective for such esterifications without DCC. In the case of 1,1′-(carbonyldioxy)dibenzotriazole, the reaction mechanism is similar to that of DSC;[6] all three reagents give a benzotriazole or 6-chlorobenzotriazole ester. Nucleophilic attack of alcohol or phenol on such esters requires an excess of alkyl alcohols[12] or phenols.[11]

Scheme I



1 BTBO

Scheme II



We now report a new activating reagent, 1,1′-bis[6-(trifluoromethyl)benzotriazolyl] oxalate (BTBO), for preparation of dipeptides, esters, and thio esters.

BTBO was easily prepared from 1-hydroxy-6-(trifluoromethyl)benzotriazole (1)[13] and oxalyl chloride in dry ether (Scheme I). It is easily purified by washing with dry ether and a trace of dry acetone and can be stored for several months in a freezer.

The reaction of BTBO with carboxylic acids **3** in the presence of pyridine as catalyst in acetonitrile at room temperature resulted in rapid liberation of carbon monoxide and carbon dioxide to give activated esters **4** in good yields. The conversions of carboxylic acids to amides **5–8**, esters **9–12**, or thio esters **13–15** using BTBO were carried out by a one-pot procedure at room temperature in the presence of tertiary amines, using equimolar amounts of carboxylic acids, nucleophiles, and coupling reagent. This procedure consists essentially of two reactions: formation of the activated esters from the carboxylic acids in step 1 and subsequent aminolysis, alcoholysis, or thioalcoholysis of the active esters **4** in step 2 shown in Scheme II. Alcoholysis and thioalcoholysis required the presence of an equimolar amount of a tertiary amine such as 4-(dimethylamino)pyridine (DMAP) or triethylamine (NEt_3) in step 2.

The reactions of BTBO with *N*-benzyloxycarbonyl (Z) amino acids quickly gave a clear solution of the activated ester, which without isolation was reacted directly with the amino acid ester hydrochloride and NEt_3. The dipeptide esters **5–8** were isolated by concentrating the solutions and removal of 1-hydroxy-6-(trifluoromethyl)benzotriazole (1) by washing with aqueous alkali; the results are summarized in Table I. Peptides prepared by using BTBO were optically pure, judging from the specific rotation data in Table I.

Products from the esterifications and thioesterifications were isolated by preparative thin-layer chromatography

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Table I. Preparation of Dipeptides Using BTBO

entry	R^1	R^2	product	yield, %	mp, °C	lit. mp, °C	$[\alpha]_D$, deg (c, solvent, °C)	lit. $[\alpha]_D$, deg (c, solvent, °C)
5	Z-Ala	Ala-OEt	Z-Ala-Ala-OEt	99	116.5	113–115[a]	−42.6 (1, EtOH, 21)	−42.4 (1, EtOH, 25)[b]
6	Z-Ala	Gly-OEt	Z-Ala-Gly-OEt	86	99–101	99–101[c]	−21.6 (1, EtOH, 23)	−22.1 (3.08, EtOH, 20)[c]
7	Z-Phe	Gly-OEt	Z-Phe-Gly-OEt	90	111–113	109–110[d]	−16.4 (1, EtOH, 22)	−17.0 (1, EtOH, 20)[d]
8	Z-Val	Gly-OEt	Z-Val-Gly-OEt	70	162–164	162–164[d]	−26.2 (0.5, EtOH, 22)	−27.0 (1, EtOH, 20)[d]

[a] Reference 15. [b] Reference 16. [c] Reference 17. [d] Reference 18.

Table II. Preparation of Esters and Thio Esters Using BTBO

entry	R^1	R^3	product	yield, %	amine step 1	amine step 2	IR (neat) $\nu_{C=O}$, cm^{-1}
9	Ph	CH_3	$PhCOOCH_3$	100	pyridine	DMAP	1720[a]
10	$PhCH_2$	C_2H_5	$PhCH_2COOC_2H_5$	89	pyridine	DMAP	1725[b]
11	$PhCH_2$	$CH(CH_3)_2$	$PhCH_2COOCH(CH_3)_2$	82	pyridine	DMAP	1720[c]
12	Z-Phe	CH_3	Z-Phe-OCH_3	98	pyridine	pyridine	1730[d]
13	Ph	C_2H_5	$PhCOSC_2H_5$	93	pyridine	triethylamine	1660[e]
14	$PhCH_2$	C_2H_5	$PhCH_2COSC_2H_5$	100	pyridine	triethylamine	1680[f]
15	$PhCH_2$	$C(CH_3)_3$	$PhCH_2COSC(CH_3)_3$	20	pyridine	triethylamine	1685[g]

[a,b] Reference 19. [c] MS, m/z 166 (M^+); ^1H NMR ($CDCl_3$) δ 1.20 (6 H, d, $(CH_3)_2$), 3.95 (2 H, s, CH_2), 4.98 (1 H, m, CH), 7.25 (5 H, s, C_6H_5). [d] MS, m/z 313 (M^+); ^1H NMR ($CDCl_3$) δ 3.05 (2 H, d, CH_2CH), 3.63 (3 H, s, CH_3), 4.57 (1 H, m, CH), 5.03 (2 H, m, CH_2), 5.29 (1 H, bd, NH), 6.87–7.18 (5 H, m, C_6H_5), 7.23 (5 H, s, C_6H_5). [e] MS, m/z 166 (M^+); ^1H NMR ($CDCl_3$) δ 1.37 (3 H, t, CH_3), 3.10 (2 H, q, CH_2), 7.33–8.02 (5 H, m, C_6H_5). [f] MS, m/z 180 (M^+); ^1H NMR ($CDCl_3$) δ 1.22 (3 H, t, CH_3), 2.82 (2 H, q, CH_2), 3.76 (2 H, s, $CH_2C_6H_5$), 7.22 (5 H, s, C_6H_5). [g] MS, m/z 208 (M^+); ^1H NMR ($CDCl_3$) δ 1.50 (9 H, s, $(CH_3)_3$), 3.77 (2 H, s, CH_2), 7.27 (5 H, s, C_6H_5).

or column chromatography on silica gel. As shown in Table II, yields were almost quantitative except in the case of *tert*-butyl thio ester **15**. With BTBO, nucleophilic attack of alcohol to active ester **4** occurs stoichiometrically, while excess alcohols or phenols is required with benzotriazole[11] and 6-chlorobenzotriazole esters.[12] Although the yields of peptides with BTBO were lower than those with BCTO,[8] the yield of esters was higher, indicating than BTBO is more reactive than other oxalate reagents.[8]

This study indicates than BTBO is a very useful reagent for the formation of peptides, esters, and thio esters. BTBO can be synthesized more conveniently and economically than DSC and SDPP. Furthermore, BTBO is not a skin irritant as is DCC, and BTBO active esterifications proceed much faster and produce only three byproducts, carbon monoxide, carbon dioxide, and 1-hydroxy-6-(trifluoromethyl)benzotriazole.

Experimental Section

N-Benzyloxycarbonyl amino acids were obtained commercially. Solvents were purified in the usual manner. All melting points are uncorrected. IR spectra were recorded on a JASCO A-2 spectrometer. NMR spectra were measured with a Varian T-60 spectrometer, using Me_4Si as an internal reference. Mass spectra (MS) were determined with a JMS-D-100 spectrometer at 75 eV by the direct inlet system. Specific rotations were measured with a JASCO Model DIP-181 polarimeter. Properties (IR, NMR, and MS spectra) of compounds synthesized were compared with those of authentic samples.

1-Hydroxy-6-(trifluoromethyl)benzotriazole (1). A mixture of 4-chloro-3-nitro-α,α,α-trifluorotoluene (25.0 g, 0.11 mol) and hydrazine hydrate (16.5 g, 0.33 mol) in 99% ethanol (34 mL) was refluxed for 24 h. After removal of the solvent under reduced pressure, the residue was dissolved in 10% aqueous Na_2CO_3 solution. The solution was washed with ether to remove the starting material and acidified with concentrated HCl to precipitate the product, which was washed with water and dried to obtain 21.6 g (96%) of 1; mp 143–147 °C.[14] This product was recrystallized from ether/isopropyl ether: MS, m/z 203 (M^+); IR (KBr) 1630 (aromatic) cm^{-1}; ^1H NMR (acetone-d_6) δ 7.50 (3 H, m, C_6H_3), 10.94 (1 H, b, OH). Anal. Calcd for $C_7H_4N_3OF_3$: C, 41.39; H, 1.98; N, 20.68. Found: C, 41.17; H, 1.90; N, 20.87.

1,1′-Bis[6-(trifluoromethyl)benzotriazolyl] Oxalate (BTBO). A solution of 1 (20.3 g, 0.1 mol) in 300 mL of dry ether was vigorously stirred with a mechanical stirrer, whereupon 25 g (0.2 mol) of oxalyl chloride was slowly added at room temperature. After stirring for 3 h, a white precipitate was filtered and washed with dry ether and a trace of dry acetone. Almost pure crystals of BTBO were obtained without recrystallization: 17.9 g (78%); mp 141–145 °C; MS, m/z 460 (M^+); IR (KBr) 1750, 1730 (CO), 1600 (aromatic) cm^{-1}; ^1H NMR (acetone-d_6) δ 7.50–8.25 (6 H, m, $C_6H_3 \times 2$). Anal. Calcd for $C_{16}H_6N_6O_4F_6$: C, 41.75; H, 1.31; N, 18.25. Found: C, 41.50; H, 1.44; N, 18.24.

Preparation of Dipeptides Using BTBO. A typical example is as follows: suspended BTBO (460 mg, 1 mmol) in acetonitrile (10 mL) was added to a solution of Z-L-alanine (223 mg, 1 mmol) and pyridine (79 mg, 1 mmol) in acetonitrile (10 mL). The reaction mixture became a clear solution in a second. After the reaction mixture was stirred for 1 h at room temperature, L-alanine ethyl ester hydrochloride (153.6 mg, 1 mmol) in acetonitrile solution (10 mL) and triethylamine (101 mg, 1 mmol) were added to it without isolation of active ester, and the resulting reaction mixture was stirred for 4 h. After evaporation of the solvent under reduced pressure, the residue was extracted with ethyl acetate. The organic layer was successively washed with 4% aqueous $NaHCO_3$, 1 N HCl, water, and brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residue was recrystallized from ethanol/hexane to yield Z-Ala-Ala-Oet (318 mg, 99%): mp 116.5 °C (lit.[13] mp 113–115 °C); $[\alpha]^{23}_D$ −42.6° (*c* 1.0, ethanol) (lit.[16] $[\alpha]^{25}_D$ −42.4° (*c* 1.0, ethanol)).

Preparation of Esters Using BTBO. A typical example is as follows: suspended BTBO (460 mg, 1 mmol) in acetonitrile (10 mL) was added to a solution of benzoic acid (122 mg, 1 mmol) and pyridine (79 mg, 1 mmol) in acetonitrile (10 mL). The reaction mixture became a clear solution in a second. After the reaction mixture was stirred for 1 h at room temperature, a solution of methanol (35 mg, 1.1 mmol) and 4-(dimethylamino)pyridine (DMAP) (134 mg, 1.1 mmol) in acetonitrile (2 mL) was added at room temperature. Stirring was continued for an additional 8 h. The reaction mixture was quenched with water and product was extracted 3 times with ethyl acetate; then the combined ethyl acetate layer was successively washed with 4% $NaHCO_3$ solution, 1 N HCl solution, water, and brine and dried over sodium sulfate.

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After removal of the solvent under reduced pressure, the residue was purified on silica gel thin-layer chromatography to afford methyl benzoate (136 mg, 100%); MS, m/z 136 (M^+). This compound was identified with an authentic sample[19] by comparing their NMR and IR spectra.

Preparation of Thio Esters Using BTBO. A typical example is as follows: suspended BTBO (460 mg, 1 mmol) in acetonitrile (10 mL) was added to a solution of benzoic acid (122 mg, 1 mmol) and pyridine (79 mg, 1 mmol) in acetonitrile (10 mL). The reaction mixture became a clear solution in a second. After the reaction mixture was stirred for 1 h at room temperature, a solution of ethanethiol (69 mg, 1.1 mmol) and triethylamine (111 mg, 1.1 mmol) in acetonitrile (2 mL) was added at room temperature. Stirring was continued for an additional 5 h. The reaction mixture was quenched with water and product was extracted 3 times with ethyl acetate; then the combined ethyl acetate layer was successively washed with 4% $NaHCO_3$ solution, 1 H HCl solution, water, and brine, and dried over sodium sulfate. After removal of solvent under reduced pressure, the residue was separated by silica gel thin-layer chromatography to afford ethyl thiobenzoate: 154 mg (93%); MS, m/z 166 (M^+); IR (KBr) 1660 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (3 H, t, CH_3), 3.10 (2 H, q, CH_2), 7.33-8.02 (5 H, m, C_6H_5).

Registry No. 1, 26198-21-0; BTBO, 93605-83-5; Z-Ala-Ala-OEt, 5673-69-8; Z-Ala-Gly-OEt, 2503-32-4; Z-Phe-Gly-OEt, 2778-34-9; Z-Val-Gly-OEt, 2766-17-8; $PhCOOCH_3$, 93-58-3; $PhCH_2COOC_2H_5$, 101-97-3; $PhCH_2COOCH(CH_3)_2$, 4861-85-2; Z-Phe-OMe, 35909-92-3; $PhCOSC_2H_5$, 1484-17-9; $PhCH_2COSC_2H_5$, 14476-63-2; $PhCH_2COSC(CH_3)_3$, 61049-77-2; Z-Ala, 1142-20-7; Z-Phe, 1161-13-3; Z-Val, 1149-26-4; Ala-OEt·HCl, 1115-59-9; Gly-OEt, 459-73-4; 4-chloro-3-nitro-α,α,α-trifluorotoluene, 121-17-5; hydrazine, 302-01-2; oxalyl chloride, 79-37-8; benzoic acid, 65-85-0; benzeneacetic acid, 103-82-2.

(19) The authentic samples were supplied from Aldrich Chemical Co.

Formation of Ethers from Ozonides by Reductive Cleavage of the Two C-O Bonds of the Peroxide Bridge

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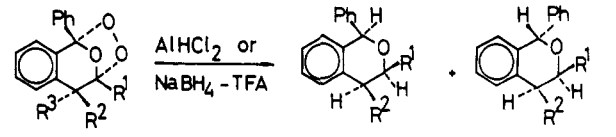
While developing a new transformation of ozonide (1,2,4-trioxolane),[1] it has been found that the reaction of *exo,endo*-1-methyl-3-phenyl- and *exo,endo*-1-methyl-2,3-diphenylidene ozonides **1e-h** with $AlHCl_2$ gives in each case a mixture of isomeric ethers (eq 1). Moreover, the product composition has been found to be a marked function of the stereochemistry of the ozonides.[1a] To obtain further insight into this novel transformation, we performed the reactions of a series of bicyclic and monocyclic ozonides (**1a-m**) with $AlHCl_2$ in diethyl ether[2] or with sodium borohydride in trifluoroacetic acid (TFA).[3]

Results and Discussion

Under the two reduction conditions, bicyclic ozonides **1a-j** were effectively reduced to give the corresponding ethers in 5-66% yield (Table I). Not only the stereochemistry of the bicylic ozonides **1a-h** but also the reduction conditions affected the stereochemistry of the



(1)

1

a; R^1=Ph, R^2=R^3=H
b; R^1=Me, R^2=R^3=H
c; R^1=R^2=Ph, R^3=H
d; R^1=R^3=Ph, R^2=H
e; R^1=Ph, R^2=Me, R^3=H
f; R^1=Ph, R^2=H, R^3=Me
g; R^1=R^3=H, R^2=Me
h; R^1=R^2=H, R^3=Me
i; R^1=R^2=R^3=H

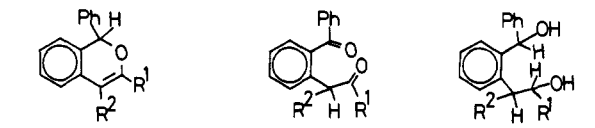
2

a; R^1=Ph, R^2=H
b; R^1=Me, R^2=H
c; R^1=R^2=Ph
d; R^1=Ph, R^2=Me
e; R^1=H, R^2=Me
f; R^1=R^2=H

3

a; R^1=Ph, R^2=H
b; R^1=Me, R^2=H
c; R^1=R^2=Ph
d; R^1=Ph, R^2=Me
e; R^1=H, R^2=Me

product ethers. Treatment of 2,3-diphenylindene ozonide (**1a**) with 8 molar equiv of $AlHCl_2$ in ether, gave together with diol **6a**, a mixture of *cis*-3,4-dihydro-1,3-diphenyl-1*H*-2-benzopyran (**2a**) and the trans isomer **3a** in 49% yield, the **2a**/**3a** ratio being 21:79. The reaction of **1a** in the system $NaBH_4$-TFA gave, however, a mixture of 73% **2a** and 27% **3a**.[4] The byproducts were diketone **5a** and 1,3-diphenyl-1*H*-2-benzopyran (**4a**). From *endo*-1-



4a; R^1=Ph, R^2=H
4b; R^1=Me, R^2=H
4c; R^1=H, R^2=Me

5

a; R^1=Ph, R^2=H
b; R^1=Me, R^2=H
c; R^1=R^2=Ph
d; R^1=Ph, R^2=Me
e; R^1=H, R^2=Me

6

a; R^1=Ph, R^2=H
b; R^1=Me, R^2=H
c; R^1=Ph, R^2=Me
d; R^1=H, R^2=Me
e; R^1=R^2=H

methyl-2,3-diphenylindene ozonide (**1f**) four isomeric ethers might have been formed. In reality, only two isomers, *cis,cis*- and *trans,cis*-3,4-dihydro-1,3-diphenyl-4-methyl-1*H*-2-benzopyrans (**2d**/**3d**), were produced. the trans, cis isomer **3d** was the major product in the reduction by $AlHCl_2$, whereas the reduction in the system $NaBH_4$-TFA gave predominantly the cis,cis isomer **2d**.

The observed reagent-dependent product composition would be interpreted as follows (Scheme I). For $AlHCl_2$ reduction of **1f**, cleavage of the C-O bond of the peroxide bridge by $AlHCl_2$ would provide the carboxonium ion intermediate **13**. Since the $AlHCl_2$ coordinated to the peroxidic oxygen occupies a favorable position for hydride transfer, hydride transfer to **13** would occur predominantly from the same side as the methyl group to afford **14**. The absence of the cis,trans isomeric ether in the products would suggest that hydride transfer to **14** occurs exclusively from the less-hindered side. In the system $NaBH_4$-TFA, cleavage of the C-O bond leads to the formation of the carboxonium ion **15**. Attack by BH_4^- on **15** from the same direction as the methyl group is likely to be significantly prevented by the pseudoaxial methyl group. From **15**, therefore, the intermediate **16** is mainly produced, followed by hydride transfer from the less hindered side to yield the cis,cis ether **2d**.

In marked contrast to the case of endo ozonide **1f**, the compositions of the isomeric ethers from the exo isomer **1e** under two different conditions were almost reagent independent, cis,cis ether **2d** being obtained predominantly. A similar trend was also observed for *exo*-1,2,3-triphenylindene ozonide (**1c**). This preference of cis,cis ether **2d** clearly indicates that the transfer of the two

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