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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 ($MeOCO_2Me$, DMC) is a highly chemoselective methylating 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 [XC_6H_4NHMe, X = *o*-, *m*-, and *p*-OH; *o*- and *p*-CH_2OH; *o*- and *p*-CO_2H; *o*- and *p*-$CONH_2$] 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).

Introduction

The mono-*N*-methylation of primary aromatic amines is a key transformation in many organic syntheses.[1] However, both direct and indirect alkylation methods are often problematic from synthetic and environmental standpoints: (i) the reaction selectivity suffers from competing bis-*N*-alkylation side reactions,[2] (ii) common methylating reagents (methyl halides and dimethyl sulfate) are toxic and dangerous,[3] and (iii) multistep sequences (e.g., Eschweiler−Clarke-type reactions[4] and reduction processes[5]) may require harsh conditions not compatible with labile functional groups or not readily available starting materials.

We have recently reported that in the presence of alkali-metal-exchanged Y-faujasites, a direct and high-yield mono-*N*-methylation reaction of anilines can be performed with the use of both dimethyl and alkylmethyl carbonates [$ROCO_2Me$; R = Me, $MeO(CH_2)_2O(CH_2)_2$] as the alkylating agents.[6] Accordingly, the corresponding *N*-methylamines are prepared with an unprecedented selectivity of 90−97% at substantially quantitative conversions (Scheme 1).

SCHEME 1

$$XC_6H_4NH_2 + ROCO_2Me \xrightarrow[130\text{-}160\ ^\circ C]{NaY} XC_6H_4NHMe + ROH + CO_2$$

R = Me, $MeO(CH_2)_2O(CH_2)_2$; X = H, *p*-NC, *p*-O_2N, *p*-Cl, *o*-MeO_2C, 2,6-di-Me

Besides, the reaction is a truly environmentally friendly procedure: dialkyl carbonates, particularly dimethyl carbonate (DMC), are nontoxic compounds, which allow catalytic alkylation processes without the production of inorganic or organic wastes.[3,6,7]

In this paper, we report that the combined use of DMC and sodium-exchanged Y-zeolite (NaY) is a valuable protocol for the *N*-methylation of functionalized anilines such as aminophenols (**1**), aminobenzyl alcohols (**2**), aminobenzoic acids (**3**), and aminobenzamides (**4**). In these cases, the reaction not only shows a very high mono-*N*-methyl selectivity (up to 99%), but it proceeds with a complete chemoselectivity toward the amino group, the other functionalities (OH, CO_2H, $CONH_2$) being fully preserved from alkylation and/or transesterification reactions.

Results and Discussion

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

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TABLE 1. Reaction of Aminophenols (1a−c) with DMC[a]

							products		
entry	substrate	catalyst	cosolvent (mL)	*T*, °C	*t*, h	% conv		%, by GC	% yield[b]
1	**1a**	K_2CO_3	triglyme (35)	135	5	2.5	*p*-HOC_6H_4NHMe	1.7	
							p-$MeOC_6H_4NH_2$	0.7	
2	**1a**	K_2CO_3	DME (35)	150	5	2	*p*-HOC_6H_4NHMe	0.7	
							p-$MeOC_6H_4NH_2$	0.8	
3	**1a**	K_2CO_3	DMF (15)	125	4	8	*p*-HOC_6H_4NHMe	5	
							p-$MeOC_6H_4NH_2$	2	
	1a	K_2CO_3	DMF (15)	125	19	77	*p*-$MeOC_6H_4NHMe$	22	
							p-$MeOC_6H_4NH_2$	23	
							p-$MeOC_6H_4NMe_2$	18	
							p-$MeOC_6H_4NHCO_2Me$	6	
							p-$MeOC_6H_4N(Me)CO_2Me$	8	
4	**1a**	NaY	triglyme (35)	90	5	99	*p*-HOC_6H_4NHMe (**5a**)	99	
5	**1a**	NaY	DME (35)	86	7	100	*p*-HOC_6H_4NHMe (**5a**)	99	91
6a	**1a**	NaY	DMF (15)	90	24	<1	*p*-HOC_6H_4NHMe, trace		
6b	**1a**	NaY	MeCN (35)	81	24	<1	*p*-HOC_6H_4NHMe, trace		
7	**1b**	NaY	−	90	3	100	*o*-HOC_6H_4NHMe (**5b**)	99	99
8	**1b**	*p*-TsOH	−	130	4	35	*o*-HOC_6H_4NHMe	15	
							unidentified product[c]	18	
9	**1c**	NaY	−	90	7	97	*m*-HOC_6H_4NHMe (**5c**)	96	89

[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.

lating reagents is unsatisfactory: because of the ambident nucleophilicity of such compounds, both *N*,*N*-dimethyl and *N*,*O*-dimethyl byproducts form.[8] Indirect procedures that involve reductive alkylations,[4b,9] hydrolytic cleavage of benzoxazoles,[10] and *O*-demethylation reactions[11] are often preferred, even though sometimes *N*,*N*-dimethyl derivatives are still the major products.[12]

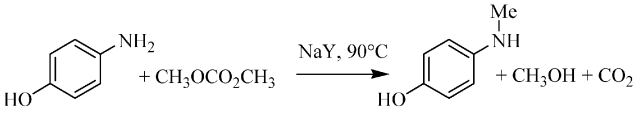
To test the applicability of DMC as an alternative methylating agent, *p*-aminophenol (**1a**) was chosen as a model compound. Initial reactions were carried out at temperatures of 90−150 °C using solutions of **1a** (1.0 g, 9.2 mmol), DMC (10 mL, 0.12 mol), and a cosolvent (DMF, DME, triglyme, and MeCN[13]) in the presence of both K_2CO_3 (2 equiv with respect to **1a**) and NaY (**1a**: NaY in a 1:1 weight ratio).

Successively, solutions of *o*-aminophenol (**1b**) and *m*-aminophenol (**1c**) in DMC (0.31 M, 30 mL) were made to react with NaY as a catalyst (**1b,c**: NaY in a 1:1 weight ratio). Both **1b** and **1c** were sufficiently soluble in DMC so that a cosolvent was not required. For a comparison, the reaction of **1b** was also run with an acid catalyst (*p*-$CH_3C_6H_4SO_3H$, 2 equiv with respect to **1b**).

Results are reported in Table 1.

In the presence of K_2CO_3, the reaction of **1a** is not selective: for example, at a conversion of 77%, a variety of products of *N*- and *O*-methylation as well as of *N*-methoxy carbonylation are observed (entry 3). Even at very low conversions (∼2%), both *N*- and *O*-methylation 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 alkylating agent of phenols,[14] and under basic catalysis, it exhibits a double reactivity with anilines yielding both *N*-methylanilines and urethanes [$ArN(R)CO_2Me$, R = H, Me].[6,15]

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



By contrast, in the presence of an amphoteric catalyst such as the NaY zeolite,[16] 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*-HOC_6H_4NHMe (**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

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(13) Due to the poor solubility of **1a** in DMC, the use of a cosolvent was necessary. For any given cosolvent, a minumum volume was used to obtain the complete solubilization of the substrate at room temperature (see Table 1).

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(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.

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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

						products		
entry	substrate (M)[a]	*T*, °C	*t*, h	% conv	% $S_{M/D}$[b]		%, by GC	% isolated yield
1	**2a** (0.32)	90	8	90	94	(*p*-HO)$CH_2C_6H_4NHMe$ (**6a**)	85	77
2	**2b** (0.32)	90	12	99	99	(*o*-HO)$CH_2C_6H_4NHMe$ (**6b**)	98	92
3	**3a** (0.12)	130	9	100	90	(*p*-HO_2C)C_6H_4NHMe (**7a**)	90[c]	74
4	**3b** (0.12)	90	8	–		–		
5	**3b** (0.12)	150	5	95	95	(*o*-HO_2C)C_6H_4NHMe (**7b**)	90	83
6	**4a** (0.15)	90	24	96	93	(*p*-H_2NOC)C_6H_4NHMe (**8a**)	89	86
7	**4b** (0.32)	90	22	100	94	(*o*-H_2NOC)C_6H_4NHMe (**8b**)	94	91

[a] In parentheses, the molar concentration of the solution of the substrate in DMC is reported. [b] $S_{M/D}$ was the selectivity of mono-*N*-methyl to *N*,*N*-dimethyl derivative expressed as the ratio {[ArNHMe]/([ArNHMe] + [$ArNMe_2$])} × 100. [c] The product (*p*-HO_2C)$CH_2C_6H_4NHMe$ could not be analyzed by GC; the reported percentage was calculated from the ^1H NMR spectrum.

methylation processes usually take place at high temperatures (120−220 °C). This is also manifest in the reaction of **1a** carried out with K_2CO_3 (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]

Analogous results in terms of chemo- and mono-*N*-methyl-selectivity are obtained in the NaY-catalyzed reaction of *o*- and *m*-aminophenols with DMC: at 90 °C, compounds **1b** and **1c** give the corresponding mono-*N*-methyl derivatives [XC_6H_4NHMe, X = *o*-OH (**5b**), *m*-OH (**5c**)] in very high isolated yields (**5b**, 99%; **5c**, 89%) and without any concurrent *O*-methylation or methoxycarbonylation reactions (entries 7 and 9). On the contrary, the use of an acidic catalyst (*p*-TsOH) strongly lowers the overall reaction selectivity (entry 8).[20]

Finally, two preliminary experiments were run to assay the catalytic activity of NaY: solutions of compounds **1b** and **1c** in DMC (0.31 M, 30 mL) were made to react in the presence of a lower amount of the zeolite (1: NaY = 10 weight ratio). As expected, both reactions were slower, but isolated yields of **5b** and **5c** were still satisfactorily: 93% and 92% after 38 and 42 h, respectively.

Aminobenzyl Alcohols (2), Aminobenzoic Acids (3), and Aminobenzamides (4). The direct methylation of compounds **2**−**4** with MeI or Me_2SO_4,[21] as well as the reductive methylation,[22] affords mainly or exclusively *N*,*N*-dimethyl derivatives, while indirect methods via *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*-aminobenzyl alcohols and *o*-aminobenzamide (**2a,b** and **4b**) in DMC (0.32 M, 30 mL) were made to react at 90 °C, while for *p*-aminobenzamide **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.

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 ($ArCH_2OCO_2Me$ and RCO_2Me).[19,24,25] And, although with more difficulty, carboxamides gives *N*-methylamides[26] (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, CO_2H, and $CONH_2$ groups do not react at all. Particularly, in all cases the corresponding mono-*N*-methyl derivatives [XC_6H_4NHMe; X = CH_2OH (**6**), CO_2H (**7**), and $CONH_2$ (**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,[6,18,27,28] this reactivity scale is likely due

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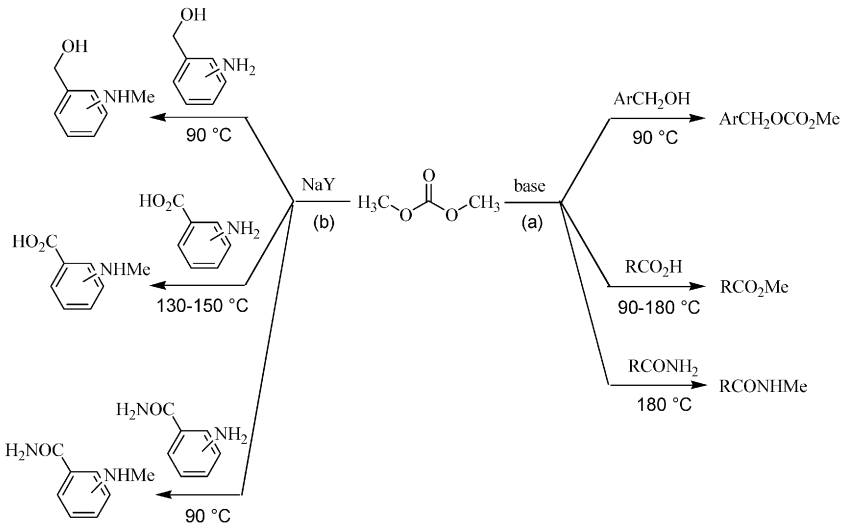
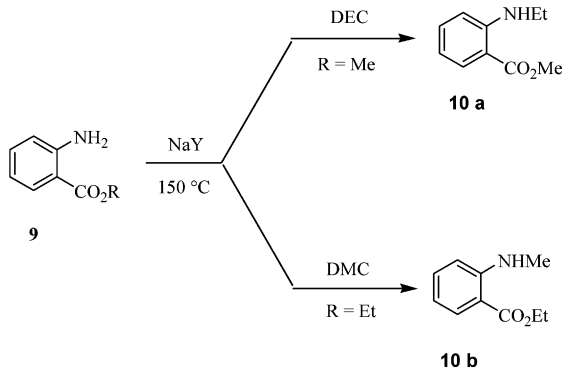
SCHEME 3



SCHEME 4



to the electronic effects of substituents,[29] rather than to their steric requisites.

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

Both reactions yielded exclusively the corresponding mono-*N*-alkylated derivatives (**10a,b**). Although the alkylation of the esters **9** was slow even at 150 °C (after 8 h, conversions of **9a** and **9b** were of 25% and 65%, respectively), no trace of the transesterification products [(*o*-$MeO_2C)C_6H_4NHMe$ or (*o*-$EtO_2C)C_6H_4NHEt$] 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.[30]

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 *o*- and *m*-aminophenols (**1b,c**, 1.0 g, 9.2 mmol), (ii) 0.32 M solutions (30 mL) of *o*- and *p*-aminobenzyl alcohols (**2a,b**: 1.18 g, 9.6 mmol), (iii) 0.32 M solution (30 mL) of *o*-aminobenzamide (**4b**: 1.30 g, 0.0096 mmol), (iv); 0.15 M solution (50 mL) of *p*-aminobenzamide (**4a**: 1.0 g, 0.0075 mmol). In the case of *p*-aminophenol **1a**, solutions of **1a** (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 minimun 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.

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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 XC_6H_4NHMe, X = *o*-, *m*-, and *p*-OH (**5a, 5b,** and **5c**); *o*-CH_2OH (**6b**); and *o*-$CONH_2$ (**8b**) were pure (94−99% by GC) and characterized as such. Compounds **6a** (*p*-$HOCH_2C_6H_4NHMe$) and **8a** (*p*-$H_2NCOC_6H_4NHMe$) were purified by flash chromatography (eluant: AcOEt/petroleum ether, 1:4 v/v).

p-Aminophenol **1a** was also made to react with DMC in the presence of K_2CO_3 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), K_2CO_3 (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 N_2 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 (eluant: 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 ^{1}H NMR. Spectroscopic and physical properties were in agreement with those reported in the literature: **5a**, mp 80−83 °C (dark brow solid) (lit.[31] mp 87); **5b**, mp 93−95 °C (yellow solid) (lit.[31b,32] mp 96−97 °C); **5c**, brown oil, lit.[31b] bp 190 °C/40 mm (solidifies on standing); **6a**, yellow solid at 4 °C, tends to liquefy at room temperature; **6b**, yellow oil, lit.[33] 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.[34b] mp 178−179 °C); **8a**, mp 137−139 °C (white solid) (lit.[34b,35] mp 143−145 °C); **8b**, mp 159−160.5 °C (white solid) (lit.[34b] mp 162−163 °C). Compound **7a** was characterized by ^{1}H NMR: its structure was also confirmed by comparison with an authentic commercial sample.

^{1}H 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*-ethylanthranilate [(*o*-$CO_2Me)C_6H_4NHEt$: **10a**,[36]] and ethyl *N*-methylanthranilate [(*o*-$CO_2Et)C_6H_4NHMe$: **10b**[37]] 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: ^{1}H 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.

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