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

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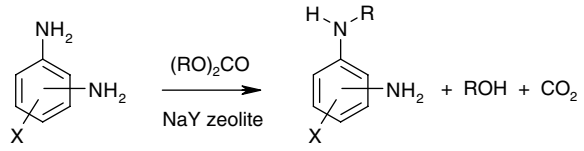
Abstract—Arylenediamines are mono-N-alkylated by dialkyl carbonates in the presence of NaY zeolite catalyst in a regioselective and nontoxic process.

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 alkylating 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 alkylating 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 conditions[3] [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-



Scheme 1. Mono-N-alkylation of arylenediamines.

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diamine (OPD) and *m*-phenylenediamine (MPD) show comparable yields and high selectivities. In the best cases (Table 1, entries 2, 4 and 5), HPLC analysis after filtration and evaporation of excess alkylating agent failed to detect additional products of any kind; monoalkylations by DEC and EC are essentially specific.

Of the more complex diamines, the reaction of 2,4,6-trimethyl-MPD (entry 6) is significantly slower, presumably reflecting the steric hindrance at the amine functionality. Introduction of an additional polar functionality in the form of a carboxyl group, as in 5-carboxy-MPD (entry 7), also reduces the reactivity. Nevertheless, a useful selectivity for mono-N-methylation persists in both cases. Reaction times for these could be reduced by conducting them under pressure in a closed vessel at temperatures above the normal boiling point of the dialkyl carbonate solvent, with no reduction of yield or selectivity. For the unsymmetrically ring-methylated diamines (entries 8 and 9) both possible mono-*N*-methyl isomers were produced and no attempt has been made to separate them. Isomer ratios (50:50 and 60:40, respectively, by NMR analysis) show that although total reactivity is reduced, the presence of a *m*- or *o*-methyl group surprisingly does not significantly affect the relative reactivity of the two primary amine groupings in these compounds in this reaction. In contrast to 2-methyl-*p*-phenylenediamine (entry 9), application of the conditions to *p*-phenylenediamine itself yielded only intractable tars, presumably the result of air oxidation.

That the zeolite is essential to both the reactivity and selectivity may be judged against the observation[6] that reaction of OPD in DMC at 160 °C in the absence of the zeolite gave only 30% conversion to a 75:20:5 mixture of *N*-methyl-OPD, *N*,*N*-dimethyl-OPD and 2-benzimidazolone. Incorporation of various metal salts enhanced conversions, but also increased the proportion of benzimidazolone. Furthermore, we have demonstrated that the zeolite is recyclable by its isolation and re-use in three successive reaction cycles between OPD and DMC.[5b] There was no observable difference in reactivity or selectivity between the three runs.

If the reaction is viewed as a sequence of first order conversions, the observed selectivity requires that the rate constant for the first alkylation of a primary amine site must be at least 10^3-fold greater than that for any second alkylation, whether at the new secondary site or at the remaining primary site. The mechanisms of these alkylations and the origins of the selectivities are of considerable interest for the optimisation of the processes, but experiments to date do not distinguish whether the major contribution to the monoalkylation/dialkylation ratio is differential adsorption on the catalyst of mono- and dialkylated material, or of differential reactivity of these substrates once adsorbed. Nevertheless, as noted earlier, selectivity between distinct primary amine sites in the alkylations of unsymmetrically ring-methylated diamines (entries 8 and 9) is low, and it seems unlikely to us that any mechanism of alkylation within the zeolite cage would favour reaction at a primary amine group in a diamine over the primary amine group in a monoalkylated diamine. This consideration applies especially in the case of MPD where the substitution pattern minimises steric and electronic interactions between the amine residues. In contrast to the OPD case, there can be no intramolecular hydrogen bonding here to be modified by an initial alkylation. (Such modification is believed to be the reason for the selective monomethylation of OPD by excess methanolic methyl iodide described by Brown and Nelson,[7] with preferential protonation and deactivation of the mono-N-methylated OPD by the HI produced in the reaction.) In the reactions with carbonates, comparable selective protonation of a more basic monomethylated product seems unlikely since the alkylation releases a non-acidic alcohol. There will, of course, be a statistical contribution from the higher availability of primary amine groups in the diamine, but we speculate that the major contributor to the selectivity is the preferential adsorption of diamine over monoalkylated diamine.

For the present, regardless of the underlying mechanistic rationale for its selectivity, this reaction of readily available arylenediamines offers a uniquely simple, nontoxic and economical route to their mono-N-alkylated derivatives, with potential additional environmental

Table 1. Zeolite catalysed alkylations of arylenediamines

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

[a] OPD = *o*-phenylenediamine; MPD = *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 spectroscopy and microanalysis.
[d] SM = starting material.
[e] After column chromatography.

benefits.[8] 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.[8] 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,[9] and are components of pharmaceuticals.[10] The new reaction may therefore have immediate industrial relevance.[11]

References and notes

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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, predried 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 chromatograph with diode array detector, on a LiChroCart 55-4 Purospher STAR RP-18 endcapped column, eluting with an acetonitrile–water gradient containing 0.25% dicyclohexylamine phosphate). The relatively high molar proportion of DEC follows the published procedure[3a,e] 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[3c] 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 methylations of OPD there was no measurable loss of activity or selectivity.
6. Fu, Y.; Baba, T.; Ono, Y. *J. Catal.* **2001**, *197*, 91.
7. Brown, H. C.; Nelson, K. L. *J. Am. Chem. Soc.* **1953**, *75*, 24.
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, alkylation), 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.
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10. For example in TF476, a potent gastrin/CCK-B antagonist Semple, G.; Ryder, H.; Rooker, D. P.; Batt, A. R.; Kendrick, D. A.; Szelke, M.; Ohta, M.; Satoh, M.; Nishida, A.; Akuzawa, S.; Miyata, K. *J. Med. Chem.* **1997**, *40*, 331.
11. The material described in this Letter is the subject of DyStar Patent Application WO2006/013164, priority date July 29th, 2004.