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

Venu Kandula,a,b Ramakrishna Gudipati,a Anindita Chatterjee,a Satyanarayana Yennama Manoranjan Behera*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

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 because the resulting formamides are useful intermediates in organic synthesis and medicinal chemistry. The formyl group, which serves as a protecting group for amines in peptide synthesis, can be easily removed using acidic or basic conditions. Formamides are important precursors for the synthesis of isocyanides, formamidines, and oxazolidinones. They are also well known reagents in the Vilsmeier reaction and act as Lewis bases for the allylation and hydrosilylation of carbonyl compounds.

Propylphosphonic anhydride (T3P®) has commonly been used as a water scavenger and coupling reagents for the synthesis of amides. 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. For these reasons, new applications have been recently developed for this reagent. 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. More recently, convenient microwave-assisted T3P® mediated one-pot pyrazolone and 4-aryl-benz-isindole-dione 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. Since then, several approaches have been reported for the synthesis of N-formamides, including reagents such as chloral, formic acid–DCC, formic acid–EDCI, formic acid–ZnCl2, formic acid–PEG 400, formic acid esters, CMT, DMF–NaOMe, formic acid–thiamine hydrochloride, and imidazole–DMF. However, many of these methods suffer from disadvantages such as harsh conditions, low yields and expense of the reagents.

In continuation of our efforts to use T3P® for various applications, 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 Et3N (2 equiv), at room temperature for 16 h, we were pleased to find that T3P® mediated this conversion (Table 1, entry 1), providing 45% of 2a.

Received: 22.02.2018
Accepted after revision: 24.04.2018
Published online: 08.06.2018
License terms: 

SYNOPEN
2509-9396
Georg Thieme Verlag  Stuttgart · New York — SynOpen 2018, 2, 176–179

Letter

V. Kandula et al.
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 EtN (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 EtN 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).

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 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>
<thead>
<tr>
<th>Entry</th>
<th>Amines</th>
<th>N-Formamides</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>2b</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>2c</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>2d</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>2e</td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>2f</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>2g</td>
<td>88</td>
</tr>
</tbody>
</table>

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

(9) Garcia, A. L. Synlett 2007, 1328.