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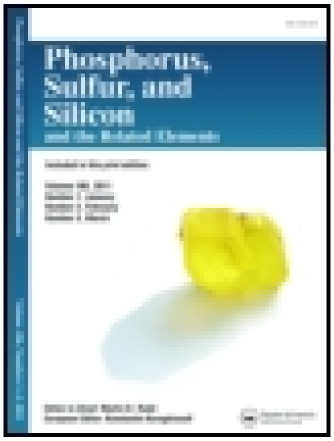

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THE APPLICATION OF N,N′DIBROMO-N,N′-1,2-ETHANEDIYL BIS(P-TOLUENESULFONAMIDE) AS A POWERFUL REAGENT FOR CONVERSION OF CARBOXYLIC ACIDS INTO ESTERS AND AMIDES WITH TRIPHENYLPHOSPHINE

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THE APPLICATION OF *N,N*′DIBROMO-*N,N*′-1,2-ETHANEDIYL BIS(*P*-TOLUENESULFONAMIDE) AS A POWERFUL REAGENT FOR CONVERSION OF CARBOXYLIC ACIDS INTO ESTERS AND AMIDES WITH TRIPHENYLPHOSPHINE

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In the presence of equivalent amounts of triphenylphenylphosphine and N,N′*-dibromo-*N,N′*-1,2-ethanediylbis(*p*-toluenesulphonamide) ester and amide compounds can be generated in high yields from the corresponding carboxylic acid and alcohols or amines.*

Keywords: Acylation; alcohol; amide; amine; BNBTS; ester; Ph_3P

The conversion of carboxylic acids to esters and amides are commonly encountered reactions in organic chemistry.

A large number of ester-protecting groups have been described in the literature.[1] Although a variety of conditions for ester formation have been developed,[2] they are not always satisfactory in yield and/or simplicity of operation. Most require either the presence of strong acids, bases, or other catalysts, or the application of heat. Simple processes that allow esterification under mild conditions are very desirable. These procedures are of considerable interest, especially in the construction of many peptides, macrolides,[3] and natural products.

Several methods were reported for activation of carboxylic acids and their conversion to esters and other derivatives. The most common

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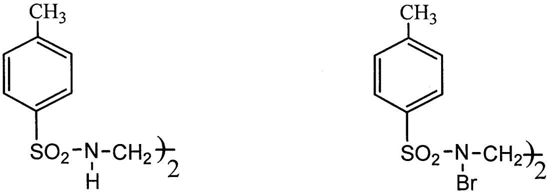


1 **2** (BNBTS)

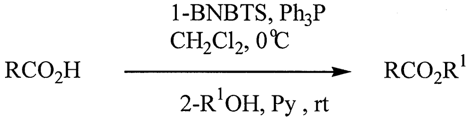
FIGURE 1

are carbodiimides,[4] *N*-acyl derivatives of imidazole,[5] acylcarbonates,[2f,6] (1,1′-carbonyldioxy)dibenzotriazoles,[7] chlorotrimethylsilane,[2a,8] several oganophosphorus reagents,[9] sulfonylchlorides,[2e] sulfuryl chlorofloride,[10] 2-ethoxy-1-(ethoxycarbonyl)-1,2-dihydroquinoline (EEDQ),[11] pyridine-2-thiol esters,[12] and alkylchloroformates.[13]

Amides can be generated from the corresponding carboxylic acids and amines by a variety of methods. The reaction has been carried out by a variety of methods such as anhydride, acid chloride, or via in situ coupling agents such as dicyclohexylcarbodiimide,[14] *N*,*N*′-carbonyldiimidazole,[15] benzotriazol-1-yldiethylphosphate(BDP),[16] 1,1′-carbonylbis(3-methylimidazo-lium)triflate (CBMIT),[17] Lawesson's reagent,[18] $Ti(OBu)_4$,[19] $Sn[N(TMS)_2]_2$,[20] 2-ethoxy-1-(ethoxycarbonyl)-1,2-dihydroquinoline (EEDQ),[21] sulfonylchloride,[22] and *N*,*N*-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride.[23]

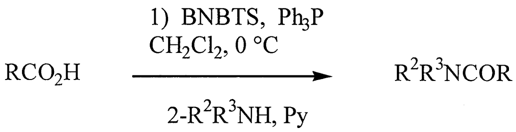
Extending our work on the use of *N*-halosulfonamides[24] in organic synthesis, we now report a convenient method for the conversion of carboxylic acids into esters and amides using a new, cheap, and easily made reagent, *N*,*N*′-dibromo-*N*,*N*′-1,2-ethanediyl bis(*p*-toluenesulfonamide), or BNBTS (Figure 1).[24a,b,c,d]

The reaction of carboxylic acids with alcohols in the presence of BNBTS and triphenylphosphine in CH_2Cl_2 afforded esters without side products (Scheme 1). The method has the advantage in terms of yields, simplicity of the reaction conditions for the conversion, short reaction time and no side products.



SCHEME 1

The reaction of carboxylic acids with amines in the presence of BNBTS and triphenylphosphine in CH_2Cl_2 afforded amides without

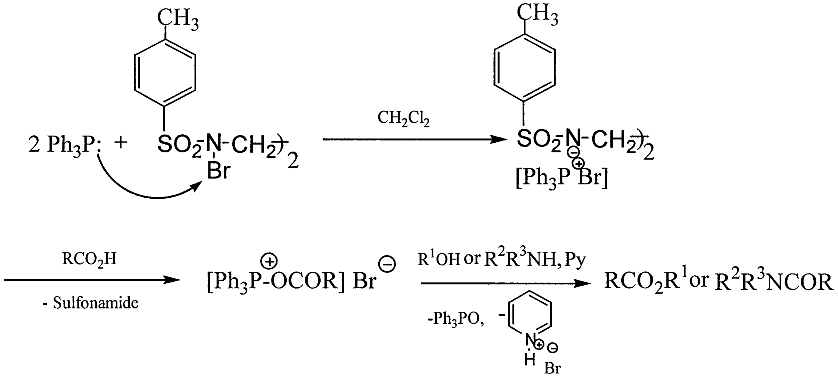


$$RCO_2H \xrightarrow[\text{2-}R^2R^3NH,\ Py]{\text{1) BNBTS, } Ph_3P,\ CH_2Cl_2,\ 0\ °C} R^2R^3NCOR$$

SCHEME 2

side products (Scheme 2). The method has the advantage in terms of yields, simplicity of the reaction conditions for the conversion, short reaction time, and no side products.

The recovered starting material (**1**) was rebrominated and also used many times without reducing the yield. We believe that the reaction is initiated via direct nucleophilic attack of triphenylphosphine at the *N*-bromosulfonamide, as indicated in Scheme 3, and then reaction with alcohol or amine affords the corresponding ester or amide in high yields.



SCHEME 3

The results of conversion of carboxylic acids into esters are presented in Table I. The results of conversion of carboxylic acids into amides are presented in Table II.

CONCLUSION

The advantages of BNBTS are as following:

1. The preparation of BNBTS is easy and simple.[24c]
2. This compound is stable for a long time under atmospheric condition and it is a solid.

TABLE I Conversion of Carboxylic Acids to Esters at Room Temperature

Entry	Acid	Alcohol	Ester[a]	Yield (%)
1	Acetic acid	Isoamyl alcohol	3-Methyl butyl ethanoate	88
2	Acetic acid	Hexanol	*n*-Hexyl ethanoate	92
3	Hexanoic acid	*n*-Propanol	Propyl hexanote	89
4	Hexanoic acid	Methanol	Methyl hexanoate	91
5	Benzoic acid	Methanol	Methyl benzoate	93
6	Formic acid	Benzyl alcohol	Benzyl formate	89
7	Formic acid	*n*-Propanol	Propyl formate	91
8	Acetic acid	*n*-Propanol	*n*-Propyl acetate	90
9	Benzoic acid	2-Methyl-2-butanol	2-Methyl-2-butyl benzoate[b]	83
10	Maleic acid	Phenol	Diphenyl maleate[b]	85

[a] Products were characterized by their physical constants, comparision with authentic samples, IR, and NMR spectra.

[b] Product were not isolated, yields were obtained by ^{31}PNMR (by calculation of the ratio by of Ph_3PO to Ph_3P integration).

3. After reaction of BNBTS with substrate, the sulphonamide (**1**) is recovered and can be reused many times without decreasing the yield.
4. The isolation of products with this reagent is simple.
5. Using an excess amount of the reagent does not cause any problem in the reaction condition.
6. The reactivity of BNBTS is high and reactions with substrate were done at 0°C to room temperature.

EXPERIMENTAL

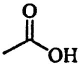
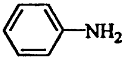
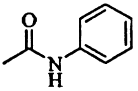
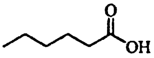
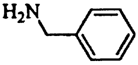
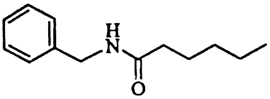
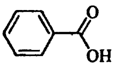
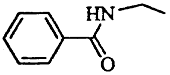
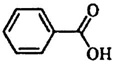
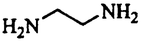
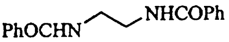
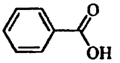
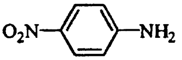
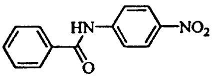
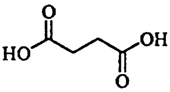
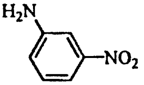
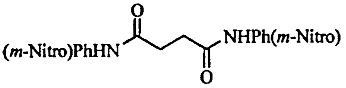
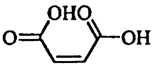
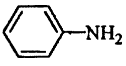
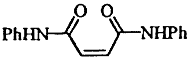
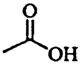
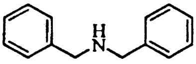
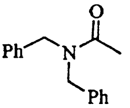
Infrared (IR) and Nuclear magnetic resonance (NMR) spectra were recorded using a Shimadzu 435-U-04 spectrophotometer and a 90 MHz Jeol FT-NMR spectrophotometer, respectively. NMR chemical shifts were measured relative to TMS (int; 1H).

General Procedure for the Conversion of Carboxylic Acids to Esters

Triphenylphosphine and carboxylic acid (10 mmol of each) were dissolved in dichloromethane (15 ml), and then BNBTS (2.63 g) added in small portion while the mixture was vigorously stirred.

The stirring was continued for a few minutes. The reaction mixture was thereafter set aside at room temperature while a new solution of alcohol (10 mmol) and pyridine (15 mmol) was being prepared; thereafter alcohol was added dropwise to the solution with vigorous stirring and stirring was continued for a few minutes. The reaction mixture

TABLE II Conversion of Carboxylic Acids to Amides

Entry	Acid	Amine	Amide	Yield (%)
1				90[a]
2				91[b]
3				93
4				92
5				90
6				94
7				84
8				92

Only *a* and *b* were isolated by column chromatography; the others were identified by TLC, and their yields were obtained by ^{31}PNMR, by integration of Ph_3PO relative to Ph_3P.

was filtered and the solid (triphenylphosphine oxide, sulfonamide, and pyridin hydrobromide) was removed, and the ester was purified by distillation.

General Procedure for Conversion of Carboxylic Acids to Amides

Triphenylphosphine and carboxylic acid (10 mmol) were dissolved in dichloromethane (15 ml), and then BNBTS (2.63 g, 5 mmol) added in small portion while the mixture was vigorously stirred. The stirring was continued for a few minutes. The reaction mixture was thereafter set aside at room temperature while a new solution of amine (10 mmol) and pyridine (15 mmol) was being prepared, then the amine solution was added dropwise to the solution with vigorous stirring and stirring was continued for a few minutes. The reaction mixture was concentrated by evaporation of the solvent. The concentrated solution was chromatographed through a column of silica gel with a 7:1 ratio of petroleum benezene (40–60) to aceton as eluent. Evaporation of the solvent gave the pure amide.

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