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An Efficient Method for the Preparation of *N*-Formyl-Imide via Amidine using Propylphosphonic Anhydride (T3P®)

M. Sambaiah[a, b], Ramakrishna Gudipati[a], K. Shiva Kumar[b], Satyanarayana Yennam[a] & Manoranjan Behera[a]*

[a] *Chemistry services, GVK Biosciences Pvt. Ltd., Survey Nos:125 (part) & 126, IDA Mallapur, Hyderabad-500076, Telangana State, India*

[b]*Department of Chemistry, GITAM University, Hyderabad Campus, Rudraram Village, Patancheru Mandal, Medak Dist.,Telangana State, 502329, India*

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 yield.

Imides are compounds consisting of two carbonyl groups bound to 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 etc.[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.

Key words: N-formylation, Imide, T3P, amidine, DMF-DMA

Corresponding author: Manoranjan Behera
Email: Manoranjan.Behera@gvkbio.com

Propylphosphonic anhydride (T3P) is a mild peptide coupling reagents 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 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, as easy work up due to water soluble by-products and non-toxic in nature. There are quite a few examples, where in 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] coumarins,[25] 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 to give symmetrical imides are the limiting factors in this 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 seems 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 procedure for the synthesis of acyclic imides involves amino carboxylation of aryl bromides,[30] reaction of azalactone with oxygen/palladium[31] and reaction of pentafluorophenyl esters with deprotonated amides.[32]

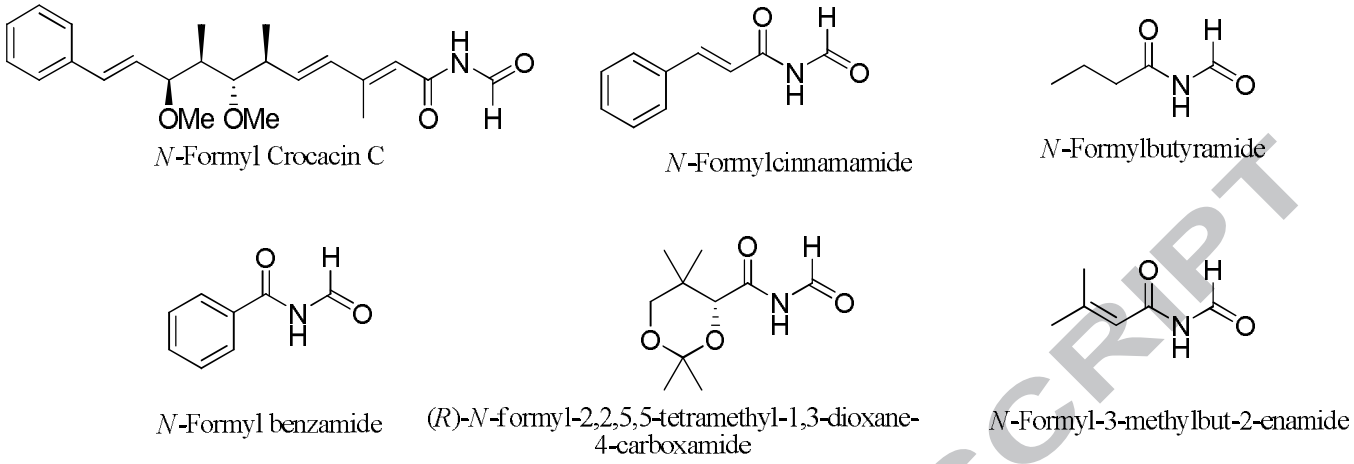
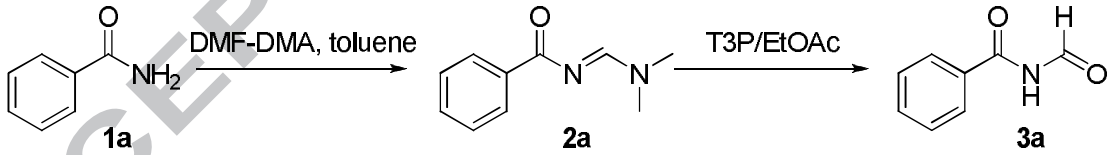


Fig 1. *N*-Formyl Imide Derivatives useful for Natural Products Synthesis

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 suffers 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 reaction of aliphatic and aromatic nitriles with acyclic carboxylic anhydrides.[39] These reported methods involve use of expensive reagents, harsh reaction conditions, elevated temperature and sophisticated reagents. So development of new methodologies for the synthesis of imides is required.



Scheme 1: Synthesis of *N*-Formyl benzamides via Imidine using T3P

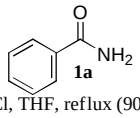
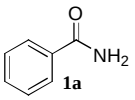
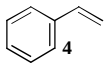
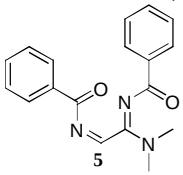
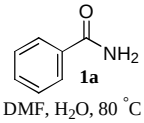
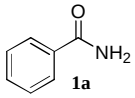
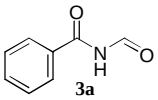
During our research program on natural product hybrid synthesis,[39-42] we need to synthesize a number of *N*-formyl imides with various degrees of substituents on aromatic ring. Herein, we wish to report that propylphosphonic anhydride (T3P®) can be used for the preparation of *N*-formyl imide via amidine (**Scheme 1**).

The amidine **2a** was prepared by 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 4M HCl in dioxane the compound **2a** was converted back to **1a**. We have observed similar results using PPA for hydrolysis. Finally, intriguing by the use of T3P for various conversions,[5] we have 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 the results were 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 yield (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 yield which are not reported in the literature.

Table 1. Different Conditions used for Hydrolysis of **2a**

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

[a] The sturcture of the product was determine by crude LC-MS analysis only

Typical experimental procedure for the preparation of(E)-N-(dimethylamino)methylene)benzamide (**2a)**:To a solution of benzamide **1a** (1g, 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 ^{0}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 ^{0}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. Combined the organic layers, 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 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

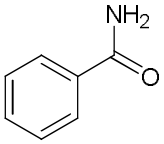
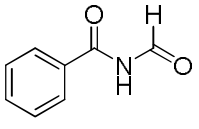
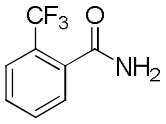
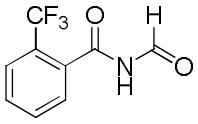
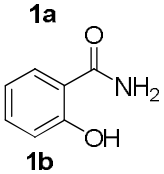
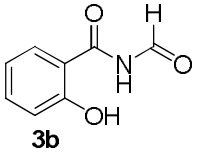
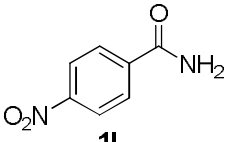
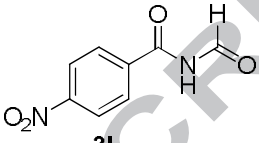
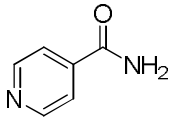
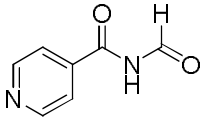
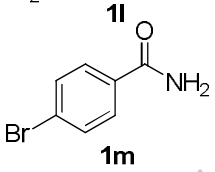
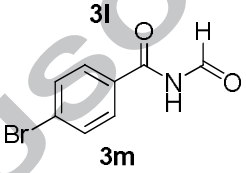
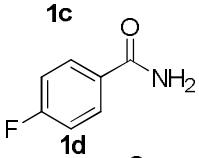
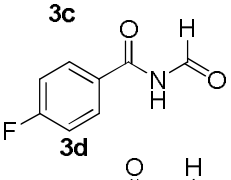
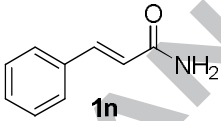
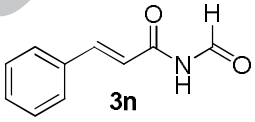
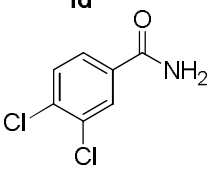
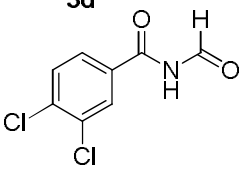
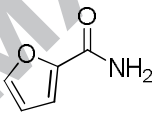
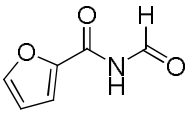
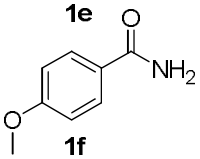
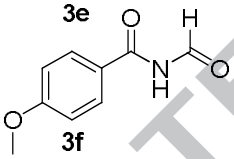
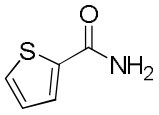
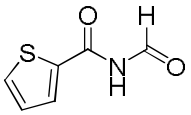
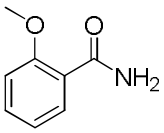
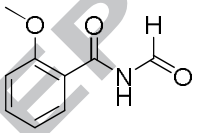
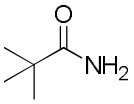
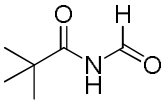
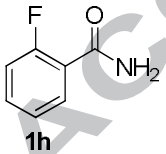
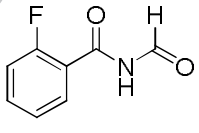
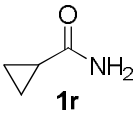
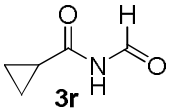
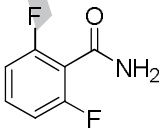
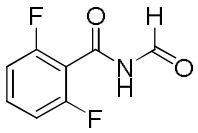
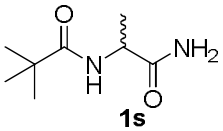
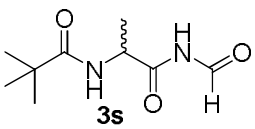
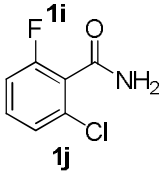
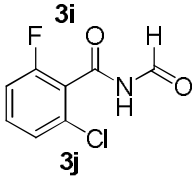
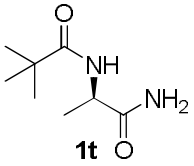
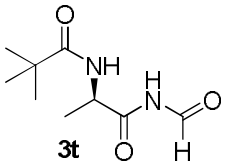
Conclusion:

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 yield.

Acknowledgements:

Authors are grateful to GVK Biosciences Pvt. Ltd., for the financial support and encouragement. Help from the analytical department for the analytical data is appreciated. We thank Dr. Sudhir Kumar Singh for his invaluable support and motivation.

Table 2. Synthesis of *N*-formyl amide using T3P

Amides	N-Formyl Amides	Yield (%)[a]	Amides	N-Formyl Amides	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

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Graphical Abstract

TETRAHEDRON
LETTERS

An Efficient Method for the Preparation of N-Formyl-Imide via Amidine using Propylphosphonic Anhydride (T3P®)

M. Sambaiah[a,b], Ramakrishna Gudipati[a], K. Shiva Kumar[b], Satyanarayana Yennam[a] & Manoranjan Behera*[a]