Acid-Catalyzed [3+2] Cycloaddition of Enones with Azomethine Imines for Easy Access to Tetrahydropyrazolopyrazolones

Jovana P. Jovanović
Goran A. Bogdanović
Ivan Damjanović

Abstract
Aluminum chloride (AlCl₃) or zirconium chloride (ZrCl₄) catalyzes efficiently the [3+2] cycloaddition of N,N'-cyclic azomethine imines with enones which contain the vinyl group. The scope of the reaction towards various azomethine imines and enones has been explored. Access to diastereomERICALLY pure 6-acyl-5-aryltetrahydropyrazolo[1,2-a]pyrazol-1(5H)-ones is provided by easy chromatographic separations.

Key words
dipolar cycloaddition, N,N'-cyclic azomethine imine, enone, N,N'-bicyclic heterocycles, Lewis acid

Dinitrogenated fused heterocycles are valuable bioactive molecules. For example, tetrahydropyrazolo[1,2-a]pyrazolones have been investigated as antibacterials and potential anti-Alzheimer’s agents while some pyrazolo-cinno-...
increase of the reaction temperature had no significant effect on the yield and cis/trans ratio (Table 1, entry 5). However, it was observed that the cis/trans ratio of the products depended on the used catalyst.

Seven more acidic catalysts were screened (Table 1, entries 8–14). The results show that Lewis acids favored a formation of the cis isomer (Table 1, entries 4, 8, 9). On the other hand, the influence of the applied Brønsted acids depended on a case-by-case basis (Table 1, entries 10–14). Evidently, the best results were achieved with AlCl₃ and ZrCl₄ (20 mol%, Table 1, entries 4 and 8), thus these two catalysts were the indispensable elements of the later investigations.

Furthermore, the effects of the seven solvents were studied in the presence of 20 mol% of AlCl₃ (Table 1, entries 15–21). After 48 hours, the use of the protic solvent such as methanol resulted in the formation of 3a in trace amounts (Table 1, entry 21). Moreover, the other examined solvents (Table 1, entries 15–19) except the toluene (Table 1, entry 20) were equally efficient for this reaction and produced 3a in good yields (65–88%).

The scope of the reaction was explored using the set of enones with the vinyl group (2a–g) and azomethine imines (1a–c) under optimized reaction conditions: AlCl₃ or ZrCl₄ as the catalyst with a loading of 20 mol%, dichloromethane as the solvent, and 20% excess of N,N’-cyclic azomethine imines 1a–c. Although the acetic acid caused highly efficient results in the preliminary investigations (reaction between 1a and 2a), its catalytic effect in the next few examples was rather poor. Since the goal of the study was to develop a widely useful methodology under mild conditions, further examinations with this catalyst were not performed.

However, the seven enones 2a–g and the three different azomethine imines 1a–c were examined in 1,3-dipolar cycloadditions catalyzed by AlCl₃ or ZrCl₄ (Scheme 1). Products, 3a–u, were obtained in moderate to very high yields of 50–98%, and the results evidently showed that the catalysis by ZrCl₄ had a minor advantage in comparison to the AlCl₃-catalyzed procedure. Although both catalytic reactions (with ZrCl₄ or AlCl₃) proceeded smoothly under the mild conditions, we observed that the AlCl₃-catalyzed processes always afforded 5% or more of the aryl-aldehyde formed by the degradation of the appropriate azomethine imine 1a–c. To determine which catalyst had the weaker influence on this degradation, we were stirring the mixtures of azomethine imine 1a/AlCl₃ and 1a/ZrCl₄ in dichloromethane for two days. The analyses of the NMR spectra of the mixture that was stirred for two days showed that the first one (1a/AlCl₃) contained 20% of the benzaldehyde, while the traces of it were detected in the mixture 1a/ZrCl₄.

In general, the catalysis of the cycloaddition with 20 mol% of a Lewis acid (ZrCl₄ or AlCl₃) provided the products 3a–u as mixtures of the corresponding diastereoisomers in which the trans isomers in most cases were major products. Yet, to our delight, these mixtures were easily separable by the column chromatography which enabled an easy access to the stable, diastereomerically pure 6-acyl-5-aryltetrahydropyrazol[1,2-a]pyrazol-1(5H)-ones (cis- and trans-3a–u).

One of them (cis-3a) was quite suitable for the crystallographic examinations, and the results helped us to determine the relative configurations of all cycloadducts by the analysis of the 1H NMR spectra of diastereoisomers. The molecular structure of the compound cis-3a (Figure 1) was determined by a single-crystal X-ray analysis. The results clearly confirmed that both nitrogen atoms are sp³-hybridized with the tetrahedral geometry of corresponding bonds (the sum of bond angles around the N1 and N2 atoms is 341° and 319°, respectively). Both five-membered rings adopt an envelope conformation since that the N1–C1–C2–C3 and N1–C7–C6–C5 fragments are practically planar (the

---

**Table 1 Optimization for the [3+2] Cycloaddition of Azomethine Imine 1a with 3-Buten-2-one (2a)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Catalyst loading (mol%)</th>
<th>Yield (%)</th>
<th>Ratio cis/trans¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>–</td>
<td>–</td>
<td>32</td>
<td>20:80</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>AlCl₃</td>
<td>5</td>
<td>57</td>
<td>42:58</td>
</tr>
<tr>
<td>3</td>
<td>CH₂Cl₂</td>
<td>AlCl₃</td>
<td>10</td>
<td>85</td>
<td>51:49</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Cl₂</td>
<td>AlCl₃</td>
<td>20</td>
<td>94</td>
<td>58:42</td>
</tr>
<tr>
<td>5</td>
<td>CH₂Cl₂</td>
<td>AlCl₃</td>
<td>20</td>
<td>93</td>
<td>57:43</td>
</tr>
<tr>
<td>6</td>
<td>CH₂Cl₂</td>
<td>AlCl₃</td>
<td>50</td>
<td>68</td>
<td>77:23</td>
</tr>
<tr>
<td>7</td>
<td>CH₂Cl₂</td>
<td>AlCl₃</td>
<td>100</td>
<td>52</td>
<td>85:15</td>
</tr>
<tr>
<td>8</td>
<td>CH₂Cl₂</td>
<td>ZrCl₄</td>
<td>20</td>
<td>89</td>
<td>61:39</td>
</tr>
<tr>
<td>9</td>
<td>CH₂Cl₂</td>
<td>FeCl₃</td>
<td>20</td>
<td>46</td>
<td>60:40</td>
</tr>
<tr>
<td>10</td>
<td>CH₂Cl₂</td>
<td>HBF₄</td>
<td>20</td>
<td>33</td>
<td>57:43</td>
</tr>
<tr>
<td>11</td>
<td>CH₂Cl₂</td>
<td>AcOH</td>
<td>20</td>
<td>94</td>
<td>24:76</td>
</tr>
<tr>
<td>12</td>
<td>CH₂Cl₂</td>
<td>l-tartaric acid</td>
<td>20</td>
<td>68</td>
<td>20:80</td>
</tr>
<tr>
<td>13</td>
<td>CH₂Cl₂</td>
<td>(S)-lactic acid</td>
<td>20</td>
<td>85</td>
<td>54:46</td>
</tr>
<tr>
<td>14</td>
<td>CH₂Cl₂</td>
<td>PTSA</td>
<td>20</td>
<td>49</td>
<td>52:48</td>
</tr>
<tr>
<td>15</td>
<td>CHCl₃</td>
<td>AlCl₃</td>
<td>20</td>
<td>65</td>
<td>77:23</td>
</tr>
<tr>
<td>16</td>
<td>CH₂Cl₂</td>
<td>AlCl₃</td>
<td>20</td>
<td>88</td>
<td>70:30</td>
</tr>
<tr>
<td>17</td>
<td>THF</td>
<td>AlCl₃</td>
<td>20</td>
<td>75</td>
<td>67:33</td>
</tr>
<tr>
<td>18</td>
<td>1,4-dioxane</td>
<td>AlCl₃</td>
<td>20</td>
<td>77</td>
<td>45:55</td>
</tr>
<tr>
<td>19</td>
<td>MeCN</td>
<td>AlCl₃</td>
<td>20</td>
<td>69</td>
<td>77:23</td>
</tr>
<tr>
<td>20</td>
<td>Tol</td>
<td>AlCl₃</td>
<td>20</td>
<td>60</td>
<td>61:39</td>
</tr>
<tr>
<td>21</td>
<td>MeOH</td>
<td>AlCl₃</td>
<td>20</td>
<td>trace</td>
<td>–</td>
</tr>
</tbody>
</table>

¹ Unless otherwise indicated, reactions were carried out with 1a (0.6 mmol, 1.2 equiv), 2a (0.5 mmol, 1 equiv), catalyst in solvent (5 mL) for 48 h at r.t.

¹ Calculated on the basis of isolated yields.

© Georg Thieme Verlag Stuttgart · New York — Synlett 2017, 28, 664–668

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.
N1–C1–C2–C3 and N1–C7–C6–C5 torsion angles are \(-1.6(2)^\circ\) and \(4.3(2)^\circ\), respectively) while the N2 atom is significantly displaced from these planes [0.394(3) Å and –0.613(3) Å]. From observing bond lengths it is obvious that all bonds within two rings are single bonds whilst the C5–C6 bond [1.564(3) Å] represents the longest bond in the whole molecule.

We also noticed that the pyrazolidinone ring has moved away from the magnetic influence of the aromatic ring. The signal in the \(^1\)H NMR spectrum which originated from the protons at C-2 is relatively simple (pseudo triplet) and appears at \(\delta = 2.71\) ppm (Figure 2). On the other hand, the shape of \(^1\)H NMR signal for the analogous methylene group in the spectrum of trans-3a is a complex multiplet at \(\delta = 2.68\) ppm, which indicates substantially shielding of protons at C-2 by the electron-rich aromatic ring (Figure 2, dashed line). This significant difference between the NMR data for the two diastereoisomers occurs in spectra of each cis/trans pair of products 3a–u and it was used for the structural identification of all diastereoisomers.

In respect of the stereochemical outcome of the reactions, we do not have firm explanations for it. Generally speaking, the use of Lewis acid vs. protic acid can affect the stereoselectivity changes, but in all cases we obtained both diastereoisomers.

Taking this into consideration, the four possible models for the intermediates were proposed (Figure 3). This can be illustrated by the synthesis of 3a. Thus, \(N,N^*\)-cyclic azomethine imine 1a can adopt the Z- or E-planar conformation.
whereupon the 2a approached it forming corresponding exo- (II and III) and endo-transition-state assemblies (I and IV). The transition states II and IV afforded the cis diastereoisomer while the trans-3a was obtained via the transition states I and III. Still, the real mechanism of these reactions will be investigated in the future.

In conclusion, enones with the vinyl group have been for the first time employed in the reaction with azomethine imines providing simple access to 6-acyl-5-aryltetrahydro-pyrazolo[1,2-a]pyrazol-1(5H)-ones in a moderate to excellent chemical yield (up to 98%). Products were easily separable which simplified isolation of the pure diastereoisomers. Eventually, they could be of interest for the bioactivity studies. Experimentally the procedure was quite a simple one carried with the inexpensive, commercially available catalysts.

Acknowledgment

We thank the Ministry of Education, Science and Technological Development of the Republic of Serbia for financial support (Grant 172034).

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588678.

References and Notes


References and Notes


Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588678.

References and Notes


Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588678.

References and Notes


Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588678.

General Procedure for [3+2] Cycloaddition of \(N,N'\)-Cyclic Azomethine Imines 1 and Enones 2

In a 25 mL flask, enone 2 (0.5 mmol) was added to a stirred mixture of \(N,N'\)-cyclic azomethine imine 1 (0.6 mmol) and catalyst (AlCl\(_3\) or ZrCl\(_4\), 0.1 mmol) in CH\(_2\)Cl\(_2\) (5.0 mL) at r.t. The mixture was stirred for 48 h. The solvent was then removed by distillation, and the crude mixture was separated by silica gel chromatography (hexane–EtOAc = 5:5 to 4:6). Fractions were collected and concentrated in vacuo to provide the pure products 3.

Selected Data for Products

trans-3a
39% yield for AlCl\(_3\)-catalyzed reaction (35% yield for ZrCl\(_4\)-catalyzed reaction), pale yellow solid; mp 90 °C. \(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta = 7.50–7.27 \text{ (m, 5 H, Ph)}, 4.13–3.92 \text{ (m, 1 H, H-6)}, 3.74–3.51 \text{ (m, 3 H, H-5, H-7a, and H-7b)}, 3.41 \text{ (ddd, } J = 11.5, 9.4, 7.6 \text{ Hz, 1 H, H-3b)}, 2.99 \text{ (ddd, } J = 11.5, 9.0, 6.6 \text{ Hz, 1 H, H-3a)}, 2.84–2.48 \text{ (m, 2 H, H-2a, and H-2b)}, 1.99 \text{ (s, 3 H, Me)}. \(^1\)C NMR (50 MHz, CDCl\(_3\)): \(\delta = 204.1 \text{ (CO)}, 172.9 \text{ (C-1)}, 136.5 \text{ (Ph)}, 128.5 \text{ (Ph)}, 128.2 \text{ (Ph)}, 127.5 \text{ (Ph)}, 70.5 \text{ (C-5)}, 61.7 \text{ (C-6)}, 45.3 \text{ (C-3)}, 42.7 \text{ (C-7)}, 30.7 \text{ (C-2)}, 29.8 \text{ (Me)}. IR (KBr): 3030, 2952, 1713, 1455, 1361, 1169, 750, 703 cm\(^{-1}\). Anal. Calcd for \(C_{14}H_{16}N_2O_2\) (244.29): C, 68.83; H, 6.60. Found: C, 68.79; H, 6.62.

cis-3a
55% yield for AlCl\(_3\)-catalyzed reaction (54% yield for ZrCl\(_4\)-catalyzed reaction), white solid; mp 160 °C. \(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta = 7.53–7.26 \text{ (m, 5 H, Ph)}, 4.04–3.71 \text{ (m, 4 H, H-5, H-6, H-7a, and H-7b)}, 3.54 \text{ (pseudo dt, } J = 11.1, 8.2 \text{ Hz, 1 H, H-3b)}, 2.91 \text{ (ddd, } J = 11.1, 9.5, 6.9 \text{ Hz, 3-Ha)}, 2.71 \text{ (pseudo dt, } J = 8.2 \text{ Hz, 2 H, H-2a, and H-2b)}, 1.52 \text{ (s, 3 H, Me)}. \(^1\)C NMR (50 MHz, CDCl\(_3\)): \(\delta = 205.4 \text{ (CO)}, 172.3 \text{ (C-1)}, 134.0 \text{ (Ph)}, 128.8 \text{ (Ph)}, 128.6 \text{ (Ph)}, 127.8 \text{ (Ph)}, 71.1 \text{ (C-5)}, 58.0 \text{ (C-6)}, 46.0 \text{ (C-3)}, 42.0 \text{ (C-2)}, 31.6 \text{ (C-2)}, 30.6 \text{ (Me)}. IR (KBr): 3062, 2966, 1709, 1699, 1458, 1357, 1175, 1090, 776, 712 cm\(^{-1}\). Anal. Calcd for \(C_{14}H_{16}N_2O_2\) (244.29): C, 68.83; H, 6.60. Found: C, 68.80; H, 6.63.

CCDC 1497416 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge via www.ccdc.cam.ac.uk/getstructures.

In the case of sp\(^2\) hybridization, this sum would be equal or close to 360°.