Asymmetric Synthesis 1-Substituted 2,6-Diazaspiro[3.3]heptanes through Addition of 3-Azetidin-carboxylate Anions to Davis–Ellman Imines

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Supporting Information

ABSTRACT: Asymmetric synthesis of 1-substituted 2,6-diazaspiro[3.3]heptane is described. This methodology affords excellent yields (up to 89%) and high diastereomeric ratios (dr up to 98:2) and delivers differentially protected amines within the products.

The 2-substituted piperazines are key intermediates in the drug discovery. Over 40 FDA-approved drugs¹ and around 15,000 bioactive compounds (Scheme 1a) containing these motifs.² In 2010, Mgller, Carreira, and co-workers³ have discovered the 1-substituted 2,6-diazaspiro[3.3]heptanes and validated their physicochemical properties in the drug discovery. These conformational restricted 1-substituted 2,6-diazaspiro[3.3]heptanes have shown better or equal physicochemical properties compared to 2-substituted piperazines (Scheme 1b). Subsequently, numerous pharmaceutical firms started applying these motifs in modern drug discovery, resulting in an exponentially increasing number of the corresponding patents over the past eight years.⁴ Nevertheless, the enantio- and diastereoselective synthesis of 1-substituted 2,6-diazaspiro[3.3]heptanes is not known in the literature.⁵ We articulated that a straightforward method to get the enantiomerically pure 1-substituted 2,6-diazaspiro[3.3]heptanes might be 3-azetidin-carboxylate anion addition to N-tert-butanessulfinyl aldimines, followed by reductive cyclization. To the best of our knowledge, it has not been described in the literature.⁶ We report herein a versatile and practical asymmetric method that affords enantioselectively pure 1-substituted 2,6-diazaspiro[3.3]heptanes in excellent yields (Scheme 2).

Scheme 1. 1-Substituted 2,6-Diazaspiro[3.3]heptane Analogues of 2-Substituted Piperazines in Drug Discovery

The N-tert-butanessulfinyl aldimine 2a⁷ was taken as a model substrate at the initial stage of investigation because these aldimines are known to be very stable and high electrophilic. Subsequently, these N-tert-butanessulfinyl aldimines persuade good diastereoselectivity with broad scope of nucleophile addition to C==N bond and serve as a base sensitive protecting group on the nitrogen. The benefits of these properties have been used in the synthesis of enantioselective 1-substituted 2,6-diazaspiro[3.3]heptanes.

Reactions of methyl 1-boc-azetidine-3-carboxylate 1a with N-tert-butanessulfinyl aldimine 2a in the presence of several bases and different temperature were studied (Table 1, entry 1–7). A survey of bases of sufficient strength to deprotonate 1a indicated that Li plays the critical role in promoting the anticipated reaction (Table 1, entries 1–7), signifying that Li

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- Some of the FDA-approved drugs
- Mgllier, Carreira, and co-workers

Scheme 2. Route Scouting Department, Piramal Discovery Solutions, Pharmaceutical Special Economic Zone, Sarkhej Bavla Highway, Ahmedabad, Gujarat 382213, India

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Scheme 2. Background of Literature and New Approach to Asymmetric Synthesis of 1-Substituted 2,6-Diazaspiro[3.3]heptanes

- Previous work

Br
N
S
O
Br
N
S
O
KOBU, THF
R\textsuperscript{1}Li, THF, -78 °C

Yield: 40 to 70%
R\textsuperscript{1} = Me, dr = 1:1
R\textsuperscript{1} = Ph, dr = 2:1
R\textsuperscript{1} = Furfuryl, dr = 1:1
only 3 examples

- This work

\textbf{Table 1. Evaluation of Reaction Conditions}\textsuperscript{a}

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>temp (°C)</th>
<th>yield (%)\textsuperscript{b}</th>
<th>dr\textsuperscript{c}</th>
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<tr>
<td>1</td>
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<td>-78</td>
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<td>0</td>
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<td>0</td>
<td>60</td>
<td>50:50</td>
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<tr>
<td>5</td>
<td>LiHMDS</td>
<td>-78</td>
<td>94</td>
<td>98:2</td>
</tr>
<tr>
<td>6</td>
<td>LDA</td>
<td>-78</td>
<td>49</td>
<td>98:2</td>
</tr>
<tr>
<td>7</td>
<td>LiTMP</td>
<td>-78</td>
<td>39</td>
<td>98:2</td>
</tr>
</tbody>
</table>

\textsuperscript{a}All of the reactions were performed with 3.0 equiv of 1a, 1.0 equiv of 2a, and 2.5 equiv of base at -78 °C for 3 h. \textsuperscript{b}Isolated yield. \textsuperscript{c}The diastereoselectivity was measured by \textsuperscript{1}H NMR analysis of crude product.

might act as a Lewis acid to initiate the Davis–Ellman imines for addition. The temperature studied has indicated that better results were obtained at lower temperature; it might be instability of 3-azetidinecarboxylate anion at higher temperature. The best results were obtained in the presence of LiHMDS in THF at -78 °C for 3 h, which afforded amino ester product 3a (94% yield and 98:2 dr) (Table 1, entry 5). Subsequently, 3a was converted to required 1-substituted 2,6-diazaspiro[3.3]heptane 4a through reductive cyclization conditions (LAH followed by p-TsCl/NaH). This optimized three-step protocol provided 4a from 2a in excellent yield (overall yield 85%).

To extend the possibility of this reaction, we checked the reaction of 1a with other aromatic Davis–Ellman aldimines 2. Excitingly, numerous aromatic Davis–Ellman aldimines such as p-fluoro (2b), p-trifluoromethyl (2c), p-fluoro-o-chloro (2d), 1-naphthyl (2e), and 9-phenanthrenyl (2f) aldimines are smoothly reacted with 1a in the ideal reaction conditions (three steps procedure) to afford the corresponding 1-substituted 2,6-diazaspiro[3.3]heptanes 4b–f in excellent yields (78–85%) with up to 98:2 diastereomeric ratios (Scheme 3, entries 2–6).

Furthermore, the heterocyclic Davis–Ellman aldimines, such as 3-furfuryl (2g) and S-thiofurfuryl (2h) derivatives, cleanly reacted with 1a under ideal conditions affording the corresponding 1-substituted 2,6-diazaspiro[3.3]heptanes 4g and 4h (Scheme 3, entries 7 and 8) in 81–85% yield and with 98:2 dr. The 4g was obtained as a colorless crystalline solid (mp 133–134 °C). The structure and absolute stereochemistry of (R,S,R)-4g were confirmed by single-crystal X-ray diffraction analysis (Figure 1).

Interestingly, several aliphatic Davis–Ellman aldimines, such as cinnamoyl 2i, phenethyl 2j, isobutyl 2k, and t-butyl 2l derivatives were reacted with 1a in the ideal reaction conditions to afford the corresponding 1-substituted 2,6-
diazaspiro[3.3]heptanes 4i−l in excellent yields (74−85%) with high diastereomeric ratios (dr, 90:10−98:2) (Scheme 3, entries 9−12). We have also investigated the reaction of N-p-toluenesulfonyl aldimine 2-tolyl with 1a under ideal reaction conditions afforded the 1-substituted 2,6-diazaspiro[3.3]-heptanes 4m with similar yield (85%) and diastereomeric ratio (dr 98:2) (Scheme 4).

Scheme 4. Reaction Scope with N-p-Toluenesulfonyl Aldimine and Also with Methyl 1-(Diphenylmethyl)azetidine-3-carboxylate

Encouraged by these results, we turned our attention to examining the methyl 1-(diphenylmethyl)azetidine-3-carboxylate 1b because this substrate will provide practical advantage of selective deprotection of the two masked amines within the products. Treatment of 1b with 2a and 2b under optimal conditions afforded corresponding 1-substituted 2,6-diazaspiro[3.3]heptanes 4n−4o (Scheme 4) in 82−85% yield and with 98:2 diastereomeric ratios.

To demonstrate the scalability of this reaction and also our internal ongoing project requirement for compound 5 in multigram level, we scaled up this reaction in the grams quantity. Treatment of 2a (5.0 g, 24.0 mmol) with 1b under optimal reaction condition afforded 4n with 85% yield (9.0 g) and with high diastereomeric ratio (dr 98:2) (Scheme 5).

The exceptional synthetic benefit of this protocol is that it delivers the differentially protected amines within the products. Conversely, the sulfinamide protecting group of 4n has selectively removed in the mild acidic conditions (4 N HCl in 1,4-dioxane at 23 °C for 2 h) to obtain the nucleophilic amine 5 with 95% yield; in these conditions, the 1-benzhydryl protecting group was not affected (Scheme 5). However, the reaction of 4b with 4 N HCl in 1,4-dioxane at 23 °C for 2 h provided di-deprotected amine 6 with 91% yield.

In conclusion, we have developed a versatile, scalable, and highly diastereoselective addition of azetidinecarboxylate anions to N-tert-butanesulfonyl imines with wide-range of substrate scope. This protocol is found to be practical for the asymmetric synthesis of a variety of aromatic, heteroaromatic, and aliphatic 1-substituted 2,6-diazaspiro[3.3]heptanes. The selective deprotection and differentially protected amines within the products will enable the practical usage of this method in the industrial application. Extension for this work is ongoing.

ASSOCIATED CONTENT

5 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00564.

Experimental procedures with spectral data (PDF)

Accession Codes

CCDC 1896854 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
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