Cross Mannich Reaction of Aldehydes; Efficient Synthesis of Substituted Pyridines

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Abstract: Symmetrically and unsymmetrically substituted pyridines were obtained in highly efficient one-pot procedures starting from α-unbranched aldehydes and iminium salts.

Key words: aldehydes, domino reactions, Mannich bases, pyridines, imines

Due to the diversity of applications and the broad distribution of pyridine derivatives in nature, numerous synthetic methods for these heterocyclic systems have been investigated.1 Our studies in the field of ternary iminium salts led to the development of efficient one-pot reactions yielding a wide range of functionalized pyridines, bipyridines and terpyridines.2 All these reactions are based on the ability of Mannich bases1 to form α,β-unsaturated ketones2 by thermally induced amine elimination. Enamines as well as ketones3 are easily alkylated by these Michael acceptors to form 1,5-diketones4 which can be converted to the corresponding pyridine derivatives5 by treatment with a source of ammonia (Scheme 1).

Scheme 1 Formation of highly substituted pyridine derivatives from Mannich bases and ketones (R1 = aryl, H; R2, R4 = aryl, alkyl or cycloalkyl; R3, R5 = H, aryl, alkyl or cycloalkyl)

A multitude of cyclic and acyclic ketones3 can be used. Either the ketone itself or the β-amino ketone 1 gives symmetrically or unsymmetrically substituted pyridine derivatives5 in very good yields.2 To the best of our knowledge, enolizable aldehydes have not yet been used in the context of pyridine syntheses. Our research on the aminoalkylation of diverse nucleophiles showed that Mannich bases obtained from α-unbranched aliphatic aldehydes6 spontaneously undergo amine elimination.3 Here, we report that these aldehydes are suitable building blocks for the selective synthesis of symmetrically 3,5-disubstituted12 or unsymmetrically substituted pyridine derivatives15.

Symmetrically 3,5-disubstituted pyridines12 are interesting components for the formation of pyridine carboxylic acids4 or macrocycles containing pyridine units.5 However, their synthesis has hardly been described in the literature.6 These methods are unfavorable because of long reaction times, formation of by-products and poor yields.

The synthesis of symmetrically 3,5-disubstituted pyridines12 (four examples) was carried out according to our procedure developed for the selective synthesis of U-shaped terpyridines.2e,7 The imines7 were generated in situ by heating a solution of the α-unbranched aldehydes6 in DMSO. A suspension of the iminium salts8 in DMSO was added to form the Mannich bases9. Under the reaction conditions the amine is eliminated. Subsequently, these Michael acceptors10 react with a further equivalent of the aldehydes6 yielding 1,5-dicarbonyl compounds11 which are converted spontaneously to the corresponding pyridine derivatives12 (Scheme 2, Table 1).

In principle, our results show, that α-unbranched aldehydes6 are well suited as the CH-acidic component for the domino synthesis of pyridine derivatives (Scheme 3). The rather low yields in the case of R1 = Et may be ascribed to the high volatility of n-butyraldehyde. This new method may provide a broad range of symmetrically 3,5-

Table 1 Preparation of Symmetrically 3,5-Disubstituted Pyridines12

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>Yield (%)</th>
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<tr>
<td>12a</td>
<td>Et</td>
<td>H</td>
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</tr>
<tr>
<td>12b</td>
<td>Et</td>
<td>Ph</td>
<td>26a</td>
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<tr>
<td>12c</td>
<td>Ph</td>
<td>H</td>
<td>53b</td>
</tr>
<tr>
<td>12d</td>
<td>Ph</td>
<td>Ph</td>
<td>48b</td>
</tr>
</tbody>
</table>

a Yield after Kugelrohr distillation.
b Yield after flash column chromatography.
A. Winter, N. Risch

Synthesis of unsymmetrically 3,5-disubstituted pyridine derivatives in a straightforward synthesis by the variation of the enolizable aldehydes 6 and the iminium salts 8 employed.

On the other hand, this strategy is less suited for the selective synthesis of unsymmetrically 3,5-disubstituted derivatives 13. If two different aldehydes 6 were applied in this domino reaction, a statistic mixture of products was formed independently of the order that the aldehydes were added to the reaction mixture (13;12a:12c, 1:1:1).

β-Amino ketone hydrochlorides 19 are excellent starting materials in the synthesis of different types of pyridine derivatives. If a mixture of the β-amino ketone hydrochloride 1 and the enolizable carbonyl compound 3 were refluxed in EtOH in the presence of NH4OAc, pyridine derivatives 5 are obtained as shown in Scheme 1. We disclose, that also α-unbranched aldehydes 6 can be used in this reaction cascade to form unsymmetrically substituted pyridine derivatives 15 in acceptable yields (Scheme 4).

Synthetic methods for the synthesis of pyridine derivatives 15 have hardly been described in the literature so far.10 Our general approach (six examples) allows the efficient and selective synthesis of unsymmetrically substituted mono- or bicyclic monopyridines and as well as bipyridines. To the best of our knowledge, compounds 15c,d represent novel classes of bipyridines as their substitution patterns have not been published before.

In extension to prior work2 that only focused on ketones 3 as building blocks for the synthesis of different types of pyridine derivatives, α-unbranched aldehydes 6 were employed as starting material for both symmetrically 3,5-disubstituted and unsymmetrically substituted pyridine derivatives 12 and 15. We expect that our methodology can be extended to broad range of aldehydes yielding pyridine derivatives with a diverse substitution pattern.

All reagents were purchased from commercial sources and used without further purification unless specified. All solvents were dried and distilled according to standard procedures and stored under argon. Chromatographic separation was performed on silica gel (Kieselgel 60, Fa. Merck AG, 0.040–0.063 mm) or aluminum oxide (neutral, Akt. III, Fa. Macherey & Nagel, 0.063–0.200 mm). Mps were obtained on a Büchi SMP-20 mp apparatus and are uncorrected. IR spectra were measured on a Nicolet 510 FT-IR spectrometer. All NMR spectra were recorded on a Bruker ARX 200 instrument (200 or 50 MHz). Mass spectra were recorded using a Finigan MAT 8230 apparatus, GC-MS spectra were recorded on a Finigan MAT Magnum TM spectrometer. Elemental analyses were obtained on a Perkin–Elmer M240 analyzer.

Iminium salts 8 and Mannich base hydrochlorides 1 were synthesized using literature procedures.7-9

Symmetrically 3,5-Disubstituted Pyridine Derivatives 12; General Procedure
A suspension of the aldehyde 6 (5.05 mmol) and the iminium salt 8 (5.1 mmol) in DMSO (10 mL) was heated under argon until a clear solution was obtained. In a second flask, a mixture of the aldehyde 6 (5.05 mmol) and ammonium acetate (5.5 mmol) in DMSO (5 mL) was heated at 60 °C for 5 min. The warm mixture of the first flask was then added to the second one and the reaction mixture was heated at 120 °C under argon for 15 h. After cooling r.t. it was poured into H2O (25 mL) and extracted with CH2Cl2 (3 × 25 mL). The combined organic extracts were washed with H2O (5 × 20 mL) and dried...
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(MgSO₄). The solvent was removed in vacuo and the crude product thus obtained was purified either by flash column chromatography (silica gel; EtOAc–hexane, 1:2) or Kugelrohr distillation.

**3,5-Diethylpyridine (12a)**
Yield: 48 mg (17%); colorless liquid; bp 53 °C/2.5 mbar (lit. 6a 52–56 °C/2.6 mbar).

**3,5-Diethyl-4-phenylpyridine (12b)**
Yield: 155 mg (26%); yellow oil (lit. 6a 150 °C/2.5 mbar).

**3,5-Diphenylpyridine (12c)**
Yield: 247 mg (53%); colorless plates; mp 136 °C (lit. 6a 138–139 °C).

**3,4,5-Triphenylpyridine (12d)**
Yield: 298 mg (48%); white powder; mp 153 °C.

**IR (KBr):** 2938, 2641, 1680, 1607, 1411, 1232, 1165, 1091, 963, 768 cm⁻¹.

**1 H NMR (CDCl₃):** δ = 8.84 (s, 2 H,), 7.61–7.68 (m, 6 H), 7.25–7.53 (m, 9 H).

**13 CN M R  ( C D C l 3 ):**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mannich base</th>
<th>Pyridine 15</th>
<th>Yield (%)¹</th>
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<tr>
<td>15a</td>
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<td>45</td>
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<td>15c</td>
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<td>41b</td>
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<td>15d</td>
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<td>39</td>
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<td>15e</td>
<td></td>
<td></td>
<td>49</td>
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<tr>
<td>15f</td>
<td></td>
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<td>41</td>
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Table 2 Preparation of Unsymmetrically Substituted Pyridines 15 Prepared from Mannich Bases 1 and Phenylacetaldehyde 6b

Unsymmetrically Substituted Pyridine Derivatives 15; General Procedure
A suspension of the aldehyde 6 (5 mmol), the Mannich base hydrochloride 1 (6 mmol) and ammonium acetate (16 mmol) in EtOH (25 mL) was heated at reflux for 3 h. After cooling, the solvent was evaporated and the oily residue was treated with aq HCl (2 M; 15 mL). Non-basic components were separated by extraction with Et₂O (2 × 25 mL). The aq phase was made basic by addition of aq ammonia (25 mL; 25% NH₃·H₂O, 1:4) and extracted with CH₂Cl₂ (3 × 20 mL). The combined organic phases were dried (MgSO₄) and the solvent was evaporated. The crude product was purified by flash column chromatography (silica gel or neutral aluminum oxide, CH₂Cl₂).

2-tert-Butyl-5-phenylpyridine (15a)
Yield: 391 mg (37%); colorless oil (lit.¹⁰ mp 60 °C).

3-Phenyl-5,6,7,8-tetrahydroquinoline (15b)
Yield: 471 mg (45%); yellow oil (lit.¹⁰ mp 60 °C).

3-Phenyl-5,6-dihydro[1,10]phenanthroline (15c)
Yield: 529 mg (41%); yellow crystals; mp 138 °C.

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**1 H NMR (CDCl₃):** δ = 8.84–9.01 (m, 1 H), 8.56–8.76 (m, 1 H), 7.67–7.72 (m, 1 H), 7.61–7.66 (m, 1 H), 7.56–7.61 (m, 1 H), 7.39–7.56 (m, 3 H), 7.13–7.25 (m, 2 H), 2.95–3.04 (m, 4 H).

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13C NMR (CDCl₃): δ = 27.7, 27.8, 123.9, 127.5, 128.6, 129.4, 129.5, 134.0, 134.4, 136.2, 136.7, 137.9, 147.7, 149.3, 150.9, 151.9.

Anal. Calcd for C₁₈H₁₄N₂ (258.2): C, 83.69; H, 5.47; N, 10.84. Found: C, 83.73; H, 5.52; N, 10.75.

5-Phenyl[2,2']bipyridyl (15d)
Yield: 432 mg (39%); yellow oil.
IR (film): 2927, 2816, 1588, 1524, 1463, 1256, 1248, 1109, 1067, 772, 695 cm⁻¹.
1H NMR (200 MHz, CDCl₃): δ = 8.79 (s, 1 H), 8.53–8.57 (m, 3 H), 7.68–7.75 (m, 2 H), 7.29–7.38 (m, 5 H), 7.06–7.09 (m, 1 H).

13C NMR (50 MHz, CDCl₃): δ = 119.7, 122.8, 123.1, 127.4, 128.0, 129.2, 131.2, 134.2, 135.9, 137.1, 149.5, 149.9, 155.7, 156.9.

GC-MS (80 eV): m/z (%) = 232 (100, M+), 204 (25), 102 (16), 78 (18).

Anal. Calcd for C₁₆H₁₂N₂ (232.3): C, 82.73; H, 5.21; N, 12.06. Found: C, 82.77; H, 5.29; N, 11.94.

2,5-Diphenyl-3-methylpyridine (15e)
Yield: 600 mg (49%); white powder; mp 130 °C (lit. 132 °C).

2,5-Diphenylpyridine (15f)
Yield: 474 mg (41%); colorless crystals; mp 175 °C (lit. 177 °C).

Acknowledgment
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References