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Concise and scalable asymmetric synthesis of 5-((1-amino-2,2,2-trifluoroethyl)thiazolo[3,2-b][1,2,4]triazoles

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This study describes asymmetric Mannich-type additions between C-5 lithiated thiazolo[3,2-b][1,2,4]triazoles and enantiomerically pure (S,S)-N-tert-butanesulfinyl-(3,3,3)-trifluoroacetaldimine.

Under the optimized conditions, these reactions proceed with good (up to 78%) chemical yields and virtually complete (99:1 to >99:1 dr) diastereoselectivity. The same stereochanical outcome was obtained using 1.05 g scale of the starting (3,3,3)-trifluoroacetaldimine. The method developed in this work provides a concise and generalized access to thiazolo[3,2-b][1,2,4]triazoles containing chiral (trifluoro)ethylamine group.

Introduction

Heterocyclic compounds are quite commonly found in nature and have been attracting passionate attention of organic chemists for many decades. In particular, the thiazolo[3,2-b][1,2,4]triazole fragment is found in many biologically active natural products. Consequently, synthesis and biological study of new thiazolo[3,2-b][1,2,4]triazole derivatives is currently an active field of multidisciplinary research.

It was found, that the most promising biologically active types of thiazolo[3,2-b][1,2,4]triazoles are usually containing functional chiral moieties. Accordingly, the development of concise and scalable methods for asymmetric modification of thiazolo[3,2-b][1,2,4]triazoles is important, yet challenging goal in synthetic organic and medicinal chemistry.

Taking into account the remarkable impact of fluorine on the development of biological active compounds and pharmaceuticals, synthesis of fluorinated thiazolo[3,2-b][1,2,4]triazoles might be of great interest. Therefore, considering our and others recent interest in the chemistry of (S,S)-N-tert-butanesulfinyl-(3,3,3)-trifluoroacetaldimine we envisioned a direct, one-step introduction of the pharmacophoric 1-amino-2,2,2-trifluoroethyl moiety onto the thiazolo[3,2-b][1,2,4]triazole rings. Herein, we report a study of asymmetric Mannich-type reactions between C-5 lithiated thiazolo[3,2-b][1,2,4]triazoles and (S,S)-N-tert-butanesulfinyl-(3,3,3)-trifluoroacetaldimine. These reactions were found to proceed with exceptional diastereoselectivity, diving rise to virtually one product in good chemical yields (Scheme 1). Mechanism, structural generality of this method and its scalability are discussed.

Results and discussion

Based on our previous studies of the asymmetric reactions with N-tert-butylsulfinylimine, the initial choice of the reaction conditions was focused on using sulfinylimine 2 with 1.5 equiv of 6-phenylthiazolo[3,2-b][1,2,4]triazole 1a in the presence of n-BuLi with THF as solvent at -78 °C. The reaction proceeded smoothly within 2 hrs, affording (entry 1, Table 1) the desired product 3a in 61% yield. Determination of the diastereomeric purity by 1H-NMR has revealed two diastereomeric products (see SI) in a ratio of 83:17. Attempts to separate these two CF3-containing products by column chromatography have failed, indicating insufficient difference in the physicochemical properties of the diastereomers. The fact that the separation of diastereomeric products is problematic, has added an extra challenge to this work as only complete diastereoselectivity in these additions could render this method synthetically useful. Thus, systematic optimization was carried out to improve both the yield and, most importantly, the diastereoselectivity. First, the effect of a base used in these reactions was investigated. It was found that strong bases could give good results while the week ones could not even catalyze the reaction (entries 2-6). LDA was found to be the best choice, providing for an acceptable yield and the desired high diastereoselectivity (62% yield and 97:3 dr, entry 2). Next, the loading amount of 6-phenylthiazolo[3,2-b][1,2,4]triazole 1a was examined. The experiments have revealed that use of 1.7 equiv of 1a leads to the high yield and excellent diastereoselectivity (71% yield and 98:2 dr, entry 8).
Reducing the amount of 1a resulted in an obvious decrease in both yield and diastereoselectivity (entry 7). Solvent was found to have significant effect on the stereochemical outcome (entries 9-12), and THF was finally confirmed to be the best choice. Furthermore, temperature was also found to be an important factor in these reactions. Elevated reaction temperature brought a slight decrease in both yield and diastereoselectivity (entries 13-15). Finally, the screening of the reaction time demonstrated that this transformation could be reasonably completed within 2 hrs. Thus, extending the reaction time resulted in a noticeable decrease in both yield and diastereoselectivity (entries 13-15). THF was finally confirmed to be the best choice.

Table 1. Optimization of the asymmetric Mannich-type addition reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
<th>Dr</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>n-BuLi 1.5</td>
<td>THF</td>
<td>2</td>
<td>-78</td>
<td>61</td>
<td>83:17</td>
</tr>
<tr>
<td>2</td>
<td>LDA 1.5</td>
<td>THF</td>
<td>2</td>
<td>-78</td>
<td>68</td>
<td>97:3</td>
</tr>
<tr>
<td>3</td>
<td>LiHDMDS 1.5</td>
<td>THF</td>
<td>2</td>
<td>-78</td>
<td>42</td>
<td>76:24</td>
</tr>
<tr>
<td>4</td>
<td>(CH3)2COLi 1.5</td>
<td>THF</td>
<td>2</td>
<td>-78</td>
<td>trace</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>Cs2CO3 1.5</td>
<td>THF</td>
<td>2</td>
<td>-78</td>
<td>40</td>
<td>87:13</td>
</tr>
<tr>
<td>6</td>
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<td>THF</td>
<td>2</td>
<td>-78</td>
<td>40</td>
<td>87:13</td>
</tr>
<tr>
<td>7</td>
<td>LDA 1.7</td>
<td>THF</td>
<td>2</td>
<td>-78</td>
<td>71</td>
<td>98:2</td>
</tr>
<tr>
<td>8</td>
<td>LDA 1.7</td>
<td>Toluene</td>
<td>2</td>
<td>-78</td>
<td>26</td>
<td>79:21</td>
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<tr>
<td>9</td>
<td>LDA 1.7</td>
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<td>2</td>
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<td>27</td>
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<tr>
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<td>CH2Cl2</td>
<td>2</td>
<td>-78</td>
<td>13</td>
<td>92:8</td>
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<tr>
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<td>2</td>
<td>-78</td>
<td>37</td>
<td>90:10</td>
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<td>12</td>
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<td>THF</td>
<td>2</td>
<td>-41</td>
<td>72</td>
<td>93:7</td>
</tr>
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<td>13</td>
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<td>THF</td>
<td>2</td>
<td>-22</td>
<td>64</td>
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</tr>
<tr>
<td>14</td>
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<td>THF</td>
<td>2</td>
<td>-37</td>
<td>61</td>
<td>94:6</td>
</tr>
<tr>
<td>15</td>
<td>LDA 1.7</td>
<td>THF</td>
<td>3</td>
<td>-78</td>
<td>65</td>
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<tr>
<td>16</td>
<td>LDA 1.7</td>
<td>THF</td>
<td>3</td>
<td>-78</td>
<td>66</td>
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<td>17</td>
<td>LDA 1.7</td>
<td>THF</td>
<td>3</td>
<td>-78</td>
<td>65</td>
<td>98:2</td>
</tr>
</tbody>
</table>

* Reaction conditions: sulfinylimine (0.5 mmol), base (1.1 equiv of 1a), solvent (5 mL). ° Isolated yields. ‡ Determined by 1F or 1H NMR analysis. § Not determined. † No reaction.

Having optimized the reaction conditions, our next goal was to examine the scope of these reactions using available thiazolo[3,2-b][1,2,4]triazoles (Table 2). Under the standard reaction conditions, all tested substrates reacted smoothly pointing to generality of this method. As shown in Table 2, the diastereoselectivity of the reactions was excellent, producing virtually single diastereomer. Variation of substituents on the aromatic ring showed no significant effect on either chemical yield or diastereoselectivity. Both electron-deficient (entries 2-6) and electron-rich (entry 7) aryl-substituted thiazolo[3,2-b][1,2,4]triazoles gave equally good stereochemical outcome. In particular, thiazolo[3,2-b][1,2,4]triazoles with di-substituted aromatic ring (1b or naphthyl substituted 11) were also well tolerated in this reaction affording products 3b, i in good yields and with excellent diastereoselectivity (entries 8 and 9). In the case of alkyl substituted derivative 1j the reaction yield was noticeably lower, however the corresponding product 3j was isolated as a single diastereomer. (entry 10).

Finally, this newly developed method we tested for its reproducibility and efficiency on a gram-scale. As one can see from the Scheme 2, the reaction conducted under the standard conditions using 1.05 g of sulfinylimine 2 afforded the target product 3a with good yield (68%) and diastereoselectivity (94:6 dr). Diastereomerically pure 3a can be prepared by crystallization of the crude product. Thus, only a slight decrease in the yield and diastereoselectivity were detected as compared to the best result obtained on a 0.10 g scale. Consequently, this approach can be reliably used for relatively large scale synthesis of various fluorinated chiral thiazolo[3,2-b][1,2,4]triazoles derivatives allowing for a systematic biological studies of these new compounds.

Scheme 2. Example of a large-scale asymmetric synthesis of compound 3a.

To determine the absolute configuration of the products 3a, we took advantage of good crystallinity of compound 3a and conducted its crystallographic analysis (Figure 1). As shown in Figure 1, the absolute configuration of the newly generated chiral center in this process is R. The absolute configurations of other corresponding products were assigned by analogy, based on similarity of their chiroptic properties and spectral data.
Consistent with the literature data,\textsuperscript{18} the asymmetric Mannich-type addition reactions of thiazolo[3,2-b][1,2,4]triazoles to sulffinylimine 2 is suggested to proceed via a non-chelated transition state model. Thus, the lithiated thiazolo[3,2-b][1,2,4]triazoles preferably approaches the imine double bond from the less hindered face, occupied by the lone pair of electrons on sulphur, to afford the major diastereomer (Figure 2).

Furthermore, via this general approach, two possible orientations of the thiazolo[3,2-b][1,2,4]triazoles anion A and B are possible. Considering obvious steric interactions of the CF\textsubscript{3} group and the substituent R in B, it is most likely that the transition state A might be preferred.

Figure 2. Proposed mechanism for the asymmetric Mannich-type addition.

As the final task of this work, we studied an example of the chiral auxiliary removal and preparation of the compound 4 with free amino function. Using relatively common conditions,\textsuperscript{15a,15b} such as treatment of 3a with aqueous HCl in methanol (Scheme 3), the target amine 4 was obtained in high isolated yield of 86%.

Conclusions

In summary, we have demonstrated that the asymmetric Mannich-type addition reactions between lithium-derived of imidazo[2,1-b]thiazoles and CF\textsubscript{3}-sulfinylimine 2 occur with reasonably good yields and excellent diastereoselectivity. These reactions are reproducible on relatively large scale and can be reliably used for preparation of various thiazolo[3,2-b][1,2,4]triazoles containing chiral 1-amino-2,2,2-trifluoroethyl group for systematic biological studies.

General information

All imine addition reactions were performed in oven-dried vials under N\textsubscript{2} atmosphere. Solvent THF was dried and distilled prior to use. Thiazolo[3,2-b][1,2,4]triazoles 1 were synthesized according to literature \cite{1}. Sulffinylimine 2 was obtained from Accela ChemBio Co., Ltd.. LDA (2 M in THF, 0.47 mL) was added dropwise. Stirring was continued at -78°C for 2 h, then the reaction was quenched with saturated NH\textsubscript{4}Cl (3.0 mL), followed by H\textsubscript{2}O (5.0 mL) and the mixture was brought to room temperature. The organic layer was taken and the aqueous layer was removed to give the crude product, which was purified by TLC plate (hexane/EtOAc, 1:1).

Typical procedure for asymmetric addition of sulffinylimine

Into an oven-dried reaction vial flushed with N\textsubscript{2} were taken compound 1 (0.85 mmol) and anhydrous THF (3.0 mL). The reaction vial was cooled to -78 °C and LDA (2 M in THF, 0.47 mL) was added dropwise with stirring. After 1 h at -78 °C, sulffinylimine 2 (0.5 mmol) dissolved in anhydrous THF (2.0 mL) was added dropwise. Stirring was continued at -78 °C for 2 h, then the reaction was quenched with saturated NH\textsubscript{4}Cl (3.0 mL), followed by H\textsubscript{2}O (5.0 mL) and the mixture was brought to room temperature. The organic layer was taken and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried with anhydrous Na\textsubscript{2}SO\textsubscript{4}, filtered and the solvent was removed to give the crude product, which was purified by TLC plate (hexane/EtOAc, 1:1).

3a: white solid, mp 192-193 °C; [\alpha]\textsubscript{D}\textsuperscript{25} +107.3 (c 1.05, CHCl\textsubscript{3} ), 1H NMR (CDCl\textsubscript{3}, 400 MHz): \( \delta = 8.18 \) (s, 1 H), 7.71-7.74 (m, 2 H), 7.57-7.62 (m, 3 H), 5.31-5.36 (m, 1 H), 3.91 (s, 1 H), 1.29 (s, 9 H), 13C NMR (CDCl\textsubscript{3}, 100 MHz): \( \delta = 156.2, 155.8, 135.5, 130.9, 129.5, 126.0, 125.1 \) (q, \( J = 281.0 \) Hz), 118.1 (t, 135.5, 130.9, 129.5, 126.0, 125.1 (q, \( J = 281.0 \) Hz), 118.1, 56.9, 54.9 (q, \( J = 32.0 \) Hz), 22.4. 19F NMR (CDCl\textsubscript{3}, 376 MHz): \( \delta = -73.8 \). HRMS (TOF MS El\textsuperscript{+}) m/z: celled for [C\textsubscript{16}H\textsubscript{17}N\textsubscript{4}O\textsubscript{3}S\textsubscript{2}] 402.0796, found 402.0785.
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Organic NMR (CDCl3, 400 MHz): δ = -73.8. HRMS [M+H+]: calcd for [C16H17BrN4OF3S2] 480.9979, found 480.9974.

NMR (CDCl3, 376 MHz): δ = -73.7. HRMS [M+Na+]: calcd for [C16H17ClN4OF3S2Na] 443.0599, found 443.0598. 25

19F NMR (CDCl3, 376 MHz): δ = -73.8. HRMS [M+Na+]: calcd for [C16H17BrN4OF3S2Na] 443.0599, found 443.0598.

Reaction of large scale application study

Into an oven-dried round-bottom flask flushed with N2, the taken compound 1a (8.5 mmol) and anhydrous THF (20.0 mL) was added dropwise with stirring. After 1 h at -78 °C, sulfinylimine 2 (5 mmol) dissolved in anhydrous THF (10.0 mL) was added dropwise. Stirring was continued at -78 °C for 2.5 h, then the reaction was quenched with saturated NH4Cl (10.0 mL), followed by H2O (15.0 mL) and the mixture was brought to room temperature. The organic layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried with anhydrous Na2SO4, filtered and the solvent was removed to give the crude product, which was purified by column chromatography (hexane/EtOAc, 1:1).

Conversion of 3a affording free chiral primary amine 4

3a (0.5 mmol) and MeOH (5.0 mL) were placed in a 25 mL round-bottom flask and aq HCl (36%, 1 mL) was added. The reaction was stirred at r.t. for 8 h, during which time the cleavage was monitored by TLC. Volatiles were removed under reduced pressure. The residue was dissolved in CH2Cl2 (10.0 mL) and Et3N (15 mmol) was added. The reaction was stirred at rt for 1 h then H2O (10.0 mL) was added. The organic layer was taken, washed with H2O (2 × 10 mL), dried with anhydrous Na2SO4, filtered and the solvent was removed to give the crude product, which was purified by TLC plate (hexane/EtOAc, 1:1).

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Notes and references

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3. Electronic Supplementary Information (ESI) available: [Experimental procedures, full spectroscopic data for compounds 3 and 4 and copies of $^1$H NMR and $^{13}$C NMR spectra]. See DOI: 10.1039/b000000x/c


