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An activated phosphate for an efficient amide and peptide coupling reagent

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Activation of diethyl phosphate was realized by attaching trifluoromethanesulfonanilide as an efficient leaving group and the phosphate 1 proved to be a promising amide and peptide coupling reagent.

Formation of amide and peptide bonds through a coupling reaction of carboxylic acids with amines is a fundamental synthetic operation. Although some coupling reagents are commercially available, coupling reactions of bulky acids with bulky amines still prove to be challenging. Therefore, continuing efforts are being made to develop more efficient coupling reagents such as aminium salts,[1] phosphonium salts,[2] halouronium or halophosphonium salts,[3] reagents forming mixed anhydrides,[4] hydroxamic acid-type reagents,[5] additives[6] and so on.[7] Utilization of a phosphate derivative as a component of a mixed anhydride has been a promising methodology for an efficient coupling reagent, in which an appropriate leaving group such as chloro,[8] azide,[9] cyano,[10] heterocyclic,[11] and phosphate[12] is attached. A more powerful but less nucleophilic leaving group should provide much more efficient phosphate coupling reagents. We examined trifluoromethanesulfonanilide[13] as the leaving group, since this group has proven its ability as a chemoselective and rapid alkoxycarbonylation reagent.[14] We describe herein that diethyl phosphate **1** bearing trifluoromethanesulfonanilide as a leaving group is a new rapid and efficient amide and peptide coupling reagent.

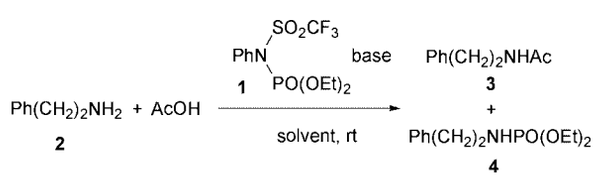
Successive treatment of trifluoromethanesulfonanilide with sodium hydride in THF at room temperature for 1 h and then with diethyl chlorophosphate at room temperature for 2 days and purification by silica gel column chromatography gave **1**[15] in 90% yield.

The coupling reaction of 2-phenylethylamine **2** with 1.5 equiv. of acetic acid proceeded smoothly using 1.2 equiv. of **1** in the presence of 2 equiv. of triethylamine in dichloromethane at room temperature for 0.5 h. The mixture was washed with saturated sodium bicarbonate and then concentrated to afford a mixture of products, which were purified by recrystallization or column chromatography to afford the corresponding acetamide **3** in 95% yield along with phosphoramide **4**[16] in 5% yield (Table 1, entry 1). The leaving group of **1**, trifluoromethanesulfonanilide, was recovered quantitatively for recycling simply by extracting from an acidified aqueous solution. Formation of **4** could be suppressed by increasing the amount of acetic acid to 2 equiv., and **3** was the only isolable product in 99% yield (entry 2). The reaction in DMF proceeded faster than that in dichloromethane, however, product distribution was not satisfactory, affording **3** in 93% yield along with **4** in 7% yield (entry 3). Exhaustive examination of organic bases to replace triethylamine, such as Hünigs base, dimethylaniline, 2,6-lutidine, and 1,8-bis(dimethylamino)naphthalene (proton sponge),[17] revealed that proton sponge was a good choice of base to provide **3** in a satisfactory yield without formation of a detectable amount of **4** (entry 6, 7). It is noteworthy that the coupling reaction proceeded in methanol to afford **3** quantitatively (entry 9).

Coupling of α-branched primary and secondary amines with acetic acid proceeded smoothly within 8 h to give the corresponding amides in high yield (Table 2, entries 1–5). Reactions of a primary amine with α-branched carboxylic acids and benzoic acid gave within 1 h the amides in quite high yield (entries 6–8). *tert*-Butylamine was coupled with α-branched carboxylic acids and benzoic acid to give the amides in satisfactory yield (entries 9–11).

As a touchstone for coupling of sterically hindered amines and carboxylic acids, Z-Aib-OH **8** (Aib = 2-aminoisobutyric acid) and H-Aib-OMe hydrochloride **9** were treated with **1** in the presence of 4 equiv. of diisopropylethylamine and 1 equiv. of 1-hydroxy-7-azabenzotriazole (HOAt)[18] in DMF for 24 h to afford Z-Aib-Aib-OMe **10** in satisfactory 70% yield (Scheme 1). These satisfactory results indicate versatility of **1** as a coupling reagent.

Table 1 Effects of base and solvent on coupling of AcOH and **2** using **1**



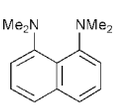
Entry	Base	Solvent	AcOH (equiv.)	Time/min	**3** (%)	**4** (%)
1	Et_3N	CH_2Cl_2	1.5	30	95	5
2		CH_2Cl_2	2.0	30	99	0
3		DMF	2.0	10	93	7
4	2,6-lutidine	CH_2Cl_2	1.5	30	96	0
5		DMF	2.0	10	88	12
6		CH_2Cl_2	1.5	30	97	0
7		DMF	2.0	10	98	0
8		MeCN	1.5	30	97	0
9		MeOH	2.0	720	99	0

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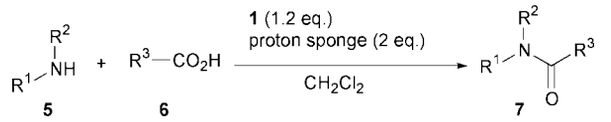
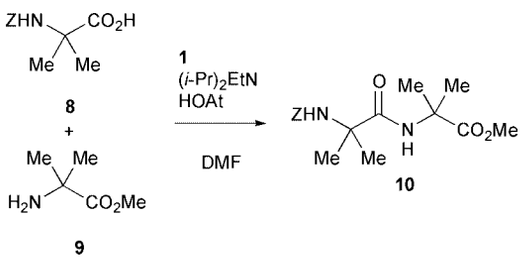
Table 2 Coupling reaction of amine **5** with carboxylic acid **6** using **1**



5 6 7

Entry	R^1	R^2	R^3	Time/h	**7** (%)
1	Ph(Me)CH	H	Me	0.5	93
2	*t*-Bu	H	Me	8.0	89
3	$PhCH_2$	Me	Me	1.0	96
4	Ph	H	Me	4.0	92
5	Ph	Me	Me	6.0	99
6	$Ph(CH_2)_2$	H	*i*-Pr	0.5	97
7	$Ph(CH_2)_2$	H	*t*-Bu	0.5	93
8	$Ph(CH_2)_2$	H	Ph	1.0	95
9	*t*-Bu	H	*i*-Pr	8.0	77
10	*t*-Bu	H	*t*-Bu	8.0	80
11	*t*-Bu	H	Ph	24.0	92



Scheme 1 Coupling reaction of 2-aminoisobutyric acid using **1**.

Phosphate **1** was also applicable for a peptide coupling reaction. Treatment of Bz-Leu-OH and H-Gly-OEt hydrochloride with **1** in the presence of proton sponge in DMF at room temperature for 30 min gave Bz-Leu-Gly-OEt in 85% yield (Young's test).[19] The extent of racemization of the peptide was determined to be 2%.[20]

In summary, based on excellent performance in coupling of bulky amines and carboxylic acids as well as low racemization in peptide coupling, the new phosphate **1** activated by trifluoromethanesulfonanilide was shown to be a promising reagent for coupling reactions.

Acknowledgements

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Notes and references

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20 Specific rotation of synthesized Bz-Leu-Gly-OEt: $[a]_D^{20}$ −33.3 (*c* 2.00, EtOH).