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An efficient method for the preparation of *N*-formyl-imide via amidine using propylphosphonic anhydride (T3P®)

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ABSTRACT

An efficient method for the preparation of *N*-formyl imide via amidine using propylphosphonic anhydride (T3P®) has been described. Using this method many aryl, hetero aryl, alkyl as well as amino acid imides were synthesized in high yields.

Imides are compounds consisting of two carbonyl groups bound to a nitrogen atom.[1] Imides are versatile building blocks in the synthesis of nitrogen heterocycles.[2] The imide moiety is also an important component in many natural products that exhibit a broad range of activities including immune-suppressants,[3] cytotoxic anticancer agents,[4] antibiotics,[5] and antifeedants.[6] Cyclic imide moiety and their derivatives play an integral part in various important molecules such as thalidomide, isogranulatimide, and rebeccamycin.[7] Unlike cyclic imides, where much is known about their synthesis and reactivity, only few methods have been reported for the preparation of acyclic imides.[8] *N*-formyl imides are acyclic imides where the formyl group is attached to amide moieties which are useful intermediates for natural product synthesis (Fig. 1).[9–13] Apart from their biological activities, imide derivatives are useful in the reactions involving Wittig reaction, condensation, alkylation, acylation, and cyclocondensation.[14]

Marquez group has extensively studied the formylation of amide in order to make enamide.[15,16] The key to their approach lies in considering that the *N*-formyl unit could potentially behave as a pseudo-aldehyde unit, as opposed to a normal amide group. It was reasoned that the nitrogen lone pair would be effectively delocalised into the adjacent carbonyl group. This delocalization would render the *N*-formyl group to being significantly more reactive than a typical formamide. Despite the importance of *N*-formyl imide in the natural product synthesis, there are very few methods available for its synthesis.

Propylphosphonic anhydride (T3P) is a mild peptide coupling reagent having low toxicity and low allergenic potential.[17] Recently, it has been used as a versatility reagent in organic chemistry beyond peptide synthesis.[18] T3P is well known for the conversion of carboxylic acids and amides to nitriles,[19] formation of Weinreb amides,[20] ester,[21] and isonitrile synthesis.[19] T3P offers several advantages over traditional reagents, such as broad functional group tolerance, low epimerization tendency, easy work up due to water soluble by-products and being non-toxic in nature. There are quite a few examples, wherein T3P is utilized in dehydration chemistry and molecular rearrangement.[22,23] Recently, it has been used as a reagent in the preparation of various heterocycles viz. quinolines,[24] coumarin[25] and indole synthesis,[26] but its synthetic utility has not been investigated in the synthesis of imide derivatives. There is no report for the synthesis of imides using T3P in the literature.

Formylation of amide is a very useful process in synthetic organic chemistry.[27] Many methods have been developed for the preparation of imides,[28] however most available methods either employ sophisticated reagents or provide only moderate yields. Also high temperature condition and scrambling of the grouping

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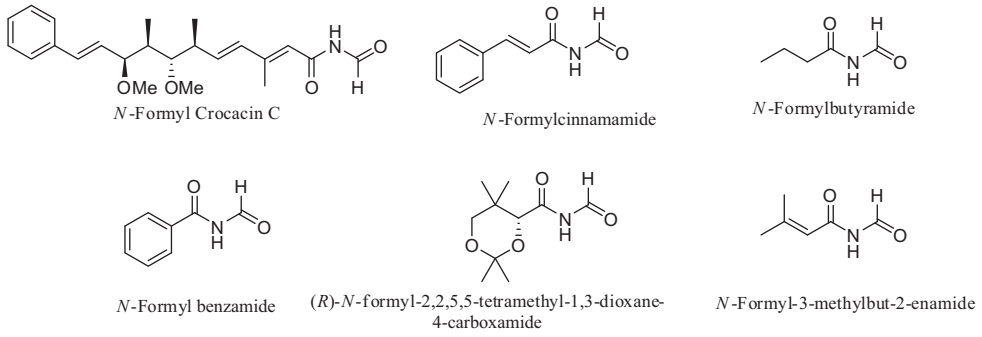
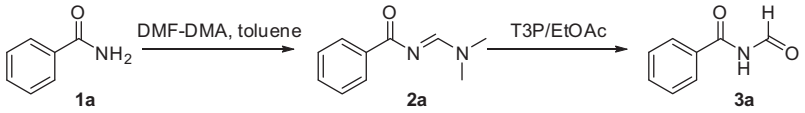
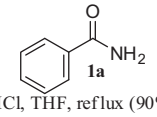
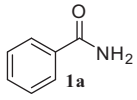
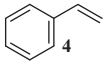
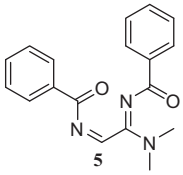
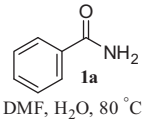
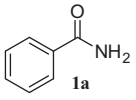
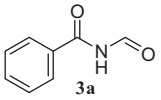


Figure 1. *N*-formyl imide derivatives useful for natural products synthesis.



Scheme 1. Synthesis of *N*-Formyl benzamides via imidine using T3P.

Table 1
Different conditions used for the hydrolysis of **2a**

Entry	Reaction conditions & product obtained (yield)[a]	Entry	Reaction conditions & product obtained (yield)[a]
1	 HCl, THF, reflux (90%)	**5**	 4M HCl, Dioxane, reflux (98%)
2	 TFA, EtOAc, reflux (83%)	**6**	 H_3PO_2, EtOAc, reflux (16%)
3	 PPA, DMF, H_2O, 80 °C (58%)		
4	 $NaIO_4$, DMF, H_2O, 80 °C (77 %)	**7**	 T3P, EtOAc, 80 °C (92%)

[a] The structure of the product was determine by crude LC–MS analysis only.

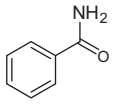
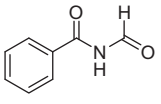
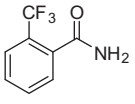
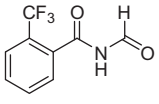
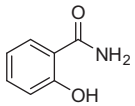
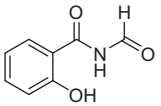
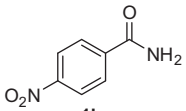
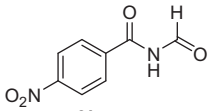
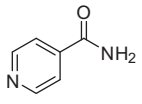
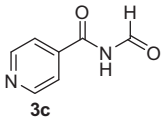
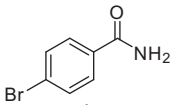
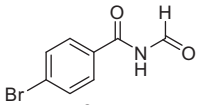
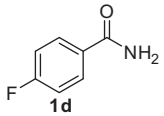
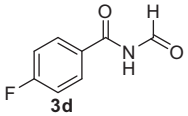
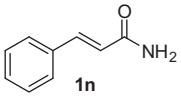
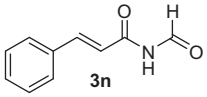
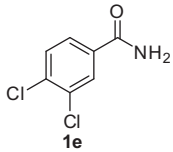
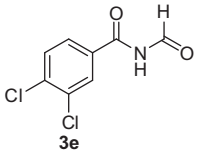
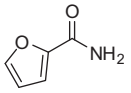
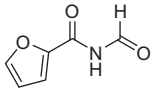
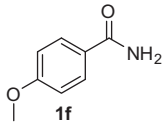
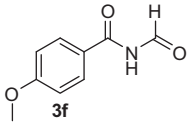
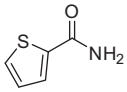
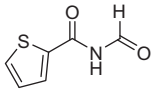
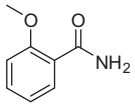
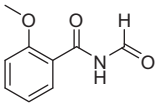
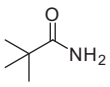
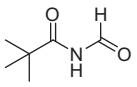
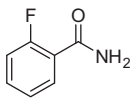
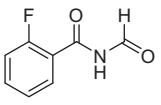
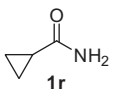
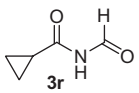
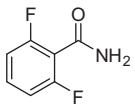
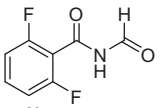
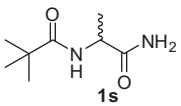
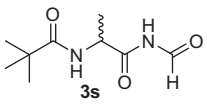
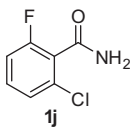
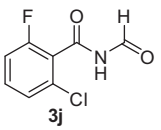
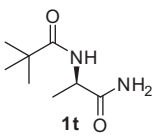
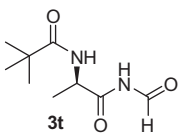
to give symmetrical imides are the limiting factors in these methodologies.[29] Classically, imides are prepared by the reaction of amides with acyl chlorides, anhydrides, and carboxylic esters or acids. However, these methods are not as straightforward as they seem to be the first glance and several side reactions such as elimination to nitriles, formation of triacyl amides, or acyl group scrambling can occur. Other procedures for the synthesis of acyclic imides involve amino carboxylation of aryl bromides,[30] reaction of azalactone with oxygen/palladium,[31] and reaction of pentafluorophenyl esters with deprotonated amides.[32]

Treatment of amides with reagents such as dimethylacetals of amides,[33] *N*,*N*-bis(trimethylsilyl) formamide, α,α,α-trichloromethyl carbonyl compounds,[34] diketenes,[35] or vinyl esters[36] are few direct methods for the synthesis of imides. The direct oxidation of *N*-alkyl amides is the simplest and most straightforward method for the preparation of imides. Unfortunately, most of the oxidations cited in the literature suffer from a competitive *N*-dealkylation and afford the corresponding imides only as minor products. Only the RuO_4 oxidation has been proven to be synthetically useful for the preparation of imide derivatives.[37] However, the synthetic scope of the RuO_4 oxidation is limited due to oxidative degradation of aromatic rings and oxidative cleavage of both carbon–carbon double bonds and carbon–carbon triple bonds. Trudell et al., have reported that *N*-alkyl amides could be oxidized to imides with chromium(VI) oxide and periodic acid in the presence of acetic anhydride in acetonitrile.[38] In another report, silica sulfuric acid has been used as a recyclable reagent for the one pot synthesis of acyclic imides by the reaction of aliphatic and aromatic nitriles with acyclic carboxylic anhydrides.[39] These reported methods involve the use of expensive reagents, harsh reaction conditions, elevated temperature, and sophisticated reagents.

So the development of new methodologies for the synthesis of imides is required.

During our research program on natural product hybrid synthesis,[39–42] we need to synthesize a number of *N*-formyl imides with various degrees of substituents on the aromatic ring. Herein, we

Table 2
Synthesis of *N*-formyl imides using T3P

Amides	*N*-formyl imides	Yield (%)[a]	Amides	*N*-formyl imides	Yield (%)[a]
 **1a**	 **3a**	89	 **1k**	 **3k**	88
 **1b**	 **3b**	75	 **1l**	 **3l**	80
 **1c**	 **3c**	78	 **1m**	 **3m**	84
 **1d**	 **3d**	93	 **1n**	 **3n**	92
 **1e**	 **3e**	90	 **1o**	 **3o**	63
 **1f**	 **3f**	73	 **1p**	 **3p**	58
 **1g**	 **3g**	90	 **1q**	 **3q**	81
 **1h**	 **3h**	92	 **1r**	 **3r**	87
 **1i**	 **3i**	74	 **1s**	 **3s**	65
 **1j**	 **3j**	87	 **1t**	 **3t**	60

[a] Isolated yield.

wish to report that propylphosphonic anhydride (T3P®) can be used for the preparation of *N*-formyl imide via amidine (Scheme 1).

The amidine **2a** was prepared by the condensation of benzamide **1a** with *N*,*N*-dimethylformamide-dimethylacetal (DMF-DMA) in refluxing toluene (Scheme 1). Initially, the hydrolysis of amidines was attempted using various conditions (Table 1). Using concentrated HCl in THF for hydrolysis, the starting material **2a** was completely consumed, but LC–MS analysis showed no desired product **3a**. When we used 4 M HCl in dioxane the compound **2a** was converted back to **1a**. We have observed similar results using PPA for hydrolysis. Finally, intrigued by the use of T3P for various conversions,[5] we treated compound **2a** with T3P in EtOAc reflux condition; the imide **3a** was formed cleanly in this condition and were able to isolate compound **3a** in 92% yield.

To prove the generality of this method various different highly substituted aryl, hetero aryl, alkyl as well as amino acid amides were examined and results are given in Table 2. Similar yields were observed for the substrates having electron withdrawing groups (compounds **3k**, **3l**) as well as electron donating groups (compound **3b**, **3f**). It is noteworthy to mention here that previously

inaccessible furan analogues and thiophene analogues were synthesized in very good yields (compound **3o**, **3p**). We did not observe the oxidation of aldehyde or degradation of amidines in any of the examples. Alkyl amides (**3n**, **3q** and **3r**) were also converted to imides in good yields which are not reported in the literature.

Typical experimental procedure for the preparation of (E)-N-((dimethylamino)methylene)benzamide (**2a**): To a solution of benzamide **1a** (1 g, 8.26 mmol) in toluene (10 ml) was added DMF-DMA (5.7 ml, 24.79 mmol) at room temperature and the reaction mixture was stirred at 100 °C for 12 h. The progress of the reaction was monitored by TLC (50% EtOAc/petroleum ether). After completion of the reaction, toluene was evaporated to give the crude product. The crude product was recrystallized with *n*-pentane to afford pure compound **2a** (1.3 g, 90%) as an off white solid.

Typical experimental procedure for the preparation N-formylbenzamide (**3a**): To a solution of compound **2a** (200 mg, 1.13 mmol) in ethyl acetate (10 ml) was added T3P (3.40 mmol, 1.02 ml) at 0 °C and the reaction mixture was stirred at 80 °C for 12 h. The progress of the reaction was monitored by TLC (50% EtOAc/petroleum ether). After completion of the reaction, water (50 ml) was added to the reaction mixture and extracted with ethyl acetate thrice. The organic layers were combined, washed with water, brine, and dried over Na_2SO_4. The solvent was evaporated to afford the crude product. The crude product was charged on a silica gel column. Elution of the column with 30% EtOAc/petroleum ether gave the pure compound **3a** (155 mg, 92%) as an off white solid.

Conclusion

In summary, we have developed an efficient and simple method for the preparation of *N*-formyl imide via amidine using propylphosphonic anhydride (T3P®) in good yields.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.12.046. These data include MOL files and InChiKeys of the most important compounds described in this article.

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