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Selective *N*-methylation of primary aliphatic amines with dimethyl carbonate in the presence of alkali cation exchanged Y-faujasites

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Abstract—The *N*-methylation of aliphatic amines [$\text{XC}_6\text{H}_4(\text{CH}_2)_n\text{NH}_2$; $n=1$, $\text{X}=\text{H}$ (**1a**), *o*-MeO (**1b**), *p*-MeO (**1c**); $n=2$, $\text{X}=\text{H}$ (**2a**), *o*-MeO (**2b**); **1d**: $\text{PhCH}(\text{Me})\text{NH}_2$] with dimethyl carbonate (DMC) is efficiently catalysed by NaY faujasite: on condition that CO_2 (a co-product of the reaction) is carefully removed, *N*-methyl- and *N,N*-dimethyl-amines (RNHMe and RNMe_2) are obtained in good overall yields (70–90%). Otherwise, in the presence of CO_2 , carbamates (RNHCO_2Me) form competitively to a large extent. The reaction probably proceeds through a $\text{B}_{\text{Al}2}$ displacement of the amine on DMC.

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In the presence of alkali cation exchanged Y-faujasites (e.g. NaY and KY), the reaction of dimethyl carbonate with primary aromatic amines affords the corresponding mono-*N*-methyl derivatives with unprecedented selectivity (92–99%). This holds even for anilines deactivated by both electronic and steric effects (Scheme 1).¹

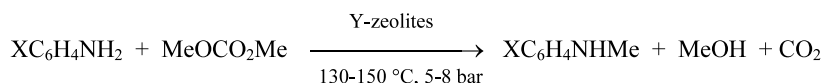
Besides the synthetic outcome, this reaction shows relevant environmentally benign features: it uses a non-toxic methylating agent (DMC) coupled with *eco-safe* solids (zeolites) as catalysts, it does not require additional solvents, and neither organic nor inorganic by-products are formed.²

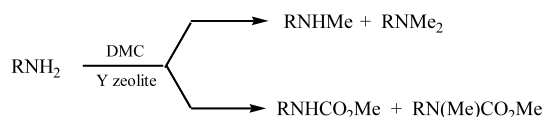
As a part of our research program on the reactivity of DMC over Y zeolites, we were interested in the *N*-methylation of primary aliphatic amines as well. The higher nucleophilicity of these substrates posed a severe limitation to the reaction selectivity, due not only to the double *N*-methylation but primarily, to the formation of carbamates (Scheme 2).^{1a,c} Apparently, $\text{B}_{\text{Ac}2}$ and $\text{B}_{\text{Al}2}$ mechanisms, i.e. the attack of the amine

to the carbonyl ($\text{B}_{\text{Ac}2}$) and to the methyl ($\text{B}_{\text{Al}2}$) groups of DMC, were possible without any discrimination.

In this paper, we wish to report a further investigation on this reaction which discloses the synthetic potential for the preparation of *N*-methyl amines and some relevant features of the methylation/methoxycarbonylation mechanisms of aliphatic amines with DMC.

Initially, benzylamine **1a**, *o*- and *p*-methoxybenzylamine, and (α -methyl)benzylamine (compounds **1b**, **1c**, and **1d** respectively) were chosen as substrates (Table 1). In a typical procedure (entry 7), a three-necked, jacketed, 25 mL round-bottomed flask fitted with a N_2 -bubbler, an adapter for the withdrawal of samples, a reflux condenser connected to a gas flowmeter, and a magnetic bar, was loaded with a solution of benzylamine (**1a**, 0.3 g, 2.8 mmol) in dimethyl carbonate (20 mL), and NaY (0.9 g). The flask was heated at the reflux temperature of DMC (90°C), while the mixture was vigorously stirred. A N_2 flow of ~ 25 mL/min was

X = H, *p*-Me, *p*-MeO, *p*-Et, *p*-EtO, *p*-O₂N, *p*-NC, *o*-CH₃OOC, 2,6-Me₂**Scheme 1.** Mono-*N*-methylation of anilines with DMC.* Corresponding author. Tel.: +39 041 234 8687; fax: +39 041 234 8620; e-mail: selva@unive.it



Scheme 2. R = CH₂Ph, Cy.

bubbled into the mixture and maintained throughout the reaction. At intervals, samples (0.1 mL) were withdrawn and were analyzed by both GC and GC/MS. The structures of the products were also confirmed by comparison with authentic samples of *N*-methylbenzylamine, *N,N*-dimethylbenzylamine, methyl *N*-benzyl carbamate, and methyl *N*-benzyl, *N*-methyl carbamate.

The same reaction was also performed under a static N₂-atmosphere (entries 1–6).

According to our previous experiments,^{1c} without the N₂-bubbling, the increase of Lewis acidity of the catalyst (going from CsY to LiY faujasites)³ shows a positive effect on the reaction rate (compare entries 1–2 and 5).

However, at higher conversions (89 and 97%: entries 3–4), the selectivity (*S*_{Met}) towards the *N*-methylation reaction is clearly variable (43 and 64%, respectively). Competitive side reactions, i.e. the carbamation (prod-

ucts **C** and **MC**, Scheme 2) and the oxidative deamination (product **E**: XC₆H₄CH₂N=CHPh) of the amine **1a** take place to a large extent.⁴ The Brønsted acidic zeolite (HY) is even more unsatisfactory (entry 6): at a 30% conversion, *S*_{Met} is only 33%. We suggest that a strong acid-base interaction may hold amine within the catalyst pores,⁵ so that any advantage due to the smaller size of the cation is cancelled.

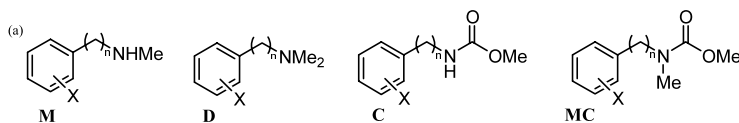
Much better results can be gathered for the *N*-methylation of compound **1a** as well as of **1b–d**, when reactions are performed over NaY—a commercially available faujasite—in the presence of a N₂ stream (entries 7–10): *S*_{Met} of 91–100% are attained at conversions of 70–94%. This improvement arises not only from the increase of the methylation versus carbamation selectivity (*S*_{Met/Carb}), but also from a fall in formation of the side-product **E**.

The same procedure is profitable also for the reaction of phenethylamine (**2a**) and its *o*-methoxyderivative [**2b**: *o*-MeOC₆H₄(CH₂)₂NH₂] with DMC. The presence of a N₂ flow is an extremely simple and efficient method to allow an excellent *N*-methylation selectivity (91–98%) for compounds **2a–b**, while the carbamation reaction is practically ruled out.

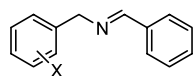
The data in Table 1 give a clear indication of the major role played by the CO₂ which, as is shown in Scheme 1,

Table 1. *N*-Methylation of amines **1a–d** and **2a–b** with DMC over MY zeolites

Entry	Amine	MY	<i>T</i> (°C)	<i>t</i> (h)	N ₂ flow	Conv. (%)	Products (%) ^a					<i>S</i> _{Met/Carb} ^b (%)	<i>S</i> _{Met} ^c (%)
							M	D	C	MC	E		
1	1a	LiY	90	7	No	43	34	9					
2	1a	NaY	90	7	No	40	30	7				3	
3	1a	NaY	90	56	No	89	8	49	7	13	12	74	64
4 ^d	1a	NaY	110	23	No	97	-	42	16	27	12	49	43
5	1a	CsY	90	22	No	36	18	8			10		72
6	1a	HY	90	23	No	30	6	4	8		12	55	33
7	1a	NaY	90	48	Yes	94	20	70	3		1	98	96
8	1b	NaY	90	23	Yes	70	30	34	5		1	91	91
9	1c	NaY	90	22	Yes	90	37	51	1		1	99	98
10 ^e	1d	NaY	90	68	Yes	70	48	22				100	100
11	2a	NaY	90	24	Yes	90	39	48	2			98	98
12	2b	NaY	90	26	Yes	63	20	37	7			91	91



if *n* = 1 (entries 1–9), X = H, *o*-MeO, *p*-MeO; if *n* = 2 (entries 11–12), X = H, *o*-MeO



E: X = H, *o*-MeO, *p*-MeO

^a The structures of all products were assigned by GC/MS analyses and by comparison with authentic samples.

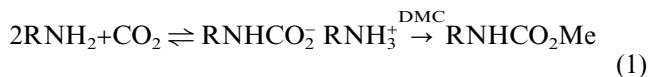
^b Methylation versus carbamation selectivity, *S*_{Met/Carb} = [M+D]/(M+D+C+MC) × 100.

^c Overall *N*-methyl selectivity, *S*_{Met} = [M+D]/(M+D+C+MC+E) × 100.

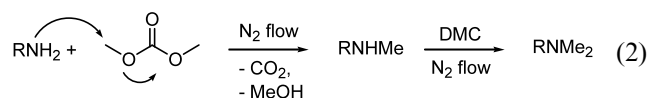
^d Entry 4: the reaction was carried out in a stainless-steel autoclave of 150 mL.

^e Products **M**, **D**, **C**, and **MC** of entry 10 were obtained according to the structure of the reacting substrate **1d**: PhCH(Me)NH₂.

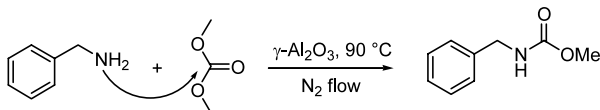
is an intrinsic co-product of DMC-mediated methylation reactions. As far as the methylation proceeds, CO₂ chemisorbs into the catalyst cages,⁶ where it becomes available for the reactant amine to form the corresponding urethanes (Eq. (1)).⁷



The B_{Ac}2 mechanism of Scheme 2 through the attack of the amine to the carbonyl of DMC cannot take place directly. On the other hand, when the zeolite surface is kept free from CO₂, the carbamation is hindered and the aliphatic amine reacts only via the B_{Al}2 mechanism: *N*-methylation takes place exclusively (Eq. (2)).



It should be noted that this behavior is peculiar to the explored conditions and particularly to the catalyst used. While the reaction of aliphatic amines and DMC does not proceed significantly without a catalyst, in the presence of γ -Al₂O₃, carbamates form in good to excellent yields (80–95%).⁸ Furthermore, this reaction occurs without any CO₂ promotion: under the conditions of entries 7–12 of Table 1, benzylamine reacts with DMC over γ -Al₂O₃,⁹ to give methyl *N*-benzylcarbamate as the sole product (24% after 4 h, Scheme 3).



Scheme 3. Direct B_{Ac}2 attack of benzylamine on DMC.

The direct B_{Ac}2 attack of the amine on the DMC carbonyl is allowed in this case.

With Y faujasites, the involvement of CO₂ in the reaction of aliphatic amines with DMC may also account

for the lack of mono-*N*-methyl selectivity in such reactions. In fact, the mechanism proposed for the formation of mono-*N*-methylanilines as well as mono-*C*-methyl derivatives of CH₂-active compounds—though with different catalysts—involves the sequence shown in Scheme 4.^{1,10} The nucleophile (NuH₂) reacts first with DMC via the B_{Ac}2 mechanism to yield the methoxycarbonylated derivative [Nu(CO₂Me)H, Eq. (2)]. Then methylation (B_{Al}2 mechanism) and demethoxycarbonylation reactions (Eqs. 5–6) lead to the final product [Nu(Me)H]. The sequence of B_{Ac}2–B_{Al}2 processes preserves NuH₂ from a double methylation.

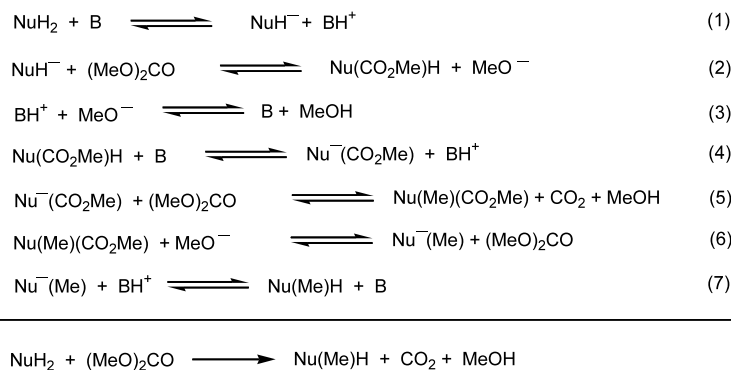
By contrast, the more nucleophilic aliphatic amines directly attack the methyl group of DMC as is shown in Eq. (2), and when CO₂ is purged from the reaction mixture, a reversible methoxycarbonylation reaction is not possible. Any selectivity towards mono-*N*-methyl products is ruled out.

On the whole, the following conclusions can be drawn:

- (i) MY faujasites are efficient catalysts for the *N*-methylation of aliphatic amines, but a high chemoselectivity (methylation versus carbamation) is reached through the tuning of the acid–base properties of the zeolites and most of all, through the removal of CO₂ from the reactant mixture;
- (ii) The B_{Al}2 displacement of the amine on DMC is the likely reaction mechanism. Accordingly, since the mono-*N*- versus *N,N*-dimethylation selectivity cannot be controlled, the procedure has valuable potential for synthesis of tertiary amines.

Acknowledgements

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Scheme 4. Mono-methylation selectivity with DMC. NuH₂: nucleophile susceptible of double alkylation; B: a basic site of the catalyst.

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