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Preparation of Carboxamides via Carboxylic−Phosphoric Anhydrides

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Abstract:

A number of reagents used to prepare carboxamides via a carboxylic−phosphoric anhydride intermediate have been re-examined. It was found that a simple carboxylic−phosphoric anhydride prepared from a carboxylic acid and commercially available diethyl chlorophosphate provided several significant advantages over more complex intermediates in many cases.

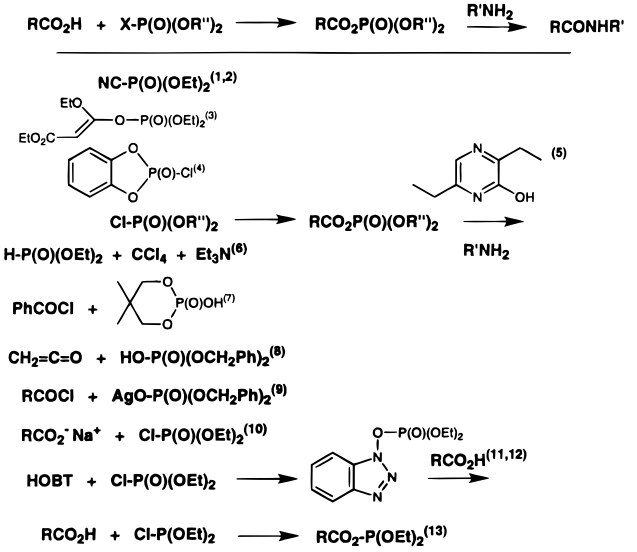
Introduction

The formation of a carboxamide from a carboxylic acid and an amine is a common operation in organic processes. The classical approach involving conversion of the carboxylic acid to an acid chloride followed by reaction with the amine in the presence of a base often gives rise to problems of selectivity due to the highly reactive reagents employed and the highly reactive nature of carboxylic acid chlorides. An array of alternative reagents have been developed to activate the carboxylic acid in the formation of amides, and each offers particular advantages of selectivity or ease of purification that make the selection of the correct reagent the key to a successful chemical process.

On a laboratory scale, it is often convenient to employ a carbodiimide reagent for this purpose since these reagents are readily available and give good selectivity while maintaining high reactivity. Carbodiimide reagents are often expensive, however, and they are inconvenient to use on a large scale due to toxicology and waste handling issues. In the course of investigating alternatives to the carbodiimide coupling for the formation of amides, it was found that mixed carboxylic−phosphoric anhydrides are convenient activated intermediates for reaction with amines. Furthermore, it was found that a simple reaction procedure was often just as effective in carrying out the transformation as more elaborate reactions using exotic reagents. This procedure may provide a useful alternative to other methods which cannot be used due to considerations of selectivity, or where patent considerations prevent the use of more commonly encountered reagents.

Some reagents used in the preparation of carboxylic−phosphoric anhydrides are shown in Scheme 1. These reagents are often derived from dialkylphosphoryl halides[1−3] or are diarylphosphoryl halides.[4] Dialkylphosphoryl halide is used in conjunction with an acyl-transfer reagent, although

Scheme 1



it is not clear if the auxiliary reagent plays any role in the formation of the anhydride.[5] Other approaches to the anhydride intermediate include the use of dialkyl phosphites,[6] dialkylphosphoric acids,[7,8] and their salts.[9] The few cases where dialkylphosphorus halides have been used directly do not involve direct formation of the mixed anhydride. One account uses reaction of dialkylphosphorus halide with the sodium salt of a carboxylic acid.[10] Dialkylphosphorus halide is used with *N*-hydroxybenzotriazole (HOBT), another acyl-transfer reagent, but there is some confusion as to whether this reagent serves to form the phosphorus anhydride of the carboxylic acid[11] or to form the HOBT ester.[12] Yet another account uses a dialkyl chlorophosphite.[13]

Results

Selected examples prepared by some of these methods have been repeated using the simple reaction sequence shown in Scheme 2. A carboxylic acid (**1**) is reacted with the inexpensive reagent diethyl chlorophosphate (**2**) in tetrahydrofuran in the presence of triethylamine. The resulting carboxylic−phosphoric anhydride (**3**) is reacted in situ with

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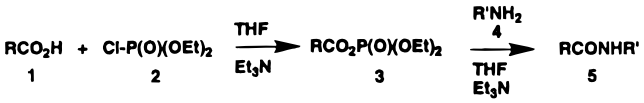
Table 1

literature method: reagent (ref) R	R′	product	yield (%)	diethyl chlorophosphate method yield[b] (%)
	Diethyl Cyanophosphate[1,2]			
Ph	c-Hex	**5a**	97	80
$PhCH_2$	Ph	**5b**	83	60
	Diethyl α-Ethoxy-β-carboxyethylvinyl phosphate[3]			
Cbz-NH−CH_2	Ph	**5c**	62	68[c]
Cbz-NH−CH_2	CH_2CO_2Et	**5d**	74	66
Cbz-NHCH-($CH_2CH(CH_3)_2$)	CH_2CO_2Et	**5e**	63	53
	2-Chloro-2-oxo-1,3,2-benzodioxaphosphole[4]			
CH_3	CH_2Ph	**5f**	84	36
Ph	CH_2Ph	**5g**	42	93
Cbz-NH−CH_2	CH_2Ph	**5h**	63	60[c]
Cbz-NH−CH_2	CH_2CO_2Et	**5d**	76	66
	Diethyl Chlorophosphate + 3,6-Diethyl-2-hydroxypyrazine[5]			
Ph	Ph	**5i**	81	86
Ph	CH_2Ph	**5g**	83	93
	2-Benzoyloxy-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane[7]			
Ph	Ph	**5i**	90	86
	Acetyldibenzylphosphate[8]			
CH_3	Ph	**5j**	*a*	52
	Diethylchlorophosphate + Na Salt of Acid[10]			
CF_3	Ph	**5k**	*a*	*d*
t-Bu	Ph	**5l**	*a*	87
	Diethylchlorophosphate + HOBT[11,12]			
Ph	c-Hex	**5a**	93	80
$PhCH_2$	Ph	**5b**	96	60
CH_3	CH_2Ph	**5f**	92	36
Ph	Ph	**5i**	96	86

[a] No yield given. [b] Recrystallized yields. [c] Product somewhat impure by NMR. [d] Intractable mixture.

Scheme 2



the amine component (**4**) to form the amide (**5**). The results are shown in Table 1.

In most cases, the amides **5** are formed using the diethyl chlorophosphate reagent in yields comparable to those which are observed using the reagents shown in Scheme 1. Exceptions are the acetamides **5f** and **5j**, which are difficult to recrystallize efficiently, and the trifluoroacetamide **5k**, which gives predominately the phosphoramide resulting from attack of the amine on the phosphorus side of the mixed anhydride **3** ($R = CF_3$).

Often an optically active component is included in the examples to determine if the amidation method is mild enough to avoid racemization of the asymmetric component or product. Example **5e** is included to determine if the phosphoric anhydride method is compatible with optically active components. The resulting Cbz-leucylglycine ethyl ester (**5e**) retains 77% optical purity. This indicates that, by adjusting reaction conditions, it may be possible to preserve optical activity during this reaction.

Table 2

product	recrystallization solvent	mp[a] (°C)	lit. mp (°C)	yield (%)
5a	EtOH/H_2O	147−147.5	151−152[1]	80
5b	EtOH	114−115	118−119[1]	60
5c	EtOAc/heptane	142−147	146[3]	68
5d	EtOAc/heptane	100−104[b]	82[3]	66
5e	EtOH/H_2O	86−89	101[3]	53[c]
5f	$PhCH_3$/heptane	56−58	61[4b]	36
5g	EtOH	103	104−105[4b]	93
5h	EtOAc/heptane	105−106	118−119[4b]	60
5i	EtOH	161−162	164−165[5]	86
5j	$PhCH_3$	105−107	115[8] (108−109[d])[14]	52
5l	Heptane	117−121	118−120[15]	87

[a] Uncorrected. [b] Higher mp unexplained. ^1H NMR consistent with expected structure. [c] Compound **5e**: $[\alpha]^{25}_D = -20.8°$ (lit.[3] −27°). [d] From benzene.

Conclusion

It has been shown that mixed carboxylic−phosphoric anhydrides can be easily prepared from a carboxylic acid and diethyl chlorophosphate, and that these intermediates can be reacted with amines to form amides in one-pot procedure. This simple procedure replaces a number of elaborate methods using exotic reagents which have appeared in the literature for generating the activated intermediates. This gives the process chemist another viable choice for carrying out the transformation of a carboxylic acid and an amine to a carboxamide.

Experimental Section

Starting materials, reagents, and solvents were obtained from Aldrich Chemical Co., Milwaukee, WI, and were used as received.

CAUTION: *Diethyl chlorophosphate is highly toxic, paticularly by absorption through the skin. Personal protective equipment should be evaluated for suitability for use with this compound.*

General Procedure. A mixture of 1.00 equiv of the carboxylic acid component and 2.20 equiv of triethylamine is dissolved in tetrahydrofuran (1000 mL/mol). To this mixture is added 1.05 equiv of diethyl chlorophosphate with stirring and cooling over 5−10 min at 15−20 °C. The resulting white suspension is stirred 3 h at ambient temperature. To this mixture is added a solution of 1 equiv of amine in tetrahydrofuran (200 mL/mol) at 20−25 °C. The reaction is stirred for 1 h, whereupon TLC analysis shows that acid and amine have been consumed. The reaction is transferred to a separatory funnel with ethyl acetate (1200 mL/mol) and water (500 mL/mol). The layers are separated, and the organic layer is washed with 500 mL/mol portions of 1 N hydrochloric acid, saturated sodium bicarbonate solution (2×), and brine. The organic layer is dried over anhydrous magnesium sulfate, filtered, and evaporated. The crude amines are recrystallized and dried. Recrystallization solvents, melting points, and yields for the various amides are shown in Table 2. In addition, ^1H NMR spectra have been obtained for each amide. The spectra are consistent with the structure or match published spectra for each compound.

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