Pot, Atom, and Step Economic (PASE) Synthesis of Highly Substituted Piperidines: A Five-Component Condensation

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Abstract: The diastereoselective pot, atom, and step economic (PASE) synthesis of highly functionalized piperidines is reported. The procedure simply involves mixing methyl acetoacetate, two equivalents of aldehyde and two equivalents of aniline together in the presence of indium(III) chloride. In most cases the piperidine precipitates out of solution.

Key words: piperidines, PASE, one pot, multicomponent

Introduction

Functionalized piperidines and their derivatives are important pharmacophores which are present in many pharmaceuticals and many molecules in clinical and preclinical trials.1 Piperidines also occur with great regularity in the natural product arena and many of these natural products possess promising pharmaceutical potential. Consequently a huge amount of effort has been directed at their construction by synthetic chemists the world over.2

We recently reported the Pot, Atom, and Step Economic (PASE) synthesis of functionalized tetrahydropyran-4-ones.3 This involved the condensation of diketene with an equivalent of two different aldehydes under the promotion of a Lewis acid, all in one pot. With the success in applying a PASE approach to the synthesis of THPs, we wished to investigate the possibility of extending this methodology to the synthesis of highly functionalized piperidines.4

While our work on the synthesis of THPs used diketene as a β-keto ester derivative, we reasoned that the synthesis of piperidines may grant us the opportunity to use a β-keto ester itself. Our idea was to increase the nucleophilicity of the β-keto ester’s α-carbon by the formation of an enamine derivative (Scheme 1). We hoped that it may prove possible to develop a one-pot, multicomponent reaction which coupled the in situ formation of the enamine of the β-keto ester with formation of an imine and sequential condensation of the enamine with the aldehyde (Knoevenagel reaction), followed by condensation with the imine (Mannich reaction) and cyclization (Michael reaction) to form the piperidine. If successful this would generate the desired piperidine in a pot, atom, and step economic manner. A survey of the literature indicated that indium(III) chloride was efficient at promoting imine formation,5 Mannich reactions,6 and Michael reactions,7 so this was chosen as the Lewis acid.

We initially focused on the reaction of methyl acetoacetate, aniline, and benzaldehyde. Mixing the pre-formed enamine 1 (X = H), the pre-formed imine 2 (Y = H) in acetonitrile with benzaldehyde and indium(III) chloride (33 mol%) led to the formation of 3 (X = Y = H) in 46% yield. Piperidine 3 (X = Y = H) could also be formed in 44% yield by mixing the pre-formed Knoevenagel adduct of methyl acetoacetate and benzaldehyde with imine 2 (X = H) in acetonitrile with indium(III) chloride (33 mol%). Gratifyingly, a simpler procedure was developed that involved mixing methyl acetoacetate, aniline (2 equiv), and benzaldehyde (2 equiv) with indium(III) chlo-
ride (33 mol%) in acetonitrile. This furnished piperidine 3 \((X = Y = H)\) in 60% yield.

**Scope and Limitations**

A variety of piperidines were formed using this procedure (Table 1).

**Table 1** Piperidines Prepared

<table>
<thead>
<tr>
<th>Entry</th>
<th>(Ar^1)CHO</th>
<th>(Ar^2)NH₂</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
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<tr>
<td>1</td>
<td>Ph</td>
<td>Ph</td>
<td>3a</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>4-MeOC₆H₄</td>
<td>Ph</td>
<td>3b</td>
<td>52</td>
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<tr>
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<td>Ph</td>
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</tr>
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<td>4</td>
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<td>Ph</td>
<td>3d</td>
<td>64</td>
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<tr>
<td>5</td>
<td>4-O₂NC₆H₄</td>
<td>Ph</td>
<td>3e</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>4-MeO₂CC₆H₄</td>
<td>Ph</td>
<td>3f</td>
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</tr>
<tr>
<td>7</td>
<td>2-MeC₆H₄</td>
<td>Ph</td>
<td>3g</td>
<td>16</td>
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<td>4-MeC₆H₄</td>
<td>4-MeOC₆H₄</td>
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<td>45</td>
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<tr>
<td>9</td>
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<td>4-MeOC₆H₄</td>
<td>3i</td>
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</tr>
<tr>
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<td>Ph</td>
<td>4-MeOC₆H₄</td>
<td>3j</td>
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<tr>
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<td>4-MeOC₆H₄</td>
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<tr>
<td>13</td>
<td>4-MeOC₆H₄</td>
<td>4-CIC₆H₄</td>
<td>3m</td>
<td>52</td>
</tr>
</tbody>
</table>

We chose a number of electronically and sterically different aldehydes and elected to react these with either aniline, \(p\)-anisidine, \(p\)-chloroaniline, or \(p\)-nitroaniline, which covered the range of electronically activated through to electronically deactivated aromatic amines. The general trends in the series of anilines was not surprising, with \(p\)-anisidine reacting the fastest. In general when \(p\)-anisidine was used (entries 8–12) the reactions were over in 24 hours rather than the usual 48 hours as was the case when aniline was used (entries 1–7). When \(p\)-chloroaniline was used (entry 13) the reaction was much slower and took 7 days to produce a 52% yield of the piperidine. \(p\)-Nitroaniline did not react at all. This trend undoubtedly reflects the relative nucleophilicities of the aniline nitrogen’s lone pair, and hence the relative abilities to form the imine 2 and the enamine 1, as well as the nucleophilicity of the resulting enamine 1. While the nature of the electronic substitution on the aldehyde did not seem to have a great effect on the rate of the reaction, if the aldehyde was substituted in the \(ortho\)-position then the yields of piperidine formed were low (entries 7 and 11), probably due to increased steric congestion around the carbonyl group. Other points of note were that in the cases of aniline/4-tolualdehyde (entry 3) and aniline/benzaldehyde (entry 1), hydrolysis of the final enamine-piperidine occurred to some extent yielding the enol-piperidines in 3% and 11%, respectively. The stereochemistry of the 2,6-substituents was determined as \(trans\) by single crystal X-ray analysis (Figure 1) and the lack of a NOE between H2 and H6, which would have been expected if the relative stereochemistry of these substituents were \(cis\). It was also found that certain aldehyde–aniline combinations did not form any piperidine, as the reaction stopped due to the precipitation of an insoluble imine (Table 2).

We attempted to extend this procedure to the formation of piperidines with alkyl substituents in the 2,6-positions. Use of aliphatic aldehydes (benzyloxy)acetaldehyde, butanal, and isobutyraldehyde with both aniline and anis...
dine led in all cases to multiple and intractable products. We believe that this was due to the propensity for aliphatic aldehydes to favour enamine formation rather than imine formation and, that these enamines formed preferentially to the desired enamine of the β-keto ester and then condensed with any remaining aldehyde before the desired piperidine forming reaction occurred.

Additionally we attempted to form piperidines using benzylamine rather than an aniline. However, in this instance benzylamine hydrochloride precipitated from the reaction mixture. This is probably due to the higher basicity of benzylamine compared to aniline, and hence salt formation with any HCl present in the indium(III) chloride.

In conclusion we have developed straightforward and robust procedure for the one-pot, multicomponent formation of highly substituted piperidines from commercially available starting materials. The procedure is applicable to a wide range of aromatic aldehydes and amines and in general the product precipitated from the reaction solvent. Sadly, this procedure is incompatible with either alkyl-substituted aldehydes or alkylamines. The attractive features of this chemistry are that all the reagents can be stirred together in one pot and, in the majority of cases, the products can be collected by filtration after 24 hours or 48 hours.

Reagents and solvents were used as purchased from the suppliers. The MeCN was used directly from the bottle and was not dried, the HRMS data for the other piperidines prepared can be found in the supporting information.

Methyl 1,2,5,6-Tetrahydro-2,6-bis(4-methoxyphenyl)-1-phenyl-4-(4-phenylamino)pyridine-3-carboxylate (3b); Typical Procedure

A round-bottom flask was charged with MeCN (4 mL) and to this was added methyl acetoacetate (0.232 g, 2.0 mmol), aniline (0.37 g, 3.71 (s, 3 H, OCH3), 3.70 (s, 3 H, OCH3), 2.77 (dd, J = 5.6, 2.8 Hz, 1 H, H5), 2.67 (dd, J = 14.9, 2.5 Hz, 1 H, H5), 2.61 (dd, J = 15.3, 2.8 Hz, 1 H, H5). 2.33 (s, 3 H, CH3), 2.30 (s, 3 H, CH3).

IR (KBr): 3446, 2949, 2837, 1653, 1610, 1593, 1505, 1498, 1247, 1189, 1071, 1033 cm−1.

HRMS (ESI): m/z [M + H]+ calcd for C35H37N2O4: 549.2748; found: 549.2744.

Anal. Calcd for C35H37N2O4: C, 81.12; H, 6.60; N, 5.73. Found: C, 81.04; H, 6.62; N, 5.70.

Methyl 1,2,5,6-Tetrahydro-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-2,6-bis(4-tol)pyridine-3-carboxylate (3b); Typical Procedure

A round-bottom flask was charged with MeCN (4 mL) and to this was added methyl acetoacetate (0.232 g, 2.0 mmol), p-anisidine (0.492 g, 4.0 mmol), p-toluicdethyle (0.48 g, 4.0 mmol), and InCl3 (0.148 g, 0.67 mmol). The mixture was stirred at r.t. for 24 h. After this time the product was isolated by filtration of the precipitate and washing with a small amount of MeCN. The product was recrystallized (CH2Cl2–MeOH) to yield piperidine 3b as a white solid; yield: 0.495 g (45%); mp 203 °C.

\[ V \text{ NMR (400 MZH, CDCl}_3): \delta = 10.08 (s, 1 H, NH), 7.16 (d, J = 7.9 Hz, 2 H, Ar), 7.01–7.00 (m, 6 H, Ar), 6.63 (d, J = 9.2 Hz, 2 H, Ar), 6.59 (d, J = 8.8 Hz, 2 H, Ar), 6.42 (d, J = 9.2 Hz, 2 H, Ar), 6.26 (s, 1 H, H6), 6.19 (d, J = 8.8 Hz, 2 H, Ar), 4.99 (br dd, J = 5.6, 2.8 Hz, 1 H, H6), 3.86 (s, 3 H, COOCH3), 3.73 (s, 3 H, OCH3), 3.64 (s, 3 H, OCH3), 2.76 (dd, J = 15.3, 5.6 Hz, 1 H, H5), 2.61 (dd, J = 15.3, 2.8 Hz, 1 H, H5), 2.33 (s, 3 H, CH3), 2.30 (s, 3 H, CH3).

\[ 1^H \text{ NMR (400 MZH, CDCl}_3): \delta = 10.08 (s, 1 H, NH), 7.16 (d, J = 7.9 Hz, 2 H, Ar), 7.01–7.00 (m, 6 H, Ar), 6.63 (d, J = 9.2 Hz, 2 H, Ar), 6.59 (d, J = 8.8 Hz, 2 H, Ar), 6.42 (d, J = 9.2 Hz, 2 H, Ar), 6.26 (s, 1 H, H6), 6.19 (d, J = 8.8 Hz, 2 H, Ar), 4.99 (br dd, J = 5.6, 2.8 Hz, 1 H, H6), 3.86 (s, 3 H, COOCH3), 3.73 (s, 3 H, OCH3), 3.64 (s, 3 H, OCH3), 2.76 (dd, J = 15.3, 5.6 Hz, 1 H, H5), 2.61 (dd, J = 15.3, 2.8 Hz, 1 H, H5), 2.33 (s, 3 H, CH3), 2.30 (s, 3 H, CH3).

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References


(2) For recent reviews on the synthesis of piperidines see:


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