Reaction of Functionalized Anilines with Dimethyl Carbonate over NaY Faujasite. 3. Chemoselectivity toward Mono-N-methylation

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In the presence of NaY faujasite, dimethyl carbonate (MeOCO2Me, DMC) is a highly chemoselective methylation agent of functionalized anilines such as aminophenols (1), aminobenzyl alcohols (2), aminobenzoic acids (3), and aminobenzamides (4). The reaction proceeds with the exclusive formation of N-methylanilines without any concurrent O-methylation or N/O-methoxy carbonylation side processes. Particularly, only mono-N-methyl derivatives [X(C6H4)NHMe, X = o-, m-, and p-OH; o- and p-CH3OH; o- and p-CO2H; o- and p-CO2H] are obtained with selectivity up to 99% and isolated yields of 74–99%. DMC, which usually promotes methylations only at T > 120 °C, is activated by the zeolite catalyst and it reacts with compounds 1, 2, and 4, at 90 °C. Aminobenzoic acids (3) require a higher reaction temperature (≥130 °C).

Scheme 1

\[
X(C_6H_4)NH_2 + \text{ROCO}_2\text{Me} \xrightarrow{\text{NaY}} X(C_6H_4)\text{NMe} + \text{ROH} + \text{CO}_2
\]

R = Me, MeO(CH2)2O(CH2)2; X = H, p-NC, p-O2N, p-Cl, o-MeOC, 2,6-di-Me

Results and Discussion

Aminophenols (1). The direct alkylation, particularly methylation, of aminophenols with conventional methyla-


TABLE 1. Reaction of Aminophenols (1a–c) with DMC

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>catalyst</th>
<th>cosolvent (mL)</th>
<th>T, °C</th>
<th>t, h</th>
<th>% conv</th>
<th>products</th>
<th>% by GC</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>K₂CO₃</td>
<td>triglyme (35)</td>
<td>135</td>
<td>5</td>
<td>2.5</td>
<td>p-HOC₆H₄NHMe</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>K₂CO₃</td>
<td>DME (35)</td>
<td>150</td>
<td>5</td>
<td>2</td>
<td>p-HOC₆H₄NHMe</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>K₂CO₃</td>
<td>DMF (15)</td>
<td>125</td>
<td>4</td>
<td>8</td>
<td>p-HOC₆H₄NHMe</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>NaY</td>
<td>triglyme (35)</td>
<td>90</td>
<td>5</td>
<td>99</td>
<td>p-HOC₆H₄NHMe</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>NaY</td>
<td>DME (35)</td>
<td>86</td>
<td>7</td>
<td>100</td>
<td>p-HOC₆H₄NHMe</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>6a</td>
<td>1a</td>
<td>NaY</td>
<td>DMF (15)</td>
<td>90</td>
<td>24</td>
<td>&lt;1</td>
<td>p-HOC₆H₄NHMe</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>6b</td>
<td>1a</td>
<td>NaY</td>
<td>MeCN (35)</td>
<td>81</td>
<td>24</td>
<td>&lt;1</td>
<td>p-HOC₆H₄NHMe</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1b</td>
<td>NaY</td>
<td>–</td>
<td>90</td>
<td>3</td>
<td>100</td>
<td>o-HOC₆H₄NHMe</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1b</td>
<td>p-TsOH</td>
<td>–</td>
<td>130</td>
<td>4</td>
<td>35</td>
<td>o-HOC₆H₄NHMe</td>
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</tr>
<tr>
<td>9</td>
<td>1c</td>
<td>NaY</td>
<td>–</td>
<td>90</td>
<td>7</td>
<td>97</td>
<td>m-HOC₆H₄NHMe</td>
<td>96</td>
<td></td>
</tr>
</tbody>
</table>

a Reactions were carried out using a DMC/substrate molar ratio of 13 and of 39 for compounds 1a and 1b,c, respectively. The 1:NaY weight ratio was of 1. b Isolated yield. c Unknown compound. Mass spectrum (M⁺, m/z = 137) suggests the formation of a dimethyl derivative.

SCHEME 2. Mono-N-methylation of p-Aminophenol

\[
\text{HO} + \text{CH₂CO₂CH₃} \xrightarrow{\text{NaY, 90°C}} \text{MeNH} + \text{CH₃OH} + \text{CO₂}
\]

tation of 1a take place simultaneously (entries 1 and 2). This behavior reflects known aspects of the chemistry of DMC: DMC, in fact, is reported as an alkylation agent of phenols,14 and under basic catalysis, it exhibits a double reactivity with anilines yielding both N-methyl-anilines and urethanes [ArN(R)CO₂Me, R = H, Me].15

By contrast, in the presence of an amphoteric catalyst such as the NaY zeolite,10 DMC turns out to be an excellent chemoselective reagent: at quantitative conversions, only N-methylation of 1a takes place in a very high mono-N-methyl selectivity (> 99%) and yield [p-HOC₆H₄NHMe (5a)] in isolated yield of 91% (entries 4 and 5) (Scheme 2).

The nature of the cosolvent is critical for the reaction: glycol-derived dimethyl ethers such as triglyme and DME give the best results (entries 4 and 5),17 while the methylation is hindered when carried out in DMF and MeCN (entry 6). This strong inhibiting effect can be ascribed to a competitive adsorption of the polar cosolvent and the substrate for the catalytic cages of the zeolite.6c,18

The data of Table 1 disclose a further relevant aspect. As described by us and by others,3,14,15,17 DMC-mediated

(16) Barthomeuf, D. J. Phys. Chem. 1984, 88, 42. The basicity of the solid comes from the basic oxygen atoms of its framework, while Lewis acidity is due to alkaline metal cations.
(17) Triglyme and diglyme have been already reported by us in the alkylation of both phenols and amines with dialkyl carbonates. Perosa, A.; Selva, M.; Tundo, P.; Zordan, F. Synlett 2000, 1, 272–274, and ref 6b.
methylation processes usually take place at high temperatures (120–220 °C). This is also manifest in the reaction of 1a carried out with K2CO3 (entries 1–3). However, in the presence of NaY, the reaction of 1a proceeds smoothly at the boiling point of DMC (90 °C). The OH-substituent may account for this results with two effects on the reactant amine: (i) the enhancement of nucleophilicity and (ii) the easier diffusion/adsorption through the polar channel and cages of the catalyst. It should be noted that low-temperature methylations with DMC have been recently reported in only a few instances and they require activation with the use of very strong bases (DBU) or microwave irradiation.19

Table 2. Mono-N-methylation of p- and o-Aminobenzyl Alcohols (2a,b), p- and o-Aminobenzoic Acids (3a,b), and p- and o-Aminobenzamides (4a,b) with DMC and NaY as Catalyst

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate (M)</th>
<th>T, °C</th>
<th>t, h</th>
<th>% conv</th>
<th>% SMI</th>
<th>products</th>
<th>% by GC</th>
<th>% isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a (0.32)</td>
<td>90</td>
<td>8</td>
<td>90</td>
<td>94</td>
<td>(p-HO)CH2C6H4NHMe (6a)</td>
<td>85</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>2b (0.32)</td>
<td>90</td>
<td>12</td>
<td>99</td>
<td>99</td>
<td>(p-HO)CH2C6H4NHMe (6b)</td>
<td>98</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>3a (0.12)</td>
<td>130</td>
<td>9</td>
<td>100</td>
<td>90</td>
<td>(p-HO)C6H4NHMe (7a)</td>
<td>90</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>3b (0.12)</td>
<td>90</td>
<td>12</td>
<td>96</td>
<td>93</td>
<td>(p-HO)C6H4NHMe (7b)</td>
<td>90</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>4a (0.15)</td>
<td>150</td>
<td>5</td>
<td>95</td>
<td>95</td>
<td>(p-HNO)C6H4NHMe (8a)</td>
<td>98</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>4b (0.32)</td>
<td>90</td>
<td>22</td>
<td>100</td>
<td>94</td>
<td>(p-HNO)C6H4NHMe (8b)</td>
<td>94</td>
<td>91</td>
</tr>
</tbody>
</table>

*In parentheses, the molar concentration of the solution of the substrate in DMC is reported. **SMI was the selectivity of mono-N-methyl to N,N-dimethyl derivatives expressed as the ratio ([ArNHMe]/[ArNHMe + [ArNMe2]]) × 100. *The product (p-HO)CH2C6H4NHMe could not be analyzed by GC; the reported percentage was calculated from the 1H NMR spectrum.

It should be first noted that under alkaline conditions, dimethyl carbonate readily reacts with primary alcohols, especially benzyl alcohols, and carboxylic acids to yield transesterification and esterification products, respectively (ArCH2OOC2Me and RCO2Me).19,24,25 And, although with more difficulty, carboxamides gives N-methylamides (Scheme 3, path a).

The use of NaY as a catalyst completely modifies this scenario. Table 2 shows that reactions of DMC with substrates 2–4 are highly chemoselective: only the amine function undergoes methylation, while OH, CO2H, and CONH2 groups do not react at all. Particularly, in all cases the corresponding mono-N-methyl derivatives [XC6H4NHMe; X = O-H2NOC6H4NHMe (7a), CO2H (6), CO2H (7), and CONH2 (8)] are obtained with a selectivity of 90–99% and isolated yields of 74–92% (Scheme 3, path b).

Table 2 also indicates that aminobenzyl alcohols 2 are the more active substrates (entries 1 and 2), while aminobenzamides 4, which still react at 90 °C, require longer reaction times (entries 6 and 7). Aminobenzoic acids 3 yield mono-N-methyl derivatives only at temperature over 130 °C (entries 3–5). Although the N-alkylation of anilines over NaY is expected to occur within the zeolitic cages,5,8,18,17,28 this reactivity scale is likely due to N-acyl protection of amine groups give moderate yields of mono-N-methyl products.23

Under the conditions previously described for 1b,c (Table 1, entries 7 and 9), solutions of p- and o-aminobenzoic alcohols and o-aminobenzamides (2a,b and 4b) in DMC (0.32 M, 30 mL) were made to react at 90 °C, while p-aminobenzoic acid 4a and o- and p-aminobenzoic acids (3a and 3b)—which were less soluble in DMC with respect to compounds 2a,b and 4b—more dilute solutions were used: experiments were run with 0.15 M (50 mL) solution of 4a and 0.12 M (30 mL) solution of 3a,b in DMC, respectively. Moreover, reactions of compounds 3 were carried out at a higher temperature (130–150 °C). In all cases, the weight ratio NaY/substrate was of 1.

Results are reported in Table 2.

Aminobenzyl Alcohols (2), Aminobenzoic Acids (3), and Aminobenzamides (4). The direct methylation of compounds 2–4 with MeI or Me2SO4,21 as well as the reductive methylation,22 affords mainly or exclusively N,N-dimethyl derivatives, while indirect methods via...
to the electronic effects of substituents,\(^2\) rather than to their steric requisites.

A high chemoselectivity was also evident in the NaY-catalyzed reactions of methyl and ethyl anthranilates (compounds 9\(a\) and 9\(b\)) with diethyl carbonate (DEC) and DMC, respectively (Scheme 4).

Both reactions yielded exclusively the corresponding mono-\(N\)-alkylated derivatives (10\(a, b\)). Although the alkylation of the esters 9 was slow even at 150 °C (after 8 h, conversions of 9\(a\) and 9\(b\) were of 25% and 65%, respectively), no trace of the transesterification products [\((\text{o-\text{MeO}}_2\text{C})\text{C}_6\text{H}_4\text{NHMe}\) or \((\text{o-\text{EtO}}_2\text{C})\text{C}_6\text{H}_4\text{NHEt}\)] was observed.

Conclusions

A powerful method is described for a straightforward and selective \(N\)-methylation of anilines bearing a variety of functional groups which, though susceptible to undergo themselves methylation reactions, are kept untouched. This fine control of the chemoselectivity is made possible by the use of NaY zeolite as a catalyst with amphoteric properties able to promote exclusively the reactivity of the amine function. The features of DMC as a methylating agent additionally increase the synthetic potential of the procedure, since only mono-\(N\)-methyl anilines are obtained with selectivity up to 99%.

Although the solubility of compounds 1-4 in DMC and, more generally, reaction conditions need a case-by-case optimization, other advantageous aspects are the simplicity of the procedure and its intrinsic environmentally benign character as nontoxic methylating agent/catalyst are used; no wastes are generated, and derivatization reactions with protecting groups are avoided.\(^3\)

Experimental Section

All compounds used were ACS grade and were employed without further purification. The zeolite NaY was dried before each reaction by heating at 70 °C, under vacuum overnight. \(^1\)H NMR spectra were recorded on a 300 MHz spectrometer. GLC and GC/MS (70 eV) analyses were run using CPSil24CB and HP5 capillary columns (30 m), respectively.

**Reaction of Compounds 1, 2, and 4 with DMC. General Procedure.** A two-necked, jacketed, 100 mL round-bottomed flask fitted with a reflux condenser capped with a CaCl\(_2\) tube, an adapter for the withdrawal of samples, and a magnetic bar was loaded with the titled compounds and DMC according to the following concentrations: (i) 0.31 M solutions (30 mL) of \(\text{o-}\) and \(\text{m-}\)aminophenols (1\(\text{b, c}\), 1.0 g, 9.2 mmol), (ii) 0.32 M solutions (30 mL) of \(\text{o-}\) and \(\text{p-}\)aminobenzyl alcohols (2\(\text{a, b}\): 1.18 g, 9.6 mmol), (iii) 0.32 M solution (30 mL) of \(\text{o-}\)aminobenzamide (4\(\text{b}\): 1.30 g, 0.0096 mmol), (iv) 0.32 M solution (30 mL) of \(\text{o-}\)and \(\text{p-}\)aminobenzaldehydes (2\(\text{a, b}\): 1.18 g, 9.6 mmol), (iii) 0.32 M solution (30 mL) of \(\text{o-}\)aminobenzamide (4\(\text{b}\): 1.30 g, 0.0096 mmol), (iv) 0.15 M solution (50 mL) of \(\text{p-}\)aminobenzamide (4\(\text{a}\): 1.0 g, 0.0075 mmol). In the case of \(\text{p-}\)aminophenol 1\(\text{a}\), solutions of 1\(\text{a}\) (1.0 g, 9.2 mmol), DMC (10 mL, 0.12 mol), and a cosolvent such as triglyme (35 mL), DMF (15 mL), 1,2-dimethoxyethane (DME, 35 mL), or MeCN (35 mL) were used; the cosolvent was added in the minimal volume to allow a complete solubilization of the substrate at room temperature. If not otherwise indicated, the catalyst NaY was then added in a weight ratio of 1 with respect to the reactant amines.

The flask was heated at the reflux temperature of DMC (90 °C), while the mixture was vigorously stirred. At intervals, samples (0.1 mL) were withdrawn and were analyzed by GC and GC/MS.


\(^{29}\) The OH and CH\(_2\)OH groups have electron-donating effects on the aryl ring. For the other substituents, the electron-withdrawing effect follows the order \(\text{CO}_2\)H > CONH\(_2\). (March, J. In Advanced Organic Chemistry, 4th ed.; Wiley: New York, 1991; pp 681-685). Accordingly, the nucophile order of the tested amines should be 1 > 2 > 3 > 4.

In the case of 1a, when DME and MeCN were used as cosolvents, reactions were run at 86 and 81 °C, respectively.

Once the reaction was completed, the pale yellow suspension was filtered and the solid catalyst was thoroughly washed with MeOH (15 mL). After rotary evaporation, the mono-N-methylated products XCH₂NHMe, X = o-, m-, and p-OH (5a, 5b, and 5c); o-CH₂OH (6b); and o-CONH₂ (8b) were pure (94–99% by GC) and characterized as such. Compounds 6a (p-HOC₆H₄NHMe) and 8a (p-H₄NCOCH₆H₄NHMe) were purified by flash chromatography (eluants: AcOEt/petroleum ether, 1:4 v/v).

p-Aminophenol 1a was also made to react with DMC in the presence of K₂CO₃ as a catalyst. Since no reaction took place at the reflux temperature (90 °C), experiments were run by loading an autoclave (150 mL of internal volume) with a mixture of 1a (1.0 g, 9.2 mmol), K₂CO₃ (2.53 g, 18.3 mmol), DMC (10 mL), and a cosolvent [triglyme (35 mL) or DME (35 mL), or DMF (15 mL)], which was heated at the desired temperature (125–150 °C; see Table 1, entries 1–3) and kept under magnetic stirring. After a time interval (entries 1–3, Table 1), the autoclave was cooled to room temperature and vented. Then, the mixture was analyzed by GC and GC/MS.

**Reaction of Compounds 3 with DMC. General Procedure.** A stainless steel autoclave (150 mL of internal volume) was charged with a solution of compound 3a or 3b in DMC (0.12 M, 30 mL) and NaY (3: NaY = 1 weight ratio). Before the reaction, air was removed by purging with N₂ stream at room temperature. The autoclave was then heated by an oil-circulating jacket at the desired temperature (130–150 °C), while the mixture was kept under magnetic stirring. A thermocouple fixed into the autoclave head maintained the temperature throughout the reaction. Once the reaction was completed, the autoclave was cooled to room temperature, vented, and opened. The workup of the suspension was carried out as described in the procedure above. Both compounds 7a,b were purified by flash chromatography (eluants: AcOEt/petroleum ether, 1:3 v/v).

Compound 3b was also made to react with DMC at 90 °C following the procedure above-described for amines 1, 2, and 4.

All compounds—except for 7a—were characterized by GC/MS and by ¹H NMR. Spectroscopic and physical properties were in agreement with those reported in the literature: 5a, mp 80–83 °C (dark brown solid) (lit.31 mp 87); 5b, mp 93–95 °C (yellow solid) (lit.31,32 mp 96–97 °C); 5c, brown oil, lit.31a bp 190 °C (solidifies on standing); 6a, yellow solid at 4 °C, tends to liquefy at room temperature; 6b, yellow oil, lit.32 bp 84–86 °C/0.3 mm; 7a, mp 151.5–152.5 °C (white solid) (lit.34 mp 155–157); 7b, mp 170–173 °C (lit.35 mp 176–179 °C); 8a, mp 137–139 °C (white solid) (lit.36,37 mp 143–145 °C); 8b, mp 159–160.5 °C (white solid) (lit.36 mp 162–163 °C). Compound 7a was characterized by ¹H NMR: its structure was also confirmed by comparison with an authentic commercial sample.

¹H NMR and GC/MS spectra of all compounds are available as Supporting Information.

**Reaction of Compounds 9 with DMC. General Procedure.** Compounds 9a (methyl anthranilate) and 9b (ethyl anthranilate) were made to react with DEC (diethyl carbonate) and DMC, respectively. Experiments were carried out in an autoclave at 150 °C, using the above-described procedure for the reaction of compounds 3. In particular, solutions of 9a (1.0 g, 6.6 mmol) in DEC (35 mL, 0.29 mol) and of 9b (0.9 g, 5.5 mmol) in DMC (35 mL, 0.39 mol) were employed. NaY was the catalyst (weight ratio 9: NaY = 1). After 8 h, conversions of 9a and 9b were 25% and of 65%, respectively, with the formation of the corresponding methyl N-ethylantranilinate [O-C₆Me₅CH₂NHMe: 10a,36] and ethyl N-methylantranilinate [O-C₆Et₂CH₂NHMe: 10b] as the sole products. Compounds 10a,b were not isolated from the reaction mixture; their structure was assigned by GC/MS and the related spectra are available as Supporting Information.

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**Supporting Information Available:** ¹H NMR and GC/MS spectra for all mono-N-methylated amines 5a–c, 6a,b, 7a,b, 8a,b This material is available free of charge via the Internet at http://pubs.acs.org.


