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A Mild and Efficient Amide Formation Reaction Mediated by $P(OEt)_3$ and Iodine

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With the activation of $P(OEt)_3$ and I_2, carboxylic acids can smoothly react with various primary and secondary amines, affording a series of amides, including peptides without racemization. ^{31}P NMR spectroscopy studies showed that carboxylic phosphoric mixed anhydride was the reactive intermediate and a possible mechanism was herein proposed.

Since amide moieties are ubiquitous in numerous important natural products, pharmaceuticals, and synthetic compounds, amide formation reactions are one of the most important transformations in organic chemistry.[1] To date, a large number of amidation reactions have been established. Generally, carboxylic acids need to be preactivated either by converting to more reactive acid chlorides, anhydrides and active esters, or by using coupling reagents such as carbodiimides. Unfortunately, most of these procedures produce a lot of undesirable byproducts that complicate the purification processes, require harsh conditions or lead to partial racemization. In recent years, some improved amide formation reactions using novel coupling reagents or catalysts such as XtalFluor-E $[(F_2SNEt_2)BF_4]$[2] and 2-Iodophenylboronic acid[3] have been reported. Nevertheless, more practical, mild, scalable and racemization-free amidation procedures are still in demand.[1f]

During the last decades, many phosphorus compounds, including various phosphinic and phosphric acid derivatives,[1d] phosphorus oxychloride ($POCl_3$),[4] *n*-propanephosphonic acid anhydride (T3P),[5] and triphenylphosphine (PPh_3),[6-14] have been developed as efficient coupling reagents for the synthesis of amides. Among them, the easily available and inexpensive PPh_3-mediated reactions attracted our attention. As early in 1966, Lee et al[6] found that PPh_3 and CCl_4 could convert carboxylic acids to amides efficiently. Further studies showed that PPh_3 and other halide sources, such as CCl_3CN,[7] I_2,[8] NCS,[9] NBS,[10] Br_2,[11] $BrCCl_3$[12] and CBr_4,[13] could also promote the amidation reactions. Unfortunately, one apparent disadvantage of these processes is that the byproduct triphenylphosphine oxide ($Ph_3P=O$) is hard to remove completely from the products and only separable by chromatography. To overcome this drawback, polymer-supported PPh_3 has been used and successfully simplified the purification process.[8] Very recently, Mecinović et al[14] reported a PPh_3-catalyzed amide bond formation reaction through *in situ* reduction of $Ph_3P=O$ to PPh_3. These developments were effective but complicated the reaction system and increased the expenditure. Inspired by the classic Wittig-Horner Reaction and the recent developments in the cyclodehydration reaction by Huy and Koskinen,[15] which used $P(OEt)_3$ in replace of PPh_3 and the byproduct could be readily removed via basic workup, we reasoned that $P(OEt)_3$ and I_2 might be applied to the amidation reaction and solve the problem of the removal of $Ph_3P=O$. Surprisingly, to our knowledge, there were no such reports thus far. Herein, we wish to present our results in this paper that the combination of $P(OEt)_3$ and I_2 can efficiently mediate the amidation of carbonyl acids, affording various amides, including chiral amides without racemization.

We initially selected benzoic acid **1a** and *n*-butylamine **2a** as the model substrates to examine whether $P(OEt)_3$ and I_2 can promote the amidation reaction and the results are shown in Table 1. To our delight, the reaction of **1a** with $P(OEt)_3$ and I_2 in CH_2Cl_2 in the presence of Et_3N followed by addition of *n*-$BuNH_2$ proceeded smoothly to give the desired amide **3a** in good yield (Entry 1). This process could also be scaled to 10 mmol of **1a** in one batch and 13g of **3a** was obtained in about 75% yield with good purity after simple alkanine washing workup. Further screening the solvents revealed that CH_2Cl_2, DCE (dichloroethane), $CHCl_3$ and CH_3CN were all effective, but the yield of **3a** was quite low in THF and DMF (Entries 1–6). Both organic base (DMAP, *N*-Methylmorpholine (NMM), Et_3N) and inorganic base (K_2CO_3) performed well, and Et_3N gave the best yield (Entries 1, 7–9). In the absence of $P(OEt)_3$ and I_2, only trace amount of **3a** was observed (Entry 10).

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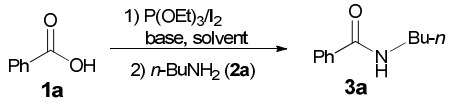
Electronic Supplementary Information (ESI) available: Experimental procedure, spectral data and ^1H, ^{13}C NMR spectrum for **3a–3r**, chiral HPLC for **3q** and **3r**. See DOI: 10.1039/x0xx00000x

Table 1 Base and Solvent Screening for the amidation of Benzoic Acid **1a**[a]



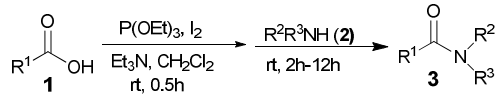
Entry	Base	Solvent	% Yield[b]
1	Et_3N	CH_2Cl_2	80 (75[c])
2	Et_3N	DCE	80
3	Et_3N	$CHCl_3$	79
4	Et_3N	CH_3CN	71
5	Et_3N	THF	29
6	Et_3N	DMF	0.4
7	DMAP	CH_2Cl_2	70
8	NMM	CH_2Cl_2	75
9	K_2CO_3	CH_2Cl_2	75
10	Et_3N	CH_2Cl_2	7[d]

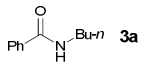
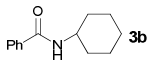
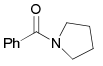
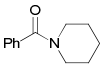
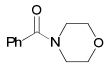
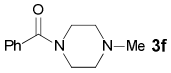
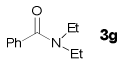
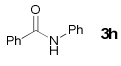
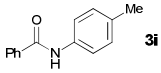
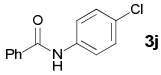
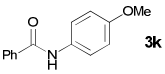
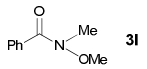
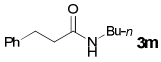
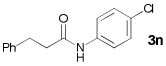
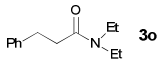
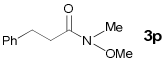
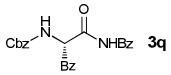
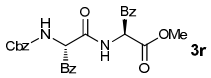
[a] Reactions were carried out with $P(OEt)_3$ (0.10 mmol), I_2 (0.10 mmol), **1a** (0.10 mmol) and base (0.15 mmol) in anhydrous solvent at 0 °C to r.t. for about 30 minutes followed by addition of **2a** (0.12 mmol) at r.t. for 6 hours. [b] Estimated by HPLC analysis. [c] Isolated yield. [d] Without addition of $P(OEt)_3$ and I_2.

With these optimization conditions in mind, we then explored the scope of this reaction and the results were summarized in Table 2. In most cases, the purification process was simple and column chromatography was not necessary, since the amidation reaction proceeded quite cleanly and the by-product diethyl phosphate could be easily removed by washing with dilute alkaline solution. As shown in Table 2, carboxylic acid **1a** or **1b** was first treated with $P(OEt)_3$, I_2 and Et_3N for about 30 minutes followed by addition of various amines at room temperature for 2 to 12 hours, leading to a series of amides in good to high yields (Entries 1–16). Both aliphatic primary amines (i.e. *n*-butylamine, cyclohexamine) and secondary amines (i.e. pyrrolidine, piperidine, morpholine, 1-methylpiperazine, diethylamine) worked well (Enties 1–7, 13, 15). Even aromatic amines with weaker nucleophilicity proceeded smoothly but needed longer reaction time, affording the desired amides in good yields (Entries 8–11, 14). Notably, *N*-methoxy-*N*-methyl (Weinreb) amides, a class of versatile building blocks to form ketones and aldehydes,[16] could be synthesized through the reaction of carboxylic acids with Me(MeO)NH·HCl using the present method under mild conditions (Entries 12, 16). As amine hydrochloride (i. e. Me(MeO)NH·HCl) is usually solid and insoluble in CH_2Cl_2, we dissolved it in anhydrous DMF with one additional equivalent of base to neutralize its hydrochloride in the second step.

This procedure can also be applied to the synthesis of chiral amides. *N*-Cbz-phenylalanine (**1c)** reacted with benzylamine and methyl ester of phenylalanine hydrochloride (Phe-Me.HCl) under similar reaction conditions, giving the desired amides **3q** and **3r** in excellent yields without noticeable racemization

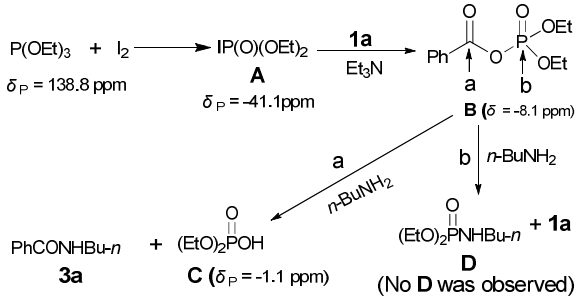
Table 2 Synthesis of various amides using $P(OEt)_3/I_2$[a]



Entry	Amide	Time (h)	% Yield[b]
1	 **3a**	2	75
2	 **3b**	2	95
3	 **3c**	2	82
4	 **3d**	2	97
5	 **3e**	2	91
6	 **3f**	2	90
7	 **3g**	12	65
8	 **3h**	12	91
9	 **3i**	12	82
10	 **3j**	12	53
11	 **3k**	12	67
12	 **3l**	2	75[c]
13	 **3m**	2	65
14	 **3n**	12	80
15	 **3o**	2	67
16	 **3p**	2	86[c]
17	 **3q**	2	85[d]
18	 **3r**	12	90[c,d]

[a] Conditions: $P(OEt)_3$ (1.0 mmol), I_2 (1.0 mmol), carboxylic acid **1** (1.0 mmol), Et_3N (1.5 mmol), anhydrous CH_2Cl_2, amine **2** (1.2 mmol), unless noted otherwise. [b] Isolated yield. [c] Use the solution of amine·HCl in DMF and Et_3N (2.0 mmol). [d] Use *N*-methylmorpholine (NMM) instead of Et_3N.

Scheme 1. ^{31}P NMR detection results and a proposed mechanism for the $P(OEt)_3/I_2$-mediated amidation of **1a**



(Table 2, Entries 17–18, see Supporting Information). Taking into account that *N*-methylmorpholine (NMM) is widely used in the synthesis of peptides as a weaker and better base than Et_3N to avoid racemization,[5,17] we used NMM instead of Et_3N as base in these cases.

In order to elucidate the role of $P(OEt)_3$ and I_2, we next used ^{31}P NMR spectroscopy to detect the reaction process and a possible mechanism was herein proposed (Scheme 1). The solution of $P(OEt)_3$ in $CDCl_3$ showed a strong singlet at 138.8 ppm. Addition of iodine led to rapid decoloration of iodine and appearance of a new signal at –41.1 ppm, indicating the formation of diethyl iodophosphate **A** [lit.[18], δ_p = –41.0 ppm]. After adding benzoic acid **1a** and Et_3N to this reaction mixture for about 30 minutes, the mixed anhydride **B** resonating at –8.1 ppm emerged and the peak of **A** disappeared gradually. In the end, the addition of *n*-$BuNH_2$ resulted in the appearance of diethyl phosphate **C** at –1.1 ppm and generation of the desired amide **3a**. The reaction exhibited high regioselectivity since no undesired by-product **D** from attacking the amine on the phosphorus center of the anhyride **B** was observed.

According to the above results, mixed carboxylic phosphoric anhydrides are the reactive intermediates for the present reaction. That means the role of $P(OEt)_3$ and I_2 is quite different from that of PPh_3 and I_2 in the literature,[8] which believed to undergo acyl phosphonium species or acyl iodide. It is reported that mixed carboxylic phosphoric anhydrides are efficient activated intermediates for amide synthesis, which generally show higher regioselectivity toward amine attack than dicarboxynic mixed anhydrides and are often more resistent to racemization.[1d] Many reagents, such as diethylcyano-phosphate (DECP),[19] diethyl phosphorochloridate (DEPC),[20] diphenylphosphoryl azide (DPPA),[21] are used to prepare the mixed phosphoric anhydrides. Unfortunately, these reagents are usually unstable, need to be prepared in advance, or only show medium reactivity. The present procedure provided a convenient and efficient way for the first time to synthesize the mixed phosphoric anhydrides via *in situ* formation of diethyl iodophosphate from readily available, cheap and stable compounds (i.e. $P(OEt)_3$ and I_2).[18b]

Conclusions

In conclusion, an efficient, mild and scalable amide formation reaction promoted by $P(OEt)_3$ and I_2 was developed. Mechanistic studies through ^{31}P NMR detection demonstrated that carboxylic-phosphoric mixed anhydrides were the key intermediates for this reaction, which led to the desired amides with very high regioselectivity. The advantageous of this procedure include mild reaction condition, broad substrate generality, easy removal of the by-product, and high resistance to racemization.

Acknowledgements

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