

View Article Online View Journal

RSC Advances

This article can be cited before page numbers have been issued, to do this please use: P. Chen, H. Wang and A. Peng, *RSC Adv.*, 2015, DOI: 10.1039/C5RA18459B.



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This Accepted Manuscript will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about *Accepted Manuscripts* in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard <u>Terms & Conditions</u> and the <u>Ethical guidelines</u> still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.



www.rsc.org/advances

Published on 29 October 2015. Downloaded by UNIVERSITY OF OTAGO on 30/10/2015 01:49:37.



Journal Name

COMMUNICATION

A Mild and Efficient Amide Formation Reaction Mediated by P(OEt)₃ and Iodine

Received 00th January 20xx, Accepted 00th January 20xx

Pei-Jiang Chen,^a Hai-Yang Wang^a and Ai-Yun Peng*^a

DOI: 10.1039/x0xx00000x

www.rsc.org/

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. ³¹P 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-lodophenylboronic acid³ 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 (POCl₃),⁴ *n*-propanephosphonic acid anhydride (T3P),⁵ and triphenylphosphine (PPh₃),⁶⁻¹⁴ have been developed as efficient coupling reagents for the synthesis of amides. Among them, the easily available and inexpensive PPh₃-mediated reactions attracted our attention. As early in 1966, Lee et al⁶ found that PPh₃ and CCl₄ could convert carboxylic acids to amides efficiently. Further studies showed

that PPh₃ and other halide sources, such as CCI_3CN , ⁷ I_2 , ⁸ NCS, ⁹ NBS,¹⁰ Br₂,¹¹ BrCCl₃¹² and CBr₄,¹³ could also promote the one Unfortunately, apparent amidation reactions. disadvantage of these processes is that the byproduct triphenylphosphine oxide (Ph₃P=O) is hard to remove completely from the products and only separable by chromatography. To overcome this drawback, polymersupported PPh₃ has been used and successfully simplified the purification process.⁸ Very recently, Mecinović et al¹⁴ reported a PPh₃-catalyzed amide bond formation reaction through in situ reduction of Ph₃P=O to PPh₃. 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 PPh₃ 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 Ph₃P=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 CH₂Cl₂ in the presence of Et₃N followed by addition of n-BuNH₂ 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 CH₂Cl₂, DCE (dichloroethane), CHCl₃ and CH₃CN 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), Et₃N) and inorganic base (K₂CO₃) performed well, and Et₃N 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).

^{a.} School of Chemistry & Chemical Engineering, Sun Yat-sen University, 135 Xingangxi Lu, Guangzhou, 510275, China. E-mail: cespay@mail.sysu.edu.cn

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

Published on 29 October 2015. Downloaded by UNIVERSITY OF OTAGO on 30/10/2015 01:49:37.

DOI: 10.1039/C5RA18459B Journal Name

	0 1) P(OEt) ₃ /l ₂ base, solvent 2) <i>n</i> -BuNH ₂ (2a)	→ Ph N 3a	_Bu-n
Entry	Base	Solvent	% Yield ^b
1	Et ₃ N	CH_2Cl_2	80 (75 ^c)
2	Et ₃ N	DCE	80
3	Et ₃ N	CHCl ₃	79
4	Et ₃ N	CH ₃ CN	71
5	Et ₃ N	THF	29
6	Et ₃ N	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 ₃ N	CH ₂ Cl ₂	7^d

Table	1	Base	and	Solvent	Screening	for	the	amidation	o
Benzo	ic /	Acid 1 a	a ^a						

^{*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 byproduct 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, I₂ and Et₃N 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, 1methylpiperazine, 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 CH₂Cl₂, 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

-	O P(OEt)a la		0
¹ 1ص		rt 2b-12b F	R ¹ N K-
R	1 rt, 0.5h	1, 21-1211	3 R ³
Entry	Amide	Time (h)	% Yield ^b
1	Ph H Bu-n 3a	2	75
2	Ph H 3b	2	95
3	Ph N 3c	2	82
4	Ph N 3d	2	97
5	Ph N o 3e	2	91
6	Ph N—Me 3f	2	90
7	Ph N Et 3g	12	65
8	Ph H 3h	12	91
9	Ph H 3i	12	82
10		12	53
11		12	67
12	Ph N Me 3I	2	75 ^c
13	Ph Y ^{Bu-n} 3m	2	65
14	Phr N 3n	12	80
15	Ph N Et 30	2	67
16	Ph Me 3p	2	86 ^c
17	Cbz ⁻ NHBz 3q	2	85 ^d
18		12 3r	90 ^{c,d}

Table 2 Synthesis of various amides using $P(OEt)_3/I_2^{a}$

^{*a*} Conditions: P(OEt)₃ (1.0 mmol), I₂ (1.0 mmol), carboxylic acid **1** (1.0 mmol), Et₃N (1.5 mmol), anhydrous CH₂Cl₂, amine **2** (1.2 mmol), unless noted otherwise. ^{*b*} Isolated yield. ^{*c*} Use the solution of amine HCl in DMF and Et₃N (2.0 mmol). ^{*d*} Use *N*-methylmorpholine (NMM) instead of Et₃N.

Scheme 1. ³¹P 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 ³¹P NMR spectroscopy to detect the reaction process and a possible mechanism was herein proposed (Scheme 1). The solution of $P(OEt)_3$ in CDCl₃ 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, $\delta_p = -41.0$ ppm]. After adding benzoic acid **1a** and Et₃N 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*-BuNH₂ 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 PPh₃ 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 I₂).^{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 ³¹P 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

This work was supported by Guangdong Natural Science Foundation (Research Grant No. S2013010012465).

Notes and references

- For recent representative eamples and reviews, see: (a) J. D. Goodreid, P. Duspara, A. C. Bosch and R. A. Batey, J. Org. Chem., 2014, **79**, 943–954. (b) T. L. Ohshima, Y. Hayashi, K. Agura, Y. Fuji, A. Yoshiyama and K. Mashima, Chem. Commun., 2012, **48**, 5434–5436. (c) B. Gnanaprakasam and D. Milstein, J. Am. Chem. Soc., 2011, **133**, 1682–1685. (d) A. El-Faham and F. Albericio, Chem. Rev., 2011, **111**, 6557–6602. (e) C. L. Allen and J. M. J. Williams, Chem. Soc. Rev., 2011, **40**, 3405–3415. (f) V. R. Pattabiraman and J. W. Bode, Nature, 2011, **480**, 471–479. (g) H. Charville, D. Jackson, G. Hodges and A. Whiting, Chem. Commun., 2010, **46**, 1813–1823.
- 2 A. Orliac, D. G. Pardo, A. Bombrun and J. Cossy, Org. Lett. 2013, 15, 902–905.
- 3 N. Gernigon, R. M. Al-Zoubi and D. G. Hall, J. Org. Chem. 2012, **77**, 8386–8400.
- 4 H. Chen, X. Xu, L. Liu, G. Tang and Y. Zhao, *RSC. Adv.*, 2013, **3**, 16247–16250.
- 5 J. R. Dunetz, Y. Xiang, A. Baldwin and J. Ringling, *Org. Lett.* 2011, **13**, 5048–5051.
- 6 J. B. Lee, J. Am. Chem. Soc., 1966, 88, 3440-3441.
- 7 H.-P. Buchstaller, H. M. Ebert and U. Anlauf, *Synth. Commun.*, 2001, **31**, 1001–1005.
- 8 A. Kumar, H. K. Akula and M. K. Lakshman. Eur. J. Org. Chem., 2010, 2709–2715.
- 9 P. Frøyen, Synth. Commun., 1995, **25**, 959–968.
- 10 B. P. Bandgar and S. V. Bettigeri, *Synth. Commun.*, 2004, **34**, 2917–2924.
- 11 J. Garcia, F. Urpí and J. Vilarrasa, *Tetrahedron Lett.*, 1984, **25**, 4841–4844.
- 12 L. E. Barstow and V. J. Hruby, *J. Org. Chem.*, 1971, **36**, 1305–1306.
- 13 S. Yamada and Y. Takeuchi, *Tetrahedron Lett.*, 1971, **12**, 3595–3598.
- 14 D. C. Lenstra, F. P. J. T. Rutjes and J. Mecinović, *Chem. Commun.*, 2014, **50**, 5763–5766.
- 15 (a) P. H. Huy, J. C. Westphal and A. M. P. Koskinen, *Beilstein J. Org. Chem.* 2014, **10**, 369–383. (b) P. H. Huy and A. M. P. Koskinen, *Org. Lett.* 2013, **15**, 5178–5181.
- 16 A recent review about Weinreb amides: M. Nowak, *Synlett*, 2015, **26**, 561–562.
- 17 G. W. Anderson, J. E. Zimmerman and F. M. Callahan, J. Am. Chem. Soc., 1967, **89**, 5012–5017.

COMMUNICATION

DOI: 10.1039/C5RA18459B Journal Name

- 18 (a) G. Mielniczak and A. Łopusiński, *Synth. Commun.*, 2003, **33**, 3851–3859. (b) H. McCombie, B. C. Saunders and G. J. Stacey, *J. Chem. Soc.*, 1945, 921–922.
- 19 A. G. Jackson, G. W. Kenner, G. A. Moore, R. Ramage and W. D. Thorpe, *Tetrahedron Lett.*, 1976, **17**, 3627– 3630.
- 20 B. Gaede, Org. Proc. Res. Dev., 1999, 3, 92–93.
- 21 T. Shioiri, K. Ninomiya and S. Yamada, J. Am. Chem. Soc., 1972, 94, 6203–6205.

RSC Advances Accepted Manuscript