A new synthesis of pyridinyl trifluoromethanesulfonates via one-pot diazotization of aminopyridines in the presence of trifluoromethanesulfonic acid

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Abstract

The first method for the direct one-pot transformation of aminopyridines into pyridinyl trifluoromethanesulfonates is developed. The procedure involves diazotization of aminopyridines with sodium nitrite in the presence of trifluoromethanesulfonic acid.

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Pyridinyl trifluoromethanesulfonates contain a triflate as a good leaving group and hence represent compounds of significant value for organic synthesis. For example, substitution of the triflate group can give valuable pyridine derivatives such as bipyridines, 1a pyridinylpiperazines, 1b highly functionalized indolizines, 1c β-carbolines, 1d arylypyridines, 1e and pyridyl guanidines, 2a–d pyrrolo-[2,3 b]pyridines, 2e and pyridinyl biosensors. 2f

Currently, the esterification of hydroxypyridine with trifluoromethanesulfonic acid anhydride and harmful and toxic trifluoromethanesulfonic acid amides in the presence of the base in organic solvents are the only methods for the synthesis of pyridinyl trifluoromethanesulfonates. In general, these methods provide good yields of pyridinyl trifluoromethanesulfonates, but the high cost of reagents, inert atmosphere in some cases, and low temperature (down to –78 °C) make the target products fairly expensive to prepare.

The goal of this work was to develop a one-pot synthesis of pyridinyl trifluoromethanesulfonates from aminopyridines which are often more accessible and cheaper starting materials in comparison with pyridinols. The background for this approach is given in our previous work. 6 We have shown that diazotization of aminopyridines with sodium nitrite in the presence of p-TsOH in water paste led to the corresponding pyridinyl tosylates in one step. 6 This differentiated significantly the aminopyridines from other aromatic amines that form stable arenediazonium tosylates 7 after diazotization in the presence of p-TsOH. The reason for these differences between aromatic amines and aminopyridines 8,7 is the well-known instability of pyridine diazonium salts compared to arenediazonium salts. 8

Initially, the approach described in our previous work 6 was utilized. p-TsOH was replaced by TfOH (Method A) in the water paste with no desirable effect. It was found that the addition of sodium nitrite to aminopyridines 1a–k in aqueous paste with 3 equiv of TfOH at ambient temperature led to a rapid release of nitrogen oxides and incomplete conversion of the initial aminopyridine. The major products were the corresponding hydroxypyridines and starting aminopyridines 1, although the desired pyridinyl trifluoromethanesulfonates 2a–k were identified in the reaction mixture. The lower selectivity of diazotization–triflation relative to diazotization–tosylation probably is a reflection of the lower nucleophilicity of TfOH. A more detailed search for suitable conditions was conducted for the synthesis of pyridinyl trifluoromethanesulfonates via diazotization of 2-amino-5-bromopyridine 1a (Table 1) in the presence of TfOH.

Diazotization of aminopyridine 1a by grinding with NaNO₂ and TfOH under solvent-free conditions (Method B) almost eliminated the side hydroxyarylpyridine formation, however, full conversion of starting substrate 1a took a long time (36 h). Using n-BuONO as the diazotizing agent instead of NaNO₂ (Method C) did not give a satisfactory result. Tar formation, a low yield of the desired triflate 2a, incomplete conversion of the starting amine, and large amounts of the 5-bromo-N-butylypyridin-2-amine side product (Table 1) were observed. Apparently, this side product is formed
by the alkylation of initial aminopyridine 1a with n-BuOTf or protonated n-BuONO, which can appear in the presence of TfOH. A similar side product 5-bromo-N-(tert-butyl)pyridin-2-amine was formed by diazotization of 1a in tert-butanol (Method D, Table 1); the alkylation process in this case was probably due to t-BuOH. Using ethanol instead of t-butanol (Method E) led to the formation of significant quantities of the side product, 5-bromo-2-ethoxy-triflate. Using ethanol instead of tert-butanol (Method D) led to the formation of tert-butanol (Method E) led to the formation of the side product, 5-bromo-2-ethoxy-triflate. A relatively high yield of the target product 2a was obtained by diazotization with n-BuONO in DMSO solution (Method G, Table 1). Previously, DMSO has been successfully used for the diazotization–iodination of the presence of p-TsOH. A relatively high yield of the target product 2a was obtained by diazotization with n-BuONO in DMSO solution (Method G, Table 1). Previously, DMSO has been successfully used for the diazotization–iodination of the presence of p-TsOH. The formation of N-(5-bromopyridin-2-yl)acetamide as a side product, probably, via the reactions shown in Scheme 1.

The formation of N-(5-bromopyridin-2-yl)acetamide as a side product in the diazotization–iodination of 1a in acetonitrile in the presence of p-TsOH has been also observed previously.

A relatively high yield of the target product 2a was obtained by diazotization with n-BuONO in DMSO solution (Method G, Table 1). Previously, DMSO has been successfully used for the diazotization–iodination of the presence of p-TsOH. A relatively high yield of the target product 2a was obtained by diazotization with n-BuONO in DMSO solution (Method G, Table 1). Previously, DMSO has been successfully used for the diazotization–iodination of the presence of p-TsOH. The formation of N-(5-bromopyridin-2-yl)acetamide as a side product, probably, via the reactions shown in Scheme 1.

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A relatively high yield of the target product 2a was obtained by diazotization with n-BuONO in DMSO solution (Method G, Table 1). Previously, DMSO has been successfully used for the diazotization–iodination of the presence of p-TsOH. The formation of N-(5-bromopyridin-2-yl)acetamide as a side product, probably, via the reactions shown in Scheme 1.

However, even in those cases complete conversion of amine 1a was not achieved. Furthermore, 5-bromopyridin-2-ol appeared as a side product due to the presence of residual water in DMSO. In addition, there were problems with preparative separation of highly soluble pyridines from DMSO solution. To reduce the amounts of DMSO and water we performed the diazotization by grinding aminopyridine 1a, NaNO2, and TfOH in DMSO and allowing the slurried mixture to stand for 5.5 h without further grinding. This method showed the optimal selectivity and efficiency with the GC yield of 2a being more than 90% (Table 1), a preparative yield of 70% was obtained (Table 2). The optimal approach H was used to obtain a series of pyridinyl trifluoromethanesulfonates 2a–k (Table 2). It is important to mention that Method H in all cases ensures complete conversion of initial aminopyridines 1a–k, and gives no side pyridinols. In general, the yields of pyridyl triflates 2a, 2c, 2g, 2h, and 2l were comparable, and for compounds 2b and 2d they were higher than obtained using traditional hydroxypyridine esterification. Moreover, Method H allowed

Table 1

<table>
<thead>
<tr>
<th>Method</th>
<th>Solvent</th>
<th>Source of [NO+]</th>
<th>The reaction mass composition (GC) (%)</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>Water paste</td>
<td>NaNO2</td>
<td>BrN-OH 27.52</td>
</tr>
<tr>
<td>B</td>
<td>None</td>
<td>NaNO2</td>
<td>BrN-OH 93.00</td>
</tr>
<tr>
<td>C</td>
<td>None</td>
<td>n-BuONO</td>
<td>BrN-NH-n-BuONa 35.20</td>
</tr>
<tr>
<td>D</td>
<td>tert-ButOH</td>
<td>n-BuONO</td>
<td>BrN-NH-t-BuONa 34.54</td>
</tr>
<tr>
<td>E</td>
<td>EtOH</td>
<td>tert-ButOH</td>
<td>BrN-ONa 18.60</td>
</tr>
<tr>
<td>F</td>
<td>MeCN</td>
<td>tert-ButOH</td>
<td>BrN-OH 30.13</td>
</tr>
<tr>
<td>G</td>
<td>DMSO</td>
<td>tert-ButOH</td>
<td>BrN-OH 83.10</td>
</tr>
<tr>
<td>H</td>
<td>DMSO paste</td>
<td>NaNO2</td>
<td>Not detected</td>
</tr>
</tbody>
</table>

* Mole ratio of 1a: [NO+]: TfOH and the reaction time: 1:2:3, 5 h (Method A); 1:2:3, 36 h (Method B); 1:2:3, 4 h (Method C); 1:2:3, 4 h (Method D); 1:2:5:3, 4 h (Method E); 1:2:3, 4 h (Method F); 1:2:5:3, 4 h (Method G); 1:2:5:3, 5.5 h (Method H).
the synthesis of novel 5-iodopyridin-2-yl trifluoromethanesulfonate 2c, pyridin-4-yl trifluoromethanesulfonate 2j, and 3,5-dibromopyridin-2-yl trifluoromethanesulfonate 2k.

Thus, unlike a number of well-established methods, the procedure presented in this Letter can be broadly applied to the synthesis of 2-, 3-, and 4-pyridine triflates in one step starting from readily available aminopyridines.

Also we tried to apply Method H on pyridine-2,6-diamine 1l and 3,5-diiodopyridine-2,6-diamine 1m with 6 equiv of TIOH, but the results were ambiguous. In both cases the diazotization reactions occurred much more slowly than for monoaminopyridines 1a–k (up to 30–38 h), and with incomplete conversion of the diazotized products of substitution only of both amine groups to triflates 2m. At the same time, the reaction mixtures contained products of substitution only of both amine groups to triflates 2f–k (GC–MS data) (Scheme 2).

In the case of the diazotization of 1m we were able to isolate product 2m in 35% preparative yield. Compound 2m represents a rare example of a pyridine with two triflate groups and possesses interesting synthetic potential because it has four active sites. As far as we know, only one pyridine with two triflate substituents has been presented for the first time. It differs from the known methods in the use of easily available reagents, and employs mild conditions and a simple synthetic procedure.

Acknowledgments

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Supplementary data

Supplementary data (the synthetic procedure and spectral and analytical data for all compounds are provided) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.05.052.

References and notes


