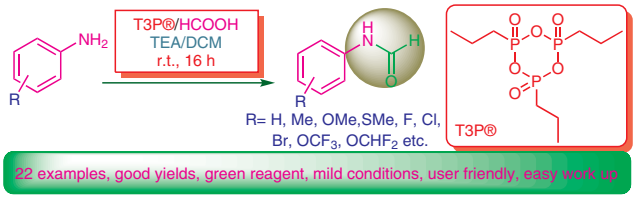
# An Efficient Method for the Preparation of *N*-Formamides using Propylphosphonic Anhydride (T3P®)

**Venu Kandula**[a,b]
**Ramakrishna Gudipati**[a]
**Anindita Chatterjee**[b]
**Satyanarayana Yennam**[a]
**Manoranjan Behera**[*a]

[a] Chemistry services, GVK Biosciences Pvt. Ltd., Survey Nos:125 (part) & 126, IDA Mallapur, Hyderabad-500076, Telangana, India
Manoranjan.Behera@gvkbio.com
[b] Department of Chemistry, K L EF, Vaddeswaram, Guntur-522502, Andhra Pradesh, India




Received: 22.02.2018
Accepted after revision: 24.04.2018
Published online: 08.06.2018
DOI: 10.1055/s-0036-1591584; Art ID: so-2018-d0021-l


**Abstract** The synthesis of *N*-formamides from aromatic amines and formic acid using propylphosphonic anhydride (T3P®) as a green coupling reagent is described. By using this method, aryl, heteroaryl and fluorinated aryl-containing formamides were synthesized in high yield and purity. The significant features of this method include easy work up, high purity and reduced toxicity of the reaction.

**Key words** N-formylation, T3P, formic acid, aromatic amine, formamide

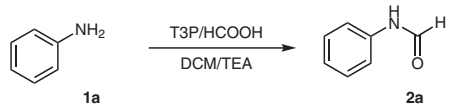
*N*-Formylation is important[1] because the resulting formamides are useful intermediates in organic synthesis and medicinal chemistry.[2] The formyl group, which serves as protecting group for amines in peptide synthesis, can be easily removed using acidic or basic conditions.[3] Formamides are important precursors for the synthesis of isocyanides,[4] formamidines,[5] and oxazolidinones.[6] They are also well known reagents in the Vilsmeier reaction and act as Lewis bases for the allylation and hydrosilylation of carbonyl compounds.[7]

Propylphosphonic anhydride (T3P®) has commonly been used as a water scavenger and coupling reagents for the synthesis of amides.[8] T3P® is a mild reagent that is available in ethyl acetate solution and is easy to handle. It has useful properties such as broad functional group tolerance and low toxicity, and its use results in simple work-up procedures.[9] For these reasons, new applications have been recently developed for this reagent.[10] For instance, T3P® has been used in dehydration chemistry that involves the conversion of carboxylic acids and amides into nitriles as in the synthesis of alkenes, isonitriles, and substituted heterocycles.[11] More recently, convenient microwave-assisted T3P® mediated one-pot pyrazolone[12] and 4-aryl-benzo-isoindole-dione[13] syntheses have been reported. However, there is no report of the synthesis of formamides using T3P®.

The reaction of amines with formic acid was first reported in 1955 by Fieser and Jones.[14] Since then, several approaches have been reported for the synthesis of *N*-formamides,[15] including reagents such as chloral, formic acid–DCC, formic acid–EDCI, formic acid–$ZnCl_2$, formic acid–PEG 400, formic acid esters, CMT, DMF–NaOMe, formic acid–thiamine hydrochloride, and imidazole–DMF.[16] However, many of these methods suffer from disadvantages such as harsh conditions, low yields and expense of the reagents.[17]

In continuation of our efforts to use T3P® for various applications,[18] we herein report a mild, efficient, and convenient procedure for the *N*-formylation of anilines with formic acid in the presence of T3P®.

Initially, the conversion of aniline **1a** into *N*-formyl aniline **2a** in the presence of T3P® was chosen as a model reaction (Scheme 1). Thus, by treating aniline **1a** (2 mmol) with formic acid (1.2 equiv) in the presence of T3P® (50% solution in EtOAc, 1.0 equiv) and $Et_3N$ (2 equiv), at room temperature for 16 h, we were pleased to find that T3P® did mediate this conversion (Table 1, entry 1), providing 45% of **2a** after 16 h. Compound **2a** was fully characterized by standard spectroscopic techniques (IR, $^1H$ and $^{13}C$ NMR). The reaction was allowed to continue at room temperature as there was no other by-product formation as evidenced by the LC-MS analysis data. However, even after 48 h, there was no increase in the percentage of product formation. Encouraged by this result, we attempted to optimize the reaction conditions by changing the solvents and bases (Table 1).




**Scheme 1** Synthesis of *N*-formamides using T3P

Thus, performing the formylation of **1a** with formic acid (1.2 equiv) (Table 1, entry 2) in the presence of T3P® (2 equiv) in dichloromethane afforded a 60% yield of the desired product **2a**. When we increased the amount of $Et_3N$ (2 equiv), the yield of the product **2a** was increased to 95% (entry 3), but the use of excess of T3P® under the same conditions did not increase the yield significantly (entry 4), which indicated that it was sufficient to have 2.0 equivalent of T3P®. Furthermore, increasing the amount of formic acid as well $Et_3N$ did not increase the yield of the reaction. Among the bases screened, pyridine gave the highest yield (entry 11), while changing solvent had no effect on the yield. Finally, to prove that the formylation was mediated by T3P®, a control experiment was conducted. As expected, treating **1a** and formic acid (1 equiv) in dichloromethane at r.t. without T3P® for 16 h gave no conversion (entry 13).

**Table 1** Screening Optimal Conditions

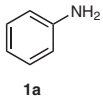
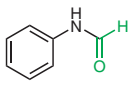
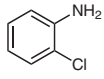
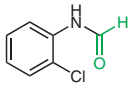
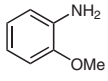
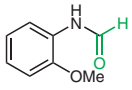
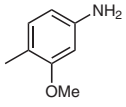
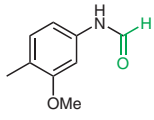
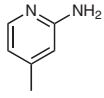
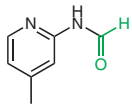
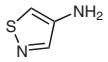
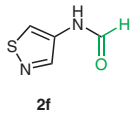
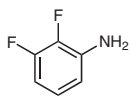
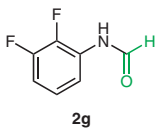
| Entry | Reaction conditions[a] | Yield (%)[b] |
|---|---|---|
| 1 | HCOOH (1.2 equiv), T3P® (1.0 equiv), $Et_3N$ (1 equiv), DCM | 45[b] |
| 2 | HCOOH (1.2 equiv), T3P® (2 equiv), $Et_3N$ (1 equiv), DCM | 60[b] |
| 3 | HCOOH (1.2 equiv), T3P® (2 equiv), $Et_3N$ (2 equiv), DCM | 95[b] |
| 4 | HCOOH (1.2 equiv), T3P® (3 equiv), $Et_3N$ (2 equiv), DCM | 94[c] |
| 5 | HCOOH (1.2 equiv), T3P® (2 equiv), $Et_3N$ (2 equiv), DMF | 98[c] |
| 6 | HCOOH (1.2 equiv), T3P® (2 equiv), $Et_3N$ (2 equiv), THF | 97[c] |
| 7 | HCOOH (1.2 equiv), T3P® (2 equiv), $Et_3N$ (2 equiv), MeCN | 97[c] |
| 8 | HCOOH (1.2 equiv), T3P® (2 equiv), $Et_3N$ (2 equiv), EtOAC | 99[c] |
| 9 | HCOOH (1.2 equiv), T3P® (2 equiv), DBU (2 equiv), DCM | 53[c] |
| 10 | HCOOH (1.2 equiv), T3P® (2 equiv), DABCO (2 equiv), DCM | 96[c] |
| 11 | HCOOH (1.2 equiv), T3P® (2 equiv), pyridine (2 equiv), DCM | 99[c] |
| 12 | HCOOH (1.2 equiv), T3P® (2 equiv), NaOAc (2 equiv), DCM | 87[c] |
| 13 | HCOOH (1.2 equiv), $Et_3N$ (2 equiv), DCM | 0[c] |

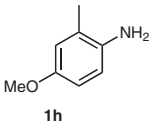
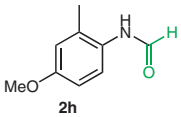
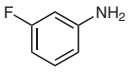
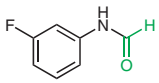
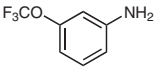
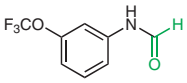
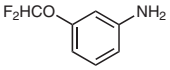
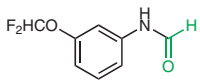
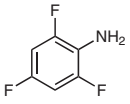
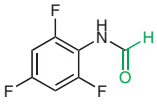
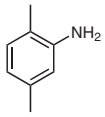
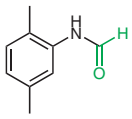
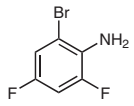
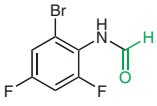
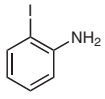
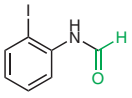
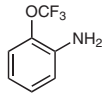
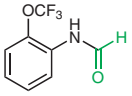
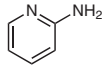
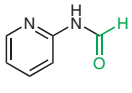
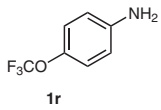
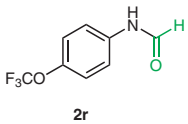
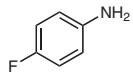
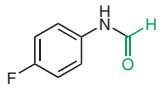
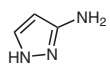
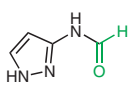
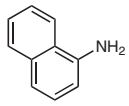
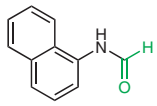
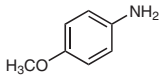
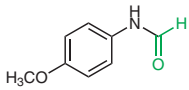
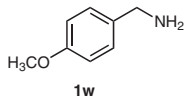
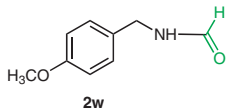
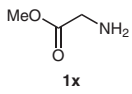
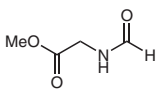
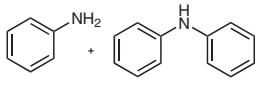
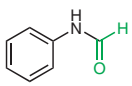
[a] All the reactions were carried out at room temperature for 16 h.
[b] Yields refer to the isolated product.
[c] Results based on LC-MS analysis.

To establish the generality of this method, various highly substituted aryl and hetero aryl anilines were examined; the results are summarized in Table 2. Importantly, previously inaccessible naphthalene and pyrazole analogues[19] were synthesized in very good yield (compounds **2u**, **2t**). We observed no effect on the yield as a result of aromatic ring substitution (*ortho*- as well *para*-substituted anilines gave similar yields). Aromatic amines having bulky substituents were also converted into *N*-formylbenzamides (e.g., **2n**) in good yields. The advantage of using T3P® in the formylation reaction compared with other available methods are its low toxicity, mild reaction conditions and formation of water-soluble by-products.

It is important to note that *N*-formyl amino acid esters could not be obtained by using the procedure outlined in this report (Table 2, entry 23). The reaction of secondary amines with formic acid under these conditions was slow in comparison to primary amines. Indeed, a mixture of primary and secondary amines furnished only **2a** (entry 23).[20]

**Table 2** T3P Catalyzed Synthesis of *N*-Formamides Prepared using Aromatic Amines and Formic Acid

| Entry | Amines | N-Formamides | Yield (%)[a] |
|---|---|---|---|
| 1 |  **1a** |  **2a** | 95 |
| 2 |  **1b** |  **2b** | 93 |
| 3 |  **1c** |  **2c** | 90 |
| 4 |  **1d** |  **2d** | 93 |
| 5 |  **1e** |  **2e** | 89 |
| 6 |  **1f** |  **2f** | 85 |
| 7 |  **1g** |  **2g** | 88 |

| Entry | Amines | N-Formamides | Yield (%)[a] |
|---|---|---|---|
| 8 |  **1h** |  **2h** | 93 |
| 9 |  **1i** |  **2i** | 85 |
| 10 |  **1j** |  **2j** | 88 |
| 11 |  **1k** |  **2k** | 93 |
| 12 |  **1l** |  **2l** | 89 |
| 13 |  **1m** |  **2m** | 85 |
| 14 |  **1n** |  **2n** | 93 |
| 15 |  **1o** |  **2o** | 89 |
| 16 |  **1p** |  **2p** | 75 |
| 17 |  **1q** |  **2q** | 78 |
| 18 |  **1r** |  **2r** | 90 |
| 19 |  **1s** |  **2s** | 92 |
| 20 |  **1t** |  **2t** | 74 |
| 21 |  **1u** |  **2u** | 95 |
| 22 |  **1v** |  **2v** | 90 |
| 23 |  **1w** |  **2w** | 2 |
| 24 |  **1x** |  **2x** | 0 |
| 25 |  **1a** **1y** |  **2a** | 90 |

In summary, we have developed a novel and efficient method for the preparation of *N*-formamides from aromatic amines and formic acid using propylphosphonic anhydride (T3P®) in good yield. This simple and rapid method offers an advantageous alternative to the existing strongly acidic conditions that are generally applied for this conversion. The reaction conditions are simple and sufficiently mild to tolerate various functional groups that can serve for further functionalization. We believe this methodology will find widespread application for the synthesis of *N*-formamide derivatives.

## Funding Information

This work was supported by GVK Biosciences Pvt. Ltd.

## Acknowledgment

The authors are grateful to GVK Biosciences Pvt. Ltd., for financial support and encouragement. Help from the analytical department is appreciated. We thank Dr. Sudhir Kumar Singh for his invaluable support and motivation and Dr. Sridhar Iyer for scientific discussion during this work.

## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591584.

## References and Notes

(1) (a) Gerack, C.; McElwee-White, L. *Molecules* **2014**, *19*, 7689. (b) Nishikawa, Y.; Nakamuira, H.; Ukai, N.; Adachi, W.; Hara, O. *Tetrahedron Lett.* **2017**, *58*, 860.
(2) Rahman, M.; Kundu, D.; Hajra, A.; Majee, A. *Tetrahedron Lett.* **2010**, *51*, 2896.
(3) Hartines, J.; Laur, J. *Synthesis* **1982**, 979.
(4) (a) Ugi, I. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 810. (b) Waki, M.; Meienhofer, J. *J. Org. Chem.* **1977**, *42*, 2019.
(5) Han, Y.; Cai, L. *Tetrahedron Lett.* **1997**, *38*, 5423.
(6) Lohray, B. B.; Baskaran, S.; Rao, B. S.; Reddy, B. Y.; Rao, I. N. *Tetrahedron Lett.* **1999**, *40*, 4855.
(7) Satasia, S. P.; Kalaria, P. N.; Raval, D. K. *J. Mol. Catal. A: Chem.* **2014**, *391*, 41.
(8) (a) Wissmann, H.; Kleiner, H. J. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 133. (b) Escher, R.; Bunning, P. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 277. (c) Martin, S. M. P.; Medina, R. F.; Castro, C. A. I.; Monroy, Z. J. R.; Castaneda, J. E. G. *Int. J. Pept. Res. Ther.* **2017**, *24*, 291.
(9) Garcia, A. L. *Synlett* **2007**, 1328.
(10) Waghmare, A. A.; Hindupur, R. M.; Pati, H. N. *Rev. J. Chem.* **2014**, *4*, 53.
(11) (a) Desroses, M.; Wieckowski, K.; Stevens, M.; Odell, L. R. *Tetrahedron Lett.* **2011**, *52*, 4417. (b) Augustine, J. K.; Atta, A. N.; Ramappa, B. K.; Boodappa, C. *Synlett* **2009**, 337. (c) Ragghavendra, G. M.; Ramesha, A. B.; Revanna, C. N.; Nandeesh, K. N. Mantelingu K.; Rangappa, K. S. *Tetrahedron Lett.* **2011**, *52*, 5507. (d) Wen, X.; El, Bakali. J.; Deprez-Poulain, B.; Deprez, B. *Tetrahedron Lett.* **2012**, *53*, 2440. (e) Poojari, S.; Parameswar, Naik. P.; Krishnamurthi, G. *Tetrahedron Lett.* **2012**, *53*, 4693. (f) Jida, M.; Deprez, B. *New J. Chem.* **2012**, *36*, 869.
(12) Desroses, M.; Cordonnier, M. C. J.; Minguez, S. L.; Jacques, S.; Koolmeister, T.; Helleday, T.; Scobie, M. *Eur. J. Org. Chem.* **2013**, 5879.
(13) Deniben, M.; Kraus, A.; Reiss, G. J.; Muller, T. J. J. *Beilstein J. Org. Chem.* **2017**, *13*, 2340.
(14) Fieser, L. F.; Jones, J. E. *Organic Syntheses: Collective Vol. III*; Wiley: New York, **1955**.
(15) (a) Ansari, M. I.; Hussai, M. K.; Yadav, N.; Gupta, P. K.; Hajela, K. *Tetrahedron Lett.* **2012**, *53*, 2063. (b) Azizi, N.; Gholibeglo, E.; Babapour, M.; Ghafuri, H.; Bolourtchian, S. M. *C. R. Chim.* **2012**, *15*, 768. (c) Brahmachari, G.; Laskar, S. *Tetrahedron Lett.* **2010**, *51*, 2319. (d) Cochet, T.; Bellosta, V.; Greiner, A.; Roche, D.; Cossy, J. *Synlett* **2011**, 1920.
(16) (a) Gerack, C. J.; McElwee-White, L. *Molecules* **2014**, *19*, 7689. (b) Lei, M.; Ma, L.; Hu, L. *Tetrahedron Lett.* **2010**, *51*, 4186. (c) Suchy, M.; Elmehriki, A. A. H.; Hudson, R. H. E. *Org. Lett.* **2011**, *13*, 3952. (d) Olah, G. A.; Ohannesian, L.; Arvanaghi, M. *Chem. Rev.* **1987**, *87*, 671.
(17) (a) Joseph, S.; Das, P.; Srivastava, B.; Nizar, H.; Prasad, M. *Tetrahedron Lett.* **2013**, *54*, 929. (b) Kotha, S.; Behera, M.; Khedkar, P. *Tetrahedron Lett.* **2004**, *45*, 7589.
(18) (a) Sambaiah, M.; Gudipati, R.; Shiva, Kumar. K.; Yennam, S.; Behera, M. *Tetrahedron Lett.* **2016**, *57*, 403. (b) Balkrishna, C.; Kandula, V.; Gudipati, R.; Yannam, S.; Uma, Devi. P.; Behera, M. *Synlett* **2018**, *29*, 1087.
(19) **Preparation of 3-Formyl-pyrazole (2t); Typical Procedure:** To a solution of compound **1t** (300 mg, 3.61 mmol) in dichloromethane (5 mL) was added $HCO_2H$ (199 mg, 4.33 mmol), T3P® (2.3 g, 7.2 mmol) and TEA (730 mg, 7.2 mmol) at 0 °C, and the reaction mixture was then stirred at r.t. for 12 h. The progress of the reaction was monitored by TLC (30% EtOAc/petroleum ether). Upon completion of the reaction, water (50 mL) was added to the reaction mixture and extracted with ethyl acetate three times. The combined organic extracts were washed with water and brine, and dried over $Na_2SO_4$. After filtration, the solvent was evaporated to afford the crude product, which was triturated with pentane to give pure **2t** (295 mg, 74 %) as a brown solid; mp 181–183 °C. IR (KBr): 3396, 2961, 2106, 1687, 1596, 1492, 1388, 1299, 1199, 1046, 765 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO): δ = 12.37 (br. s, 1 H), 10.5 (br. s, 1 H), 8.66 (br. s, 1 H), 7.62 (d, *J* = 9.2 Hz, 1 H), 5.99 (br. s, 1 H); MS (EI): *m*/*z* (%) = 112 (100) [M+1]
(20) **Typical experimental procedure for the preparation *N*-formylbenzamide (2a):** To a solution of compound **1a** (200 mg, 2.17 mmol) in dichloromethane (5 mL) was added $HCO_2H$ (118 mg, 2.58 mmol), T3P® (1.38 g, 4.34 mmol) at 0 °C and TEA (434 mg, 4.30 mmol), and the reaction mixture was stirred at r.t. for 12 h. The progress of the reaction was monitored by TLC (30% EtOAc/petroleum ether). Upon completion of reaction, water (50 mL) was added and the reaction mixture was extracted with ethyl acetate three times. The combined organic extracts were washed with water and brine, and dried over $Na_2SO_4$. After filtration, the solvent was evaporated to afford the crude product, which was purified by silica gel chromatography, eluting with 30% EtOAc/petroleum ether to give pure **2a** (250 mg, 95 % yield) as a brown semisolid. Analytical data of *N*-phenyl formamide (**2a**): IR (KBr): 3271, 2921, 1683, 1600, 1543, 1440, 1270, 754 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 9.7 (br. s, 1 H), 8.3 (br. s, 1 H), 7.5 (br. s, 2 H), 7.2 (t, 2 H), 7.0 (t, 1 H); MS (EI): *m*/*z* (%) = 122 (100) [M+1]