1,3-Dipolar cycloaddition of cyanopyridines to heterocyclic \textit{N}-imines – combined experimental and theoretical studies

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Abstract:
Series of 2-pyridyl substituted [1,2,4]triazolo[1,5-a]azines have been synthesized by reaction of cyanopyridines with N-aminoazinium mesitylenesulfonates under basic conditions. The reaction proceeds smoothly with pyridinium, 1,10-phenanthrolinium and 8-oxyquinolinium salts. In case of quinolinium and isoquinolinium salts dimers of corresponding N-imines were isolated. Pyrazinium- and pyridazinum-N-imines didn’t possess any reactivity toward cyanopyridines. DFT studies give high activation barriers for 4-cyanopyridine cycloaddition to quinolinium and pyrazinium-N-imines as well as highly negative free energy of dimerisation for quinolinium and isoquinolinium-N-imines.

Keywords: DFT; 1,3-dipolar cycloaddition; N-imines; [1,2,4]triazolo[1,5-a]azines
Introduction

[1,2,4]Triazolo[1,5-a]azines have attracted much attention from both medical chemistry and material science communities. Thus, [1,2,4]triazolo[1,5-a]pyridine scaffold was used in design of TDP2 [1], HIF PHD-1 [2], VEGFR-2 [3] and various types of JAK kinase [4,5] inhibitors. Furthermore, triazolo[1,5-a]pyridine derivatives GLPG0634 (filgotinib) and CEP33779 (Fig. 1) are highly selective inhibitors of Janus kinases type 1 and 2 respectively and are regarded as promising drug candidates. Also this heterocyclic unit was shown to be useful in design of host materials for high-performance red [6], white and RGB [7] or green [8] PhOLEDs. Similarly, [1,2,4]triazolo[1,5-a]pyrimidines, which chemistry recently was reviewed, have a broad spectrum of biological activity [9]. [1,2,4]Triazolo[1,5-a]pyrazines and quinoxalines was used in design of A2A [10,11] and A3 [12,13] adenosine receptors antagonists.

Figure 1. Medicinally important [1,2,4]triazolo[1,5-a]pyridines.

The practical significance of such scaffolds stimulated the development of viable synthetic methods for their preparation [9, 14]. One of the common approaches to [1,2,4]triazolo[1,5-a]azines is an oxidative cyclization of 2-pyridyl, pyrazinyl, pyrimidyl etc., amidines or aminoguanidines to form N-N bond with various oxidants such as Pb(OAc)4 [15], PhI(OCOCF3)2 [16], iodine [17], N-Cl reagents [18,19] or electrolysis [20]. During the past decade several catalytic procedures utilizing oxygen as oxidant and aminoguanidine [21] or 2-aminopyridine/nitrile [22] as starting materials were developed. Despite on their great potential these methods have significant limitation consisting in requirement of α-aminoazines as starting compounds. Other group of methods is based on N-aminoazinium salts, which are readily available by N-amination of parent azines with O-(mesitylenesulfonyl)hydroxylamine and related reagents [23]. 1,2-Diaminoazinium salts undergo cyclization with acid anhydrides or aldehydes [11, 24, 25] leading to corresponding triazoloazidine. However, these salts also need in α-aminoazines for preparation. N-Aminopyridinium salts readily give corresponding pyridinium-N-imines upon deprotonation. Such imines were known to react with nitriles to yield [1,2,4]triazolo[1,5-
a]pyridines [26, 27]. This reaction was applied to synthesis of deuterated [28] or 2-aryl-substituted derivatives library for antifungal [29] and anticancer [30] activity screening. Recently our group employed the N-amination combined with nitrile cycloaddition for modification of commonly used ligands such as 8-oxyquinoline and 1,10-phenanthroline [31]. The aim of this work is to study scopes of nitrile cycloaddition to various azine-N-imines. Cyanopyridines were chosen as model nitriles as obtained pyridyl substituted azoloazines could be of interest for coordination chemists.

Results and discussion
Initially, we applied previously described conditions [30] to pyridinium salt 1 and 2-cyanopyridine as model substrates (Table 1, entire 1). However, only poor yield of desired pyrazolopyridine 2a was obtained. Noticeable amount of dihydropyrazolopyridine 3a was also found in the reaction mixture. Then we screened effect of the base amount and solvent nature on the reaction yield. It turned out that increase of KOH equivalents from 1 to 5 (entries 2-5) led to rise in yield both 2a and 3a products. Further increasing of base quantity up to 10 eq (entry 6) didn’t significantly affect on triazolopyridine 2a output, however the amount of product 3a was slightly decreased. The best results were achieved in H2O as a solvent, although in EtOH similar results was obtained. However, it should be noted, that cyanopyridine should be added as solution in minimum amount of EtOH in case of multigram-scale reaction in view of worst solubility of cyanopyridines in water. Other solvent/base pairs tested (entries 10-12) didn’t give satisfactory results. The cycloaddition reaction could proceed in ionic liquids as solvent (entries 13, 14), however the yields are low. Attempts of transition metals salts addition (entry 15) were unsuccessful. Next, we tried to oxidize product 3a with different agents to improve the yield of 2a. Unfortunately, such oxidants as chloranil, DDQ, bromine, H2O2 and MnO2 led to full conversion of 3a without formation of any definite product. On the other side, when oxygen was used, no oxidation of 3a was found.
Table 1. Conditions optimization of salt 1 reaction with 2-cyanopyridine.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield of 2a, %</th>
<th>Ratio 2:3a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 eq KOH in H₂O/EtOH</td>
<td>8</td>
<td>0.23</td>
</tr>
<tr>
<td>2</td>
<td>2 eq KOH in H₂O/EtOH</td>
<td>35</td>
<td>0.39</td>
</tr>
<tr>
<td>3</td>
<td>3 eq KOH in H₂O/EtOH</td>
<td>42</td>
<td>0.40</td>
</tr>
<tr>
<td>4</td>
<td>4 eq KOH in H₂O/EtOH</td>
<td>43</td>
<td>0.35</td>
</tr>
<tr>
<td>5</td>
<td>5 eq KOH in H₂O/EtOH</td>
<td>46</td>
<td>0.28</td>
</tr>
<tr>
<td>6</td>
<td>10 eq KOH in H₂O/EtOH</td>
<td>46</td>
<td>0.15</td>
</tr>
<tr>
<td>7</td>
<td>5 eq KOH in H₂O</td>
<td>48</td>
<td>0.13</td>
</tr>
<tr>
<td>8</td>
<td>5 eq K₂CO₃ in H₂O</td>
<td>0</td>
<td>-c</td>
</tr>
<tr>
<td>9</td>
<td>5 eq KOH in EtOH</td>
<td>45</td>
<td>0.06</td>
</tr>
<tr>
<td>10</td>
<td>5 eq K₂CO₃ in MeCN</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>5 eq CH₃ONa in CH₃OH</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>5 eq t-AmONa in tAmOH</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>5 eq KOH in BMIM BF₄</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>5 eq DBU in BMIM BF₄</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>CuCl₂ or CuCl (1% mol) in H₂O</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

aThe yields and product ratios were determined by ¹H NMR with CH₂Br₂ as internal standard
bReaction was carried out at 0.1 mmol scale, 2N solution of bases in solvents were used.
cNo 3a product was formed.

With the optimized conditions in hand, the scope of this transformation was investigated. Both 3- and 4-cyanopyridines also readily reacted with N-aminopyridinium salt leading to corresponding triazolopyridines 2b,c with nearly the same yields (Table 2). For 1-amino-4,4'-bipyridinium mesitylenesulfonate two conditions (entries 7,9 from table 1) were applied, and it was found that better results could be achieved in H₂O as a solvent, so such conditions were used in further studies. 1-Amino-2,2'-bipyridinium, 1-amino-1,10-phenanthrolinium and 1-amino-8-hydroxyquinolinium mesitylenesulfonates underwent 1,3-cycloaddition with cyanopyridines to form corresponding triazoloazines 4-7a-c with satisfactory yields.
Table 2. Synthesis of [1,2,4]triazolo[1,5-a]azines.

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield, %&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Product</th>
<th>Yield, %&lt;sup&gt;a&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td><img src="image" alt="2a" /></td>
<td>48</td>
<td><img src="image" alt="2b" /></td>
<td>49</td>
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<tr>
<td><img src="image" alt="2c" /></td>
<td>43</td>
<td><img src="image" alt="4a" /></td>
<td>70 (36&lt;sup&gt;b&lt;/sup&gt;)</td>
</tr>
<tr>
<td><img src="image" alt="4b" /></td>
<td>36</td>
<td><img src="image" alt="4c" /></td>
<td>51</td>
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<tr>
<td><img src="image" alt="5a" /></td>
<td>36</td>
<td><img src="image" alt="5b" /></td>
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<tr>
<td><img src="image" alt="5c" /></td>
<td>44</td>
<td><img src="image" alt="6a" /></td>
<td>42</td>
</tr>
<tr>
<td><img src="image" alt="6b" /></td>
<td>66</td>
<td><img src="image" alt="6c" /></td>
<td>50</td>
</tr>
<tr>
<td><img src="image" alt="7a" /></td>
<td>57</td>
<td><img src="image" alt="7b" /></td>
<td>54</td>
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<tr>
<td><img src="image" alt="7c" /></td>
<td>51</td>
<td><img src="image" alt="8a-c" /></td>
<td>traces</td>
</tr>
</tbody>
</table>
In case of 1-aminoquinolinium and 2-aminoisooquinolinium mesitylenesulfonates insoluble solids were formed under standard reaction conditions. The solids were identified as dimers of corresponding N-imies according to NMR spectra. Previously such dimers were prepared from corresponding N-amino derivatives in basic media [32, 33]. Interestingly, that the quinilinium and isoquinolinium dimers reacted with a range of dipolarophiles yielding various heterocyclic products [33]. Our attempts to obtain products 8a-c from quinolinium-N-imine dimer were unsuccessful and only traces of product were observed according to GC-MS and NMR. N-Amino derivatives of pyrazine and pyridazine didn’t undergo the cycloaddition reaction, only corresponding N-imines, starting nitriles and nicotinamides were identified in the reaction mixtures by NMR. Such behavior may be explained by lower contribution of 1,3-dipolar structure 12a to the resonance hybrid along with higher role of structure 12b and, thus, low 1,3-dipolar character of N-imine (Fig. 2).

Figure 2. Dipolar resonance structures of pyrazinium-N-imine.

To get more insights into the reactivity of N-imines, DFT study (B3LYP/L1 level of theory with RI approximation and SMD solvation, see supporting information for details) of the process was performed. For cycloaddition of pyridinium-N-imine to 4-cyanopyridine transition state (TS1) corresponding to concerted mechanism was localized (Fig. 3a). The geometry of TS1 is similar to previously reported transition state structures [34, 35] of dimethyl acetylenedicarboxylate to pyridinium-N-imines cycloaddition. However, in case of nitrile later transition state is realized according to shorter distance between pyridinium-N-imine and cyanopyridine. As shown on energetic diagram (Fig. 4), the reaction is slightly exothermic and cycloadduct 13 formed is much less stable than rearrangement product 14, yet
mechanism of hydrogen atoms migration is unclear. According to reaction mechanism product 2c is formed from adduct 13 by oxidation with air.

Pyrazinium-N-imine has slightly shorter N-N bond (Fig. 3d) that reflects higher contribution of structure 12b to the resonance hybrid (Fig. 2). Also this imine has significantly lower HOMO level compared to pyridinium-N-imine, probably due to electron withdrawal properties of nitrogen atom. Thus, for pyrazinium-N-imine significantly increased activation energy was found in reaction with 4-cyanopyridine (Fig. 3b).

Figure 3. Structures of transition states of nitrile cycloaddition to pyridinium (a), quinolinium (b) and pyrazinium-N-imines (c), and structures of pyridinium and pyrazinium-N-imines with their HOMO energy level (d).

\[ \Delta G^\ne = 77.0 \text{ kJ/mol} \]
\[ \Delta G^\ne = 103.2 \text{ kJ/mol} \]
\[ \Delta G^\ne = 123.0 \text{ kJ/mol} \]

\[ E(\text{HOMO}) = -0.1782 \text{ eV} \]
\[ E(\text{HOMO}) = -0.2084 \text{ eV} \]
Figure 4. Energy diagram of 4-cyanopyridine to pyridinium-N-imine cycloaddition.

In case of quinolinium-N-imine substantially higher barrier was also observed. At the same time, dimerization of this imine is strongly favorable (Table 3). Even higher negative energy of dimerization was calculated for isoquinolinium-N-imine, and it is notably, that the most stable dimer formed by reaction at position 1 of the both rings. This is in accordance with the direction of nucleophilic attack in N-substituted isoquinolines. Pyridinium-, pyrazinium-N-imines and especially 1,10-phenanthroline-N-imine possess significantly more positive energy of dimerisation, so these imines have no dimerization as complicating factor.

Table 3. Calculated free energies of N-imines dimerization.

<table>
<thead>
<tr>
<th>N-imine dimer</th>
<th>$\Delta G^{\circ}_{298}$, kJ/mol</th>
<th>N-imine dimer</th>
<th>$\Delta G^{\circ}_{298}$, kJ/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-6.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-73.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-67.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.0</td>
</tr>
</tbody>
</table>
Conclusion
In summary, cycloaddition of cyanopyrirdines to various azinium-\(N\)-imines was studied. For pyridinium, 2,2'- and 4,4'-bipyridinium, 1,10-phenanthroline and 8-hydroxyquinolinium derivatives corresponding [1,2,4]triazolo[1,5-a]azines are formed under the air conditions. In case of quinolinium- and isoquinolinium-N-imines their dimers were isolated as only products. Pyrazinium and pyridazinium imines didn’t undergo both cycloaddition or dimerisation. Quantum chemical studies show high activation barriers for addition of 4-cyanopyridine to quinolinium and pyrazinium-\(N\)-imines. Besides, quinolinium and isoquinolinium imines possess strong tendency to dimerization according to DFT studies.

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Supporting information
Experimental procedures, computational details, characterization data and copies of \(^1\)H and \(^{13}\)C NMR spectra for obtained compounds and cartesian coordinates for DFT optimized structures.
Notes and references


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