Highly selective zeolite-catalysed mono-N-alkylation of arylenediamines by dialkyl carbonates

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Received 13 December 2006; revised 20 December 2006; accepted 21 December 2006
Available online 4 January 2007

Abstract—Arylenediamines are mono-N-alkylated by dialkyl carbonates in the presence of NaY zeolite catalyst in a regioselective and nontoxic process.

A recent analysis of the reaction classes used in the synthesis of a range of drug candidate development samples has shown that the most common is heteroatom alkylation (19% of the total), with alkylation of nitrogen comprising more than half of these.1 Additionally, the increasing problems resulting from the toxicity of common alkylation agents are highlighted, which leads the authors to sound a call for an improved alkylation methodology. A further well known and common difficulty in synthesis is the prevention of over-alkylation during the conversion of primary to secondary amines. In a recent report Hudson and co-workers address this problem by using alkylnitriles as the N-alkylating agents for anilines under particularly mild conditions. 2 An earlier work by Selva and co-workers also goes part way to addressing these concerns. 3 They have demonstrated that dialkyl carbonates efficiently mono-N-alkylate anilines on heating in the presence of the zeolite NaY (sodium-exchanged faujasite). Both the zeolite and the carbonate esters are readily available and cheap, 4 and may be recovered and recycled. The carbonate esters are much less toxic than traditional alkylation agents such as alkyl halides, sulfates or sulfonates. The by-products of reaction, the alcohol itself and carbon dioxide, are also relatively innocuous. Selva established selectivity for primary over secondary in amine alkylation and for N- over O-alkylation in the reaction of aminophenols and aminobenzoic acids. 3c

We now describe an additional useful and more surprising dimension to the selectivity displayed by this reagent combination in the alkylation of arylenediamines. When we initially exposed a phenylenediamine to the NaY-catalysed dialkyl carbonate alkylation reaction conditions, we had expected to observe N,N'-dialkylation. In fact these conditions lead to highly selective—sometimes specific—mono-N-alkylation of just one of the amino groups present (Scheme 1).

For a series of arylenediamines, application of the published conditions3 [dimethyl carbonate (DMC) or diethyl carbonate (DEC) at reflux, or ethylene carbonate (EC) at 130 °C] yielded the results presented in the table. These reactions were monitored by TLC or HPLC and stopped when the analysis indicated maximal formation of a single major product in cases 1–7 and two major products in cases 8 and 9. A typical protocol is given below. 5a

All combinations of reactants show usefully high selectivity for mono-N-alkylation. For the simplest diamines, selectivities are higher for diethyl carbonate than for dimethyl carbonate, and, surprisingly, o-phenylene-
Zeolite catalysed alkylations of arylenediamines

Table 1. Zeolite catalysed alkylations of arylenediamines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Agent (time/h)</th>
<th>Major product</th>
<th>Isolated yield (%)</th>
<th>Impurities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OPD</td>
<td>DMC (2)</td>
<td>N-MethylOPD</td>
<td>75</td>
<td>6% SM</td>
</tr>
<tr>
<td>2</td>
<td>OPD</td>
<td>DEC (12)</td>
<td>N-EthylOPD</td>
<td>78</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>MDP</td>
<td>DMC (3)</td>
<td>N-MethylMPD</td>
<td>90</td>
<td>10% Dimethylamines</td>
</tr>
<tr>
<td>4</td>
<td>MDP</td>
<td>DEC (2)</td>
<td>N-EthylMPD</td>
<td>99</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>MDP</td>
<td>EC (12)</td>
<td>N-2-HydroxyethylMPD</td>
<td>80</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>2,4,6-TrimethylMPD</td>
<td>DMC (48)</td>
<td>N,2,4,6-TetramethylMPD</td>
<td>44</td>
<td>20% Two unknown products</td>
</tr>
<tr>
<td>7</td>
<td>5-CarboxyMPD</td>
<td>DMC (120)</td>
<td>N-Methyl-5-carboxyMPD</td>
<td>64</td>
<td>15% SM, 15% Dimethylated</td>
</tr>
<tr>
<td>8</td>
<td>MethylOPD</td>
<td>DMC (12)</td>
<td>N,4- and N,5-DimethylOPD</td>
<td>60</td>
<td>1:1 Product ratio, 30% SM</td>
</tr>
<tr>
<td>9</td>
<td>2-MethylPPD</td>
<td>DMC (6)</td>
<td>N,2- and N,3-DimethylPPD</td>
<td>79</td>
<td>3:2 Mixture of isomers; 10% SM, 10% dimethylated</td>
</tr>
</tbody>
</table>

a OPD = o-phenylenediamine; MDP = m-phenylenediamine; PPD = p-phenylenediamine.
b DMC = dimethyl carbonate; DEC = diethyl carbonate; EC = ethylene carbonate (1,3-dioxolan-2-one).
c All products were characterised either by spectroscopic and chromatographic comparison with authentic samples, or by NMR and mass spectrometry and microanalysis.
d SM = starting material.
e After column chromatography.
In contrast, a typical current process for mono-\(N\)-alkyl MPD, for example, is likely to be longer and could well involve isomer separation and possible discard of unwanted isomer. The conventional process is thus less economical and on a manufacturing scale potentially less environmentally attractive. Many \(N\)-alkylated arylenediamines are commercially important building blocks in dyestuff applications, and are components of pharmaceuticals. The new reaction may therefore have immediate industrial relevance.

References and notes


4. The zeolite is currently available for $4/kg and the carbonates for less than $1.9/kg.

5. (a) General procedure for alkylations: MPD (3.98 g), diethyl carbonate (146 mL) and zeolite NaY (3.98 g, pre-dried at 70 °C in vacuo) were stirred under reflux for 2 h. HPLC analysis then showed the absence of starting material and the appearance of only one new component. The mixture was cooled and filtered. The zeolite was washed with methanol, and the combined filtrates evaporated under reduced pressure to give mono-\(N\)-ethyl MPD (5.0 g; 99%), identified by its \(^1\)H NMR spectrum which indicated also that the material was >99% pure. No other material was detectable by HPLC (HP1100 chromato-graph with diode array detector, on a LiChroCart 55-4 Purospher STAR RP-18 endcapped column, eluting with an acetonitrile–water gradient containing 0.25% di-cyclohexylamine phosphate). The relatively high molar proportion of DEC follows the published procedure and is convenient for small scale laboratory work. This may be unrealistic for larger scale synthesis, especially bulk manufacture, but satisfactory use of much lower dialkyl carbonate/amine ratios has been reported and we have also observed that the carbonate can be decreased substantially on scale-up; (b) Demonstration of catalyst reuse: OPD was methylated with DMC using the general procedure described above. On completion of the reaction, the zeolite catalyst was recovered by suction filtration and washed with methanol. The recovered zeolite was reused, following the same protocol with fresh OPD and DMC, with identical results. In three successive cycles of catalyst recovery and reuse in methyla-tions of OPD there was no measurable loss of activity or selectivity.


8. A formal process to mono-\(N\)-alkylated MPD based on the new procedure would likely comprise benzene dinitration, reduction and \(N\)-alkylation. This may be compared with the conventional alternative starting from \(N\)-alkylaniline (derived formally from benzene by halogenation and displacement by primary alkylamine, or by nitration, reduction, alkyla-tion), involving nitration and isomer separation (implying a possible discard of the \(p\)-isomer) and finally reduction. It is not our intention to provide environmental audits for these various processes, but nevertheless a simple unit operation count suggests potential environmental and economic benefits would derive from the new, more direct reaction.

