Tetrabenzylpyrophosphate: An Efficient Catalyst for the Synthesis of Carboxamides from Carboxylic Acids and Amines

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An efficient method for the synthesis of simple and sterically hindered carboxamides from various carboxylic acids and amines using tetrabenzylpyrophosphate (TBPP) as a coupling agent in the presence of 4-(dimethylamino)pyridine (DMAP) is described. The reaction is operationally straightforward, proceeds under mild conditions at room temperature, and affords the desired product in high yield.

The synthesis of carboxamides is one of the most fundamental and important processes in organic and medicinal chemistry for producing natural and unnatural bioactive compounds such as peptides, β-lactams, and macrolactams, and to date, various efficient coupling or dehydration methods for the synthesis of carboxamides have been reported.[1–4] The use of tetraethylpyrophosphate is known in the literature for the synthesis of carboxamides,[5] and very recently, Mukaiyama et al. have reported the synthesis of carboxamides using benzenesulfonic anhydride as an efficient catalyst.[6] Although many coupling reagents that afford carboxamides have been investigated, there remain disadvantages, including low yields due to increasing amounts of by-product, prolonged reaction times, use of toxic reagents and tedious workup procedures, which necessitate the development of an alternative route for the synthesis of biologically and commercially important carboxamide derivatives.

The above observations prompted us to consider the use of tetrabenzylpyrophosphate (TBPP, Figure 1) for the synthesis of various simple and sterically hindered carboxamides. TBPP can be easily prepared from inexpensive dibenzylphosphate.[7] To the best of our knowledge, the use of TBPP as a dehydrating agent for the synthesis of carboxamides from carboxylic acids and amines has not been reported. Pyrophosphates are well known as phosphorylation agents. Hence, phosphorylated carboxylic acid mixed anhydrides are expected to be active intermediates in the formation of carboxamides from amines.

We now report a new and efficient method for the synthesis of carboxamides from corresponding carboxylic acids and amines using TBPP as a coupling reagent in the presence of DMAP as a promoter.

Intially, the condensation of 4-phenoxybutyric acid with 2-phenylethylamine in the presence of TBPP and DMAP in $CHCl_3$ at room temperature was examined as a model reaction (Table 1).

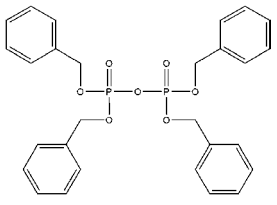


Figure 1. Tetrabenzylpyrophosphate (TBPP).

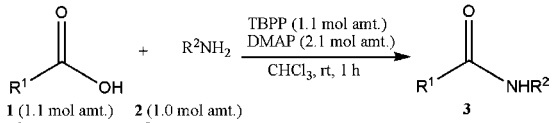
When 1.1 moles of TBPP and 2.1 moles of DMAP were used, the reaction was complete within 1 h to furnish the desired carboxamide i.e., 4-phenoxy-*N*-(2-phenylethyl)butanamide, in 95% yield (Entry 1). Furthermore, the effect of different activators was examined. Thus, 4-pyrrolidinopyridine (PPY), *N*-methylimidazole, and *N*-butylimidazole were also each successfully employed in this reaction as alternative activators to DMAP and afforded the desired carboxamide in good yield (Entries 2–4). The use of tertiary amines, such as triethylamine and ethyldiisopropylamine, as activators in such coupling reactions also afforded the desired carboxamide in moderate yield (Entries 5 and 6). The use of 1-hydroxybenzotriazole (HOBt), resulted in a decrease in the yield of the desired carboxamide to only 52% (Entry 7).

The stoichiometry of DMAP and TBPP was also examined (Table 2). The desired carboxamide was formed in quantitative yield when 1.1 to 2.2 molar ratio of TBPP and DMAP was utilized (Entry 1).[8] Interestingly, a slight deviation from this molar ratio had a significant effect on yield. Thus, a 1.1 to 2.1 molar ratio of TBPP and DMAP afforded a reduced yield of 89% of the desired carboxamide (Entry 2). The yield of carboxamide decreased to 72% when a 1.1 to 1.2 molar ratio of TBPP and DMAP was used (Entry 3).

The effect of different solvents was also examined (Table 3). The reaction proceeded smoothly in both nonpolar solvents such as $CHCl_3$, CH_2Cl_2, or toluene, and in polar solvents such as THF, DMF, or MeCN to afford the desired carboxamide in excellent yields (Entries 1 and 3–7). It was also observed that the yield of the carboxamide decreased to 83% when the reaction was carried out in $CHCl_3$ at 0 °C (Entry 2).

Examples of the synthesis of carboxamides from the coupling of various carboxylic acids and amines utilizing TBPP/DMAP under optimized conditions are listed in Table 4. The condensation reaction of 4-phenoxybutyric acid with pri-

Table 1. Effect of activating agents on carboxamide yield

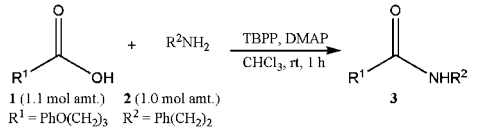


1 (1.1 mol amt.) $R^1 = PhO(CH_2)_3$ **2** (1.0 mol amt.) $R^2 = Ph(CH_2)_2$ **3**

Entry	Activator	Yield[a]/%
1	DMAP	95
2	PPY	89
3	*N*-Methylimidazole	92
4	*N*-Butylimidazole	90
5	Triethylamine	75
6	Diisopropylamine	79
7	HOBt	52

[a]Isolated yield.

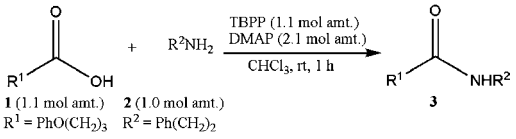
Table 2. Effect of molar amounts of TBPP and DMAP on carboxamide yield



Entry	TBPP/mol amt.	DMAP/mol amt.	Yield[a]/%
1	1.1	2.2	quant.
2	1.1	2.1	89
3	1.1	1.2	72

[a]Isolated yield.

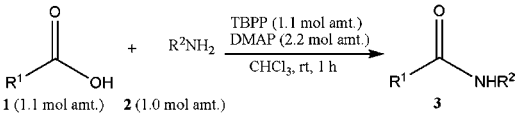
Table 3. Effect of solvents on carboxamide yield



Entry	Solvent	Yield[a]/%
1	$CHCl_3$	95
2[b]	$CHCl_3$	83
3	CH_2Cl_2	93
4	Toluene	88
5	THF	90
6	DMF	83
7	MeCN	85

[a]Isolated yield. [b]The reaction was carried out at 0 °C.

Table 4. Synthesis of various carboxamides with TBPP/DMAP



Entry	Carboxylic acid	Amine	Yield[a]/%
1	$PhO(CH_2)_2COOH$	$Ph(CH_2)_2NH_2$	quant.
2	$PhO(CH_2)_2COOH$	$PhCH(NH_2)CH_3$	97
3	$PhO(CH_2)_2COOH$	$PhCH_2NHCH_3$	94
4	$PhO(CH_2)_2COOH$	Piperidine	93
5	$PhO(CH_2)_2COOH$	$(CH_3)_3CNH_2$	91
6	$(CH_3)_2CHCOOH$	$Ph(CH_2)_2NH_2$	quant.
7	$(CH_3)_2CHCOOH$	$PhCH_2NHCH_3$	95
8	$(CH_3)_2CHCOOH$	Piperidine	92
9	$Ph_2CHCOOH$	$Ph(CH_2)_2NH_2$	quant.
10	$Ph_2CHCOOH$	$PhCH_2NHCH_3$	92
11	$Ph_2CHCOOH$	Piperidine	91
12	c-$C_6H_{11}COOH$	$Ph(CH_2)_2NH_2$	95
13	c-$C_6H_{11}COOH$	$PhCH_2NHCH_3$	91
14	c-$C_6H_{11}COOH$	Piperidine	93

[a]Isolated yield.

mary and secondary amines, including the sterically hindered *tert*-butylamine, afforded the corresponding carboxamide in excellent yield (Entries 1–5). Moreover, carboxamides were also obtained in good yields when sterically hindered 2,2′-disubstituted carboxylic acids, such as 2-methylpropanoic acid, diphenylacetic acid, and cyclohexanecarboxylic acid, were condensed with primary and secondary amines (Entries 6–14) in the presence of TBPP/DMAP. All acidic and basic impurities were easily removed by washing with 5% aqueous NaOH solution and 1 M HCl solution. The mechanism likely involves formation of a phosphoric–carboxylic mixed anhydride as the active intermediate in carboxamide formation. However, the catalytic role of DMAP in the reaction is unclear, and an alternative mechanism may involve initial formation of a transient phosphoric–4-(dimethylamino)pyridinium adduct. Of note, 2 moles of DMAP were required for optimal yields of carboxamide. Interestingly, when lower mole equivalents of DMAP were utilized, although carboxamide yield decreased, no phosphoric amide by-products were detected.

In conclusion, a convenient and effective method for the synthesis of a wide variety of carboxamides from carboxylic acids and amines is established utilizing TBPP/DMAP as coupling agent. This method appears to offer a new procedure for the synthesis of carboxamides which affords high yields, mild conditions, and short reaction times, together with a simple work-up procedure. Further studies on the applicability of TBPP/DMAP as a general utility coupling agent, are currently in progress.

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8 Typical experimental procedure for the synthesis of 4-phenoxy-*N*-(2-phenylethyl)butanamide: To a stirred solution of 4-phenoxybutyric acid (94.5 mg, 0.525 mmol) in $CHCl_3$ (5.0 mL) were successively added TBPP (295.9 mg, 0.55 mmol) and DMAP (134.2 mg, 1.1 mmol) at 25 °C. After stirring for 15 min, 2-phenylethylamine (60.5 mg, 0.50 mmol) in $CHCl_3$ (5.0 mL) was added drop-wise over 10 min and stirring continued for 1 h. The reaction was quenched with 5% aqueous NaOH solution (5 mL) and extracted with EtOAc (25 mL). The organic layer was separated, washed successively with 5% aqueous NaOH solution (5 mL), 1 M HCl (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated to dryness. The crude product was crystallised from hot EtOAc:hexanes (1:1 v/v, 50 mL) affording the product as a pure white solid.

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