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Highly Chemoselective Methylation and Esterification Reactions with Dimethyl Carbonate in the Presence of NaY Faujasite. The Case of Mercaptophenols, Mercaptobenzoic Acids, and Carboxylic Acids Bearing OH Substituents

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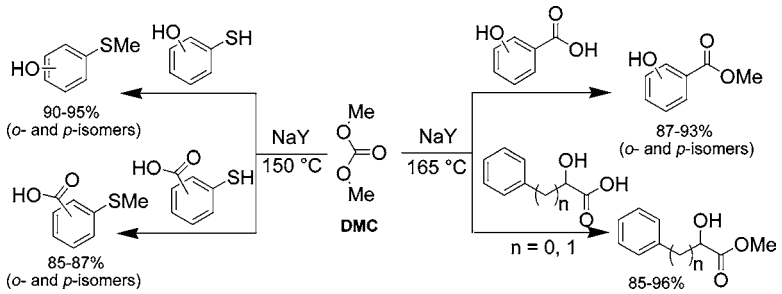

In the presence of NaY faujasite, the reactions of dimethyl carbonate (DMC) with several ambident nucleophiles such as *o*- and *p*-mercaptophenols (**1a,b**), *o*- and *p*-mercaptobenzoic acids (**2a,b**), *o*- and *p*-hydroxybenzoic acids (**3a,b**), mandelic and phenyllactic acids (**4**, **5**), have been explored under batch conditions. Highly chemoselective reactions can be performed: at 150 °C, compounds **1** and **2** undergo only a S-methylation reaction, without affecting OH and CO_2H groups; at 165 °C, acids **3**−**5** form the corresponding methyl esters, while both their aromatic and aliphatic OH substituents are fully preserved from methylation and/or transesterification processes. Typical selectivities are of 90−98% and isolated yields of products (*S*-methyl derivatives and methyl esters, respectively) are in the range of 85−96%. A comparative study with K_2CO_3 as a catalyst is also reported. Although the base (K_2CO_3) turns out to be more active than the zeolite, the chemoselectivity is elusive: compounds **2a,b** undergo simultaneous S-methylation and esterification reactions, and acids **3**−**5** yield complex mixtures of products of O-methylation, O-methoxycarbonylation, and esterification of their OH and CO_2H groups, respectively. Overall, the combined use of a nontoxic reagent/solvent (DMC) and a safe promoter (NaY) imparts a genuine ecofriendly nature to the investigated synthesis.

Introduction

In recent years, an increasing interest has been focused on dimethyl carbonate (DMC) as a reagent for safer and selective methylation and/or carboxymethylation protocols.[1] DMC in fact is a nontoxic compound that allows catalytic processes with unprecedented high selectivity (up to 99%) in the monomethylation of CH_2-active compounds and primary aromatic amines[2−3] and in the synthesis of methyl carbamates as well.[4]

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(1) (a) Shaik, A.-A. G.; Sivaram, S. *Chem. Rev.* **1996**, *96*, 951−976. (b) Tundo, P.; Selva, M. *Acc. Chem Res.* **2002**, *35*, 706−716. (c) Shieh, W.-C.; Dell, S.; Repic, O. *J. Org. Chem.* **2002**, *67*, 2188−2191. (d) Shieh, W.-C.; Dell, S.; Bach, A.; Repic, O.; Balcklock, T. J. *J. Org. Chem.* **2003**, *68*, 1954−1957.

(2) (a) Selva, M.; Marques, C. A.; Tundo, P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1323−1328. (b) Fu, Z.-H.; Ono, Y. *J. Catal.* **1994**, *145*, 166−170. (d) Selva, M.; Tundo, P.; Perosa, A.; Memoli, S. *J. Org. Chem.* **2002**, *67*, 1071−1077.

(3) (a) Fu, Z.-H.; Ono, Y. *Catal. Lett.* **1993**, *22*, 277−281. (b) Selva, M.; Bomben, A.; Tundo, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1041−1045. (c) Selva, M.; Tundo, P.; Perosa, A. *J. Org. Chem.* **2001**, *66*, 677−680. (d) Selva, M.; Tundo, P.; Perosa, A. *J. Org. Chem.* **2002**, *67*, 9238−9247.

(4) (a) Aresta, M.; Quaranta, E. *Tetrahedron* **1991**, *47*, 9489−9502. (b) Selva, M.; Tundo, P.; Perosa, A.; Dall'Acqua, F. *J. Org. Chem.* **2005**, *70*, 2771−2777.

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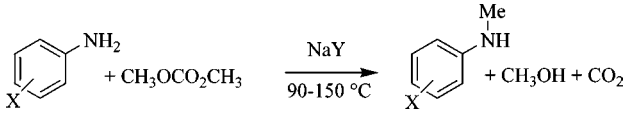
A further added value of the use of DMC is that derivatization (protection/deprotection) sequences may be avoided. In particular, we have recently reported that in the presence of sodium-exchanged Y-zeolite (NaY faujasite) as a catalyst, the reaction of dimethyl carbonate with ambident nucleophiles such as amino-phenols, -benzyl alcohols, -benzoic acids, and -benzamides not only showed a very high mono-*N*-methyl selectivity (up to 99%), but it proceeded with complete chemoselectivity toward the amino group (Scheme 1).[5] The other nucleophilic

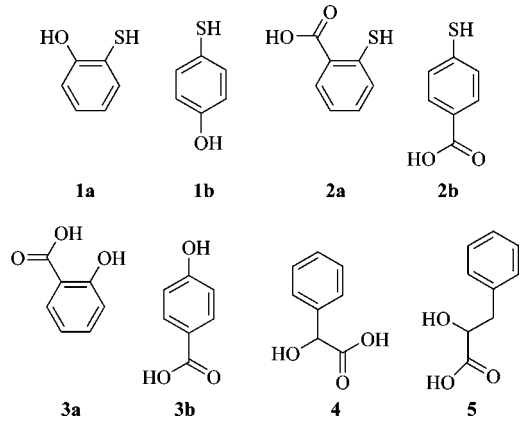
SCHEME 1. X = OH, CO_2H, CH_2OH, $CONH_2$



functionalities (OH, CO_2H, CH_2OH, $CONH_2$) were fully preserved from alkylation and/or transesterification reactions.

With the aim of further exploring the potential of the DMC/faujasite system for chemoselective green syntheses, other bifunctional substrates such as mercaptophenols (**1a,b**), mercaptobenzoic acids (**2a,b**), and carboxylic acids bearing OH substituents (**3a,b**, **4**, and **5**) (Scheme 2) were considered.

SCHEME 2



We wish to report herein that in the presence of NaY, also reactions of compounds **1**−**5** do proceed with a very high selectivity. In particular, at 150 °C, compounds **1** and **2** undergo only S-methylation, hydroxyl and carboxylic groups being unaffected, whereas at 165 °C acids **3**−**5** yield the corresponding methyl esters without any side reactions (methylation/methoxycarbonylation) of OH substituents. To further elucidate the scope and limitations of the method, a comparison between NaY and a conventional basic catalyst (K_2CO_3) for DMC-mediated methylations is also described.

Results

Mercapto-Derivatives 1 and 2. Initially, compounds **1** and **2** were investigated. Solutions of **1** and **2** in DMC (5×10^{-2} M, 30 mL; DMC serving both as a reagent and the solvent) were prepared to react at 150 °C, in a stainless steel autoclave (90 mL), in the presence of different amounts of the faujasite NaY [weight ratio NaY:substrate (*Q*) in the range of 0.5−4]. All reactions were carried out under a N_2 atmosphere and were monitored by GLC and GC−MS.

The same procedure was also used to carry out reactions of substrates **1a,b** and **2a** with K_2CO_3 as a catalyst (molar ratio K_2CO_3:substrate in the range of 0.2−2) in place of NaY. These experiments were performed at a lower temperature of 130 °C.

TABLE 1. Reactions of Compounds 1a,b with DMC

entry	substrate (XC_6H_4SH)	NaY: sub (w/w)[a]	K_2CO_3: sub (mol/mol)[b]	*t* (h)	*T* (°C)	conv (%)[c]	products (%, GC) **6**	**7**	**8**	isolated yield, **6** (%)
1	X = *o*-OH (**1a**)			20	130					
2				20	150	15			15	
3		0.5		3	150	66	7		59	
4		0.5		20	150	75	14		61	
5		2		20	150	93	76		16	60[d]
6		3		13	150	100	94		6	95[e]
7			0.2	3	130	100	100			
8	X = *p*-OH (**1b**)	1		20	150	67	36	2	29	
9		2		20	150	96	72	10	14	60[d]
10		3		13	150	99	90	1	8	90[d]
11			0.2	3	130	85	85			

[a] Weight ratio NaY:substrate. [b] Molar ratio K_2CO_3:substrate. [c] Conversion (%) by GC. [d] Yields of products **6a,b** purified by FCC (eluant: petroleum ether/diethyl ether, 4:1 v/v). [e] Yield of crude product **6a** isolated after filtration of the zeolite and vacuum distillation of DMC.

TABLE 2. Reactions of Compounds 2a,b with DMC

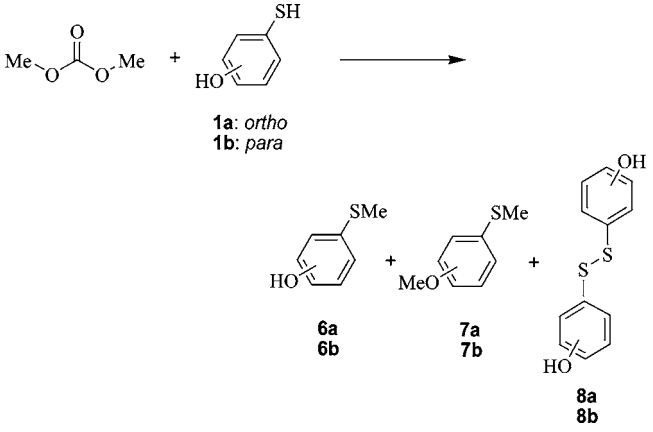
entry	substrate (XC_6H_4SH)	NaY: sub (wt/wt)[a]	K_2CO_3: sub (mol/mol)[b]	*t* (h)	*T* (°C)	conv (%)[c]	products (% GC) **9**	**10**	isolated yield, **9** (%)[d]
1	X = *o*-CO_2H (**2a**)	2		20	150	95	85	10[b]	
2		3		15	150	93	90	2[b]	87
3			2	3	130	99	22	77	
4			0.2	1	130	100	51	49	
5	X = *p*-CO_2H (**2b**)	3		13	150	69[e]	64	2	
6		3		26	150	100	90	10	85

[a] Weight ratio NaY:substrate. [b] Molar ratio K_2CO_3:substrate. [c] Conversion (%) by GC. [d] Yield of products **9a** (entry 3) and **9b** (entry 7) purified by FCC (eluant: petroleum ether/diethyl ether, 4:1 v/v). [e] Methyl *p*-mercaptobenzoate (*p*-$SHC_6H_4CO_2Me$, 3%) was also observed.

Tables 1 and 2 report the results for mercaptophenols (**1a,b**) and for mercaptobenzoic acids (**2a,b**), respectively. To allow an inspection of the chemoselectivity, the chosen reaction times and temperatures of both tables mostly refer to high, if not quantitative, substrates conversions.

In the case of mercaptophenols (**1a,b**) (Table 1), reactions showed the formation of the corresponding *S*-methyl derivatives (**6a,b**, usually main products; 75−100% at complete conversions), along with compounds **7a,b** that derived from the simultaneous S- and O-methylation of the substrates, and the disulfides **8a,b** (Scheme 3). Compounds **6a,b** were isolated, and

SCHEME 3. Reactions of Mercaptophenols 1a,b with DMC



yields of 60−95% were obtained.[6]

TABLE 3. Reactions of Carboxylic Acids 3−5 with DMC

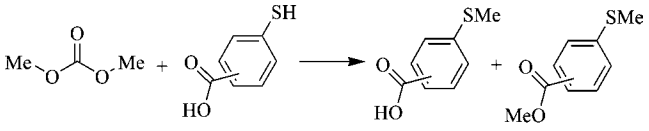
entry	substrate	Fau/base[a]	*t* (h)	*T* (°C)	conv (%)	products (% GC)	*Y* (%)[b]
1	*o*-$OHC_6H_4CO_2H$ (**3a**)	NaY	15	165	100	**13a**: *o*-$OHC_6H_4CO_2Me$ (98)	93
2		K_2CO_3	10	150	80	**16a**: *o*-$OMeC_6H_4CO_2Me$ (80)	
3	*p*-$OHC_6H_4CO_2H$ (**3b**)	NaY	24	165	100	**13b**: *p*-$OHC_6H_4CO_2Me$ (100)	87[c]
4		K_2CO_3	17	150	70	**16b**: *p*-$OMeC_6H_4CO_2Me$ (70)	
5	$PhCH(OH)CO_2H$ (**4**)	NaY	24	165	100	**14**: $PhCH(OH)CO_2Me$ (92)	96
6		K_2CO_3	9	150	85	**14**: $PhCH(OH)CO_2Me$ (10) **17**: $PhCH(OMe)CO_2Me$ (13) **18**: $PhCH(OCO_2Me)CO_2Me$ (62)	
7	(s)$PhCH(OH)CO_2H$	NaY	22	165	96	(s)$PhCH(OH)CO_2Me$ (93)	85
8	$PhCH_2CH(OH)CO_2H$ (**5**)	NaY	24	165	96	**15**: $PhCH_2CH(OH)CO_2Me$ (92) $PhCH{=}CHCO_2Me$ (4)	95

[a] Fau = NaY faujasite. Entries 1, 3, 5, 7, and 8: reactions were carried out using a NaY:substrate weight ratio of 3. Entries 2, 4, and 6: reactions were carried out using a K_2CO_3:substrate molar ratio of 1.5. [b] *Y* = isolated yields of crude methyl esters **13a**, **14**, and **15** (entries 1, 5, 7, and 8, respectively). [c] Yield of **13b** purified by FCC (eluant: petroleum ether/diethyl ether, 4:1 v/v).

Two recycling tests were also carried out. Once experiments of entries 6 and 10 of Table 1 were completed, the solid NaY was filtered, dried at 90 °C overnight, and finally, reused to repeat the two reactions. No appreciable variations of either conversion of **1a,b** or selectivity were observed.

In the case of mercaptobenzoic acids (**2a,b**) over NaY (Table 2), the corresponding *S*-methyl derivatives **9a,b** were still the major products (up to 90%, Scheme 4). They were isolated in

SCHEME 4. Reactions of Compounds 2a,b with DMC



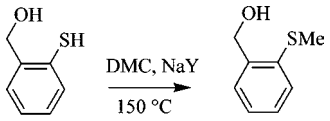
2a. *ortho* **2b**: *para** **9a** **9b** **10a** **10b**

85−87% yields. Methyl esters **10 a,b** were also observed (2−10%).

In the presence of K_2CO_3, however, the reaction of **2a** with DMC gave the ester **10a** as the predominant product (50−77%).

In a separate experiment, also 2-mercaptobenzyl alcohol (**11**) was made to react with DMC in the presence of NaY (conditions of entry 7, Table 2). After 26 h, the conversion was of 98% and 2-(methylthio)benzyl alcohol (**12**) was observed in 88% amount by GC. (Scheme 5). Compound **12** was then isolated in 67% yield.[7]

SCHEME 5



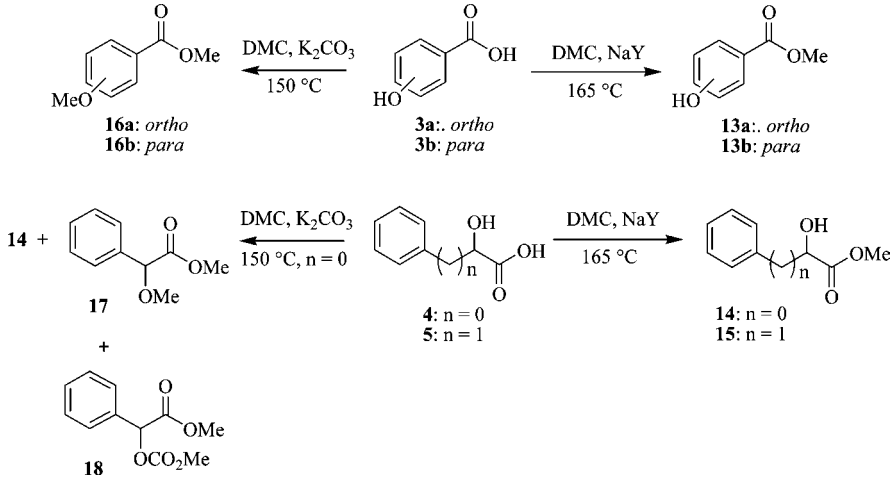
11 **12**

Carboxylic Acids Bearing OH Substituents (3−5). According to the procedure above-described for compounds **1** and **2**, solutions of hydroxybenzoic acids (**3a,b**), racemic and enantiomerically pure [(*s*)-form] mandelic acid (**4**), and racemic phenyllactic acid (**5**) in DMC (5×10^{-2} M, 30 mL) were made to react at 165 °C, in the presence of the faujasite NaY [weight ratio NaY:substrate (*Q*) of 3]. The corresponding methyl esters (**13**−**15**, Scheme 6, right) were obtained in >90% purity (by GC−MS). They were isolated in 85−96% yields, by simple filtration of the zeolite and removal of DMC under vacuum.[8]

When NaY was replaced with K_2CO_3 (1.5 molar equiv with respect to the substrate), even though experiments were carried out at a lower temperature (150 °C), the esterification of acids **3** and **4** was always accompanied by simultaneous O-methylation and O-methoxycarbonylation reactions of the OH substituents (compounds **16**−**18**; Scheme 6, left).

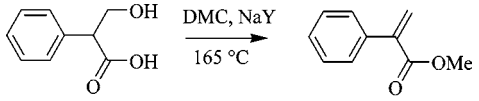
Table 3 reports the results. As for Tables 1 and 2, the chosen reaction times and temperatures of both tables mostly refer to high, if not quantitative, substrates conversions.

SCHEME 6. Reactions of Compounds 3−5 with DMC in the Presence of NaY (Right) and of K_2CO_3 (Left)



In a separate experiment, also tropic acid (**19**) was converted with DMC in the presence of NaY (conditions of entry 1, Table 3). After 15 h, the conversion was substantially quantitative; the major product, however, was methyl 2-phenylpropenoate (**20**) which derived from the simultaneous dehydration and esterification of the reagent (Scheme 7). Compound **20** was isolated in a 82% yield.

SCHEME 7. Reaction of Tropic Acid with DMC



19 **20**

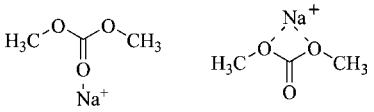
It should be noted that the dehydration product was also observed in the case of phenyllactic acid, though it was formed to a much lesser extent (4%; entry 8, Table 3).

Discussion

Mercaptophenols 1a,b. In the absence of catalysts/promoters, solutions of *o*-mercaptophenol (**1a**) in DMC do not react below 150 °C (entries 1 and 2, Table 1); under these conditions, only a small amount (15%) of disulfide **8a** is observed after a prolonged reaction time (20 h, entry 2). This reaction is reasonably due to traces of dissolved oxygen. In fact, the synthesis of both disulfides **8a,b** is reported to occur through facile oxidation of phenols **1a,b** in air.[9]

In the presence of NaY ($Q = 0.5-1$), the formation of disulfides **8** appears favored (entries 3 and 8, Table 1) for the initial period (3 h); then, it substantially stops even for a prolonged reaction time (entry 4).[10] As the amount of the zeolite is increased (*Q* ratio of 2−3), the S-methylation of phenols **1a,b** takes over and the corresponding hydroxythioanisoles **6a,b** are obtained in 90% and 95% isolated yields, respectively (entries 6 and 10, Table 1). This behavior can be ascribed to the modes of interactions of DMC with the faujasite. IR and Raman investigations demonstrate that acid−base complexes (I and II) are formed between DMC and the Lewis acidic sites (Na^+ cations) of the zeolite (Scheme 8).[11]

SCHEME 8. Interactions of DMC with Na^+ of Y-Faujasites

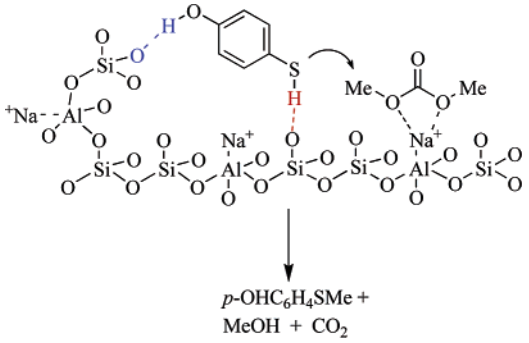


I II

In both I and II species, the O-CH_3 bonds are weakened. This implies that, after adsorption over NaY, DMC undergoes an electrophilic activation that may be favored if increasing amounts of the zeolite are used.[12] Accordingly, in the present case (entries 3−6 and 8−10), the methylation reaction can proceed faster than the competitive oxidation process.[13]

In addition, since alkali metal exchanged faujasites are amphoteric solids,[14] they may induce a slight nucleophilic activation. In fact, nucleophiles such as phenols, thiophenols, amines, etc. are adsorbed over NaY and NaX, through the formation of H-bonds with basic oxygen atoms of the zeolite framework.[15] Scheme 9 depicts the case of compounds **1b**. The methylation reaction is most possibly of an S_N2 type.

SCHEME 9. Pictorial View of the S-Methylation of *p*-Hydroxythiophenol (1b) with DMC over NaY



Potassium carbonate is often reported as a highly active catalyst for DMC-mediated methylations; these reactions proceed through a $B_{Al}2$ mechanism (Scheme 10, path a).[1−3] A $B_{Ac}2$ mechanism is also possible (Scheme 10, path b), though at temperatures ≥130 °C, the reversibility of this reaction often leads to the methyl derivative (NuMe) as the sole product.

In the presence of K_2CO_3, also the S-methylation of compounds **1a,b** with DMC proceeds efficiently (entries 7 and 11,

(5) (a) Selva, M.; Tundo, P.; Perosa, A. *J. Org. Chem.* **2003**, *68*, 7374−7378. (b) Selva, M.; Tundo, P.; Foccardi, T. *J. Org. Chem.* **2005,** *70*, 2476−2485.

(6) Compound **6a** was simply isolated by filtration of the zeolite and removal of DMC under vacuum. No further purification was necessary (see Experimental Section).

(7) The FCC purification of compound **12** was made difficult by the presence of some unidentified byproducts (10%) in the reaction mixture. For this reason, a moderate yield of **12** (67% compared to the higher GC amount of 88%) was obtained.

(8) Only compound **13b** was further purified by FCC (see Experimental Section).

(9) (a) Greenwood, D.; Stevenson, H. A. *J. Chem. Soc.* **1953**, 1514−1518. (b) Schaefer, T.; Salman, R.; Wildman, T. A.; Clark, P. D. *Can. J. Chem.* **1982**, *60*, 342−348. (c) Mahfouz, A. M. M.; Metcalf, R. L.; Fukuto, T. R. *J. Agric. Food Chem.* **1969**, *17*, 917−922.

(10) The oxidation of mercaptophenols to the corresponding disulfides can be catalyzed by Lewis acidic compounds (i.e., $FeCl_2$; see Oae, S.; Yoshihara, M. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2082−2086). This suggests that also small Lewis acidic cations of Y-faujasites (such as Li^+, Na^+; see Barthomeuf, D. *J. Phys. Chem.* **1984**, *88*, 42−45) can promote the formation of compounds **8a,b**. The oxidation however apparently stops when dissolved oxygen is consumed.

(11) (a) Beutel, T. *J. Chem. Soc., Faraday Trans.* **1998**, *94*, 985. (b) Bonino, F.; Damin, A.; Bordiga, S.; Selva, M.; Tundo, P.; Zecchina, A. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 4774−4777.

(12) From the general formula $Na_{56}[(AlO_2)_{56}(SiO_2)_{136}]\cdot 250H_2O$ of a NaY faujasite, it contains ∼7.5% sodium. However, since metal cations occupy four different positions within the framework of the Y-zeolites, only one-third of the total sodium of a NaY, i.e., ∼ 2.3%, corresponds to active Na^+ involved in adsorption and/or catalytic phenomena; the other cations, being deeply embedded into the structure, are hardly accessible. (Gates, B. C. In *Catalytic Chemistry*; Wiley: New York, 1992). In the investigated reaction of compounds **1a,b** with DMC, the 6-fold increase of the zeolite amount (entries 4−6 and 8−10, Table 1) corresponds to an increase of the molar ratio between active Na^+ and DMC, from 0.14 to 0.86.

(13) Although disulfides **8a,b** may also behave as nucleophiles, it seems rather unlikely that they act as intermediates in the formation of the final products **6a,b**. In fact, once compounds **8a,b** are formed, their amounts remain substantially constant even though *S*-methyl derivatives **6a,b** increase throughout the reaction (entries 3 and 4, Table 1). Moreover, in the reaction of mercaptobenzoic acids **2a,b** (Table 2), the corresponding disulfides are never observed.

(14) Su, B.; Barthomeuf, D. *Stud. Surf. Sci. Catal.* **1995**, *94*, 598 (see also refs in note 8).

(15) (a) Czjzek, M.; Vogt, T.; Fuess, H. *Zeolites* **1991**, *11*, 832. (b) Beutel, T.; Peltre, M.-J.; Su, B. L. *Colloids Surf., A* **2001**, *187−188*, 319−325. (c) Fu, Z.-H.; Ono, Y. *Catal. Lett.* **1993**, *21*, 43−47.

SCHEME 10. Mechanisms of DMC-Promoted Reactions Carried Out Over K_2CO_3 as a Catalyst; NuH = Generic Nucleophile

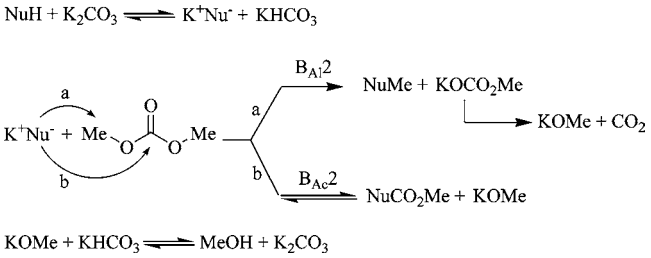


Table 1). With respect to NaY, the formation of hydroxythioanisoles **6a,b** is faster even at a lower reaction temperature (3 h at 130 °C), and most importantly, the base can be used in a catalytic amount (0.2 molar equiv with respect to compounds **1**). The nucleophilic activation of **1a,b** with a base is apparently more important than the activation of DMC within NaY, according to Scheme 8. Conventional procedures for the alkylation of mercaptophenols with alkyl halides also claim the use of basic promoters ($KHCO_3$).[16]

However, although NaY is effective only in a relatively high quantity, it can be easily reactivated and recycled.

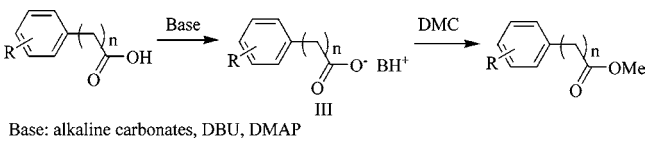
It should be finally noted that, regardless of the nature of the promoter/catalyst, the S-methylation of phenols **1a,b** is the sole observed reaction. The higher polarization of the thiol group with respect to the hydroxyl one accounts for such a chemoselectivity.

Mercaptobenzoic acids 2a,b. To avoid the formation of disulfides as side products (see Table 1), reactions of compounds **2a,b** with DMC are always carried out with relatively high amounts of NaY (entries 1 and 2, 5 and6, Table 2).

Table 2 shows that the reaction outcome is greatly affected by the type of the promoter/catalyst. At 150 °C, in the presence of NaY, methylthiobenzoic acids **9a,b** are obtained with a selectivity of 90−98%. The esterification of acid functions, as well as the transesterification of alcoholic groups (Scheme 5),[17] do not take place. This is consistent with our previous findings on the selective mono-N-methylations of aminobenzoic acids and aminobenzyl alcohols with DMC and NaY as a catalyst.[5]

On the contrary, the use of K_2CO_3 allows simultaneous methylation and esterification reactions of SH and of CO_2H groups, respectively. Both processes occur notwithstanding that a lower temperature is applied (130 °C; entries 3−4, Table 2). Under these conditions, the striking drop in chemoselectivity reflects the general reactivity of carboxylate anions with alkylating agents to yield the corresponding esters;[18] this is especially true when methyl halides are involved.[19] In the reaction with DMC, carboxylate salts may be generated by both inorganic and organic bases (Scheme 11).[20]

SCHEME 11. Base-Catalyzed Esterification of Carboxylic Acids with DMC



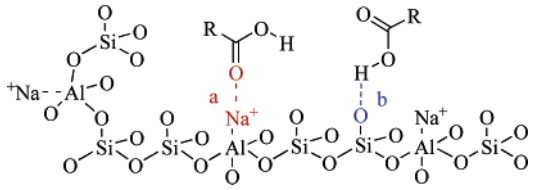
Compounds III act as nucleophiles via direct S_N2 displacements ($B_{Al}2$ mechanism) or through a nucleophilic catalysis.

Carboxylic Acids Bearing OH Substituents (3−5). A number of methods are reported for the selective synthesis of methyl esters of acids **3**−**5**.[21] These procedures normally allow good yields but also pose concerns from both the environmental and safety standpoints, as strong acids (H_2SO_4, HCl) as well as harmful reagents (MeI, $MeOSO_3Me$, CH_2N_2, $SOCl_2$) have to be used.

Despite the results shown in Table 2, the selective esterification of compounds **3**−**5** with DMC can also be promoted by the NaY faujasite. In fact, a simple increase of the reaction temperature from 150 °C (Table 2) to 165 °C (Table 3) allows the formation of methyl esters **13a,b**, **14**, and **15** with a selectivity up to 100%, at substantially quantitative conversions (entries 1, 3, 5, 7, and 8, Table 3). The reaction rate, however, is rather sensitive to the amount of the zeolite. For instance, if a weight ratio NaY:acid (*Q*) of 3 is used, the esterification of mandelic acid is completed after 24 h at 165 °C (entry 5, Table 3). Instead, when the *Q* ratio is decreased to 0.5, the same reaction shows a conversion of only 12% after 13 h. Methyl mandelate is the sole observed product in both cases.

In light of the amphoteric properties of NaY, the adsorption of carboxylic acids possibly occurs via either interactions with Na^+ cations (similarly to DMC, Scheme 9) or H-bonds with the oxygen atoms of the aluminosilicate structure (Scheme 12, a, b).[22]

SCHEME 12. Possible Modes of Adsorption of Carboxylic Acids on NaY



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(22) Based upon spectroscopic investigations, refs 9 and 11 detail the adsorption pattern of phenols and amines over NaY and NaX faujasites. Since no data are available for carboxylic acids, Scheme 12 is only a reasonable hypothesis. For clarity, the interactions of OH substituents of acids **3**−**5** with NaY (see Scheme 9) are omitted.

The tuning of the reaction temperature may affect both modes (a and b) of adsorption. Accordingly, tetrahedral or S_N2-type ($B_{Al}2$) or both mechanisms account for the esterification process.

Whatever the mechanism, aromatic and aliphatic OH substituents of acids **3**−**5** are substantially preserved. Such a high chemoselectivity in the synthesis of esters with DMC has been reported only in the preparation of methyl salicylate over protonic zeolites (Hβ and HZSM5).[23]

The unusual behavior observed for tropic acid **19** (whose alcoholic group undergoes a rapid dehydration, Scheme 7) can presently not be explained.

Table 3 also shows that a dramatic drop of chemoselectivity occurs when K_2CO_3 is the catalyst. In addition to the esterification of acid functions of compounds **3**−**5**, the methylation of aromatic and aliphatic OH substituents and the transesterification of DMC with alcoholic groups (entries 2, 4, and 6, Table 3) take place through $B_{Al}2$ and $B_{Ac}2$ mechanisms, respectively.[1] Under basic conditions, solvation phenomena can also play a role on the overall selectivity. For instance, the reaction of mandelic acid with MeI in a suspension of $NaHCO_3$/DMF is claimed to produce the methyl ester **4** in a 85% yield,[19b] whereas only the formation of (*R*)-2-methoxymandelic acid [(*R*)-PhCH(OMe)CO_2H] is reported when (*R*)-mandelic acid reacts with dimethyl sulfate in an aqueous alkaline (NaOH) solution.[24] Apparently, the two competitive esterification and O-methylation processes can be mainly discriminated by the reaction medium.

Conclusions

The combination of dimethyl carbonate and NaY faujasite makes it possible to set up methylation and esterification processes of bifunctional substrates such as mercaptophenols **1a,b**, mercaptobenzoic acids **2a,b**, and OH-substituted carboxylic acids **3**−**5**.

Under the investigated conditions, the comparison between K_2CO_3 (a typical basic catalyst for DMC-mediated reactions) and NaY faujasite shows that the zeolite is always less active than the base. However, NaY is by far superior for chemoselectivity: at 150 °C, mercaptobenzoic acids undergo S-methylation reactions without affecting the acid groups, whereas the increase of the temperature (165 °C) allows the exclusive esterification of hydroxybenzoic acids (*ortho* and *para* isomers), mandelic acid, and phenyllactic acid, their aromatic and aliphatic OH substituents being fully preserved from methylation and/or methoxycarbonylation side reactions. Typical selectivities for such processes are in the range of 90−100%. On the contrary, in the presence of K_2CO_3, competitive reactions of O- and S-methylation, esterification, and O-methoxycarboylation take place simultaneously.

K_2CO_3 and NaY allow a comparable selectivity only in the case of mercaptophenols, where hydroxythioanisoles are the only products in yields of ≥90%.

The amphoteric nature of NaY suggests that two major points should account for such results: (i) the electrophilic activation of DMC over NaY and (ii) a possible nucleophilic activation of reagents **1**−**5** that may take place through H-bonds with basic oxygen atoms of the framework of the aluminosilicate. However, the data gathered so far do not allow further substantiation of these effects or determination of whether the action of the zeolite is due only to its acid−base properties or if a shape-selectivity operates as well.

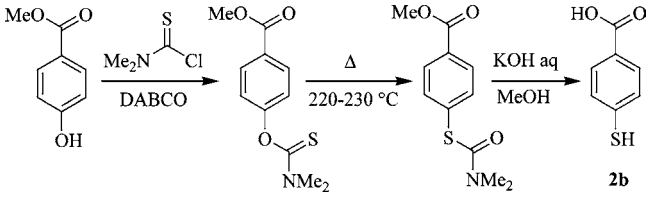
The green features of the reported protocol should also be mentioned: (i) a nontoxic compound (DMC) is used as both a reagent and a solvent, (ii) an eco-safe solid (NaY) is involved, and (iii) thanks to the high chemoselectivity, derivatization sequences can be avoided. Finally, although the zeolite must be used in a relatively high amount (weight ratios of NaY:substrate up to 3), it can be easily separated by filtration, reactivated, and recycled without any loss of activity and/or selectivity.

Experimental Section

Compounds **1a,b**, **2a**, **3a,b**, **4**, and **5** and DMC were ACS grade and were employed without further purification. The zeolite NaY was from Aldrich (no. 334448), and before each reaction it was dried under vacuum (65 °C; 8 mbar) overnight. GLC and GC−MS (70 eV) analyses were run using HP5 and HP5/MS capillary columns (30 m), respectively. ^{1}H NMR spectra were recorded on a 300 MHz spectrometer, using $CDCl_3$ or CD_3OD as solvents.

Compound **2b** (4-mercaptobenzoic acid) was not commercially available; it was prepared according to reported procedures (Scheme 13).[25−27] Starting from methyl 4-hydroxybenzoate (5.2 g, 34.2 mmol), after three steps, compound **2b** was isolated as a pale yellow solid (51%, 2.7 g, 17.4 mmol). Spectroscopic and physical properties were in agreement with literature data: mp 218 (lit.[20] 222 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 1H, SH), 7.32 (d, J = 8.5 Hz, 2H, Ar), 7.96 (d, J = 8.4 Hz, 2H, Ar). GC−MS *m*/*z*: 154 (M^+, 100%), 137 ($[M - OH]^+$, 60), 109 ($[M - CO_2H]^+$, 36), 108 (10), 65 (19), 65 (19), 45 (12).

SCHEME 13. Synthesis of 4-Mercaptobenzoic Acid 2b



Reactions Carried Out in Autoclave. General Procedure. (Tables 1−3) A stainless steel autoclave (150 mL internal volume) was charged with a solution (5×10^{-2} M; 30 mL) of the chosen substrate (**1a,b**, **2a,b**, **3**−**5**, **11**, and **19**; 1.5 mmol), dimethyl carbonate (0.36 mol), and NaY (NaY:substrate in a 0.5−4 weight ratio; see Tables 1−3 for details). At room temperature and before the reaction, air was removed by a purging valve with a N_2 stream. The autoclave was then heated by an oil-circulating jacket, while the mixture was kept under magnetic stirring throughout the reaction. A thermocouple fixed onto the autoclave head checked the temperature (150−165 °C). After different time intervals (13−24 h), the autoclave was cooled to room temperature, purged from CO_2, and finally opened. The reaction mixture was analyzed by GC and GC−MS.

The same procedure was also used for reactions carried out in the presence of K_2CO_3. In these cases (entries 6 and 11, Table 1; entries 3−4, Table 2; entries 2, 4, and 6, Table 3), the temperature was set to 130 °C (Tables 1 and 2) and to 150 °C (Table 3), and the molar ratio K_2CO_3:substrate was in the range of 0.2−2.

All products **6a,b**, **9a,b**, **13a,b**, **14**, **15**, and **20** were simply isolated by filtration of the zeolite and removal of DMC under vacuum (35 °C/250 mm). Compounds **6b**, **9a,b**, **12**, and **13b** were

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further purified by FCC on silica gel F60 (eluant: petroleum ether/diethyl ether 4:1 v/v).

Spectroscopic and physical properties were in agreement with those reported in the literature. 2-Hydroxythioanisole **6a**: pale-yellow liquid [lit.[28] bp 81−82 °C/0.5 mm]. 4-Hydroxythioanisole **6b**: mp 83−85 °C (yellow solid) [lit.[28] mp 84−85 °C]. 2-Methylthiobenzoic acid **9a***:* mp 165−167 °C (yellow solid) [lit.[29] mp 168−169 °C]. 4-Methylthiobenzoic acid **9b***:* mp 190−191 °C (white solid) [lit.[30] mp 187−190 °C]. 2-Methylthiobenzyl alcohol **12***:* pale yellow liquid [lit.[31] bp 105−110 °C/0.05 Torr]. Methyl 2-hydroxybenzoate **13a***:* pale yellow oil [lit.[32] bp 40−50 °C/3 mm]. Methyl 4-hydroxybenzoate **13b***:* mp 124−126 °C (white solid) [lit.[32−33] mp 124−125 °C]. Methyl mandelate **14**: mp 52−54 °C (yellow solid) [lit.[34] bp 118−9 °C/8 mm]. Methyl phenyllactate **15**: mp 27−29 °C (pale yellow solid) [lit.[35] mp 33 °C]. Methyl 2-phenylpropenoate **20**: yellow oil [lit.[36] colorless oil].

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Supporting Information Available: ^{1}H NMR and GC−MS spectra for compounds **6a,b**, **9a,b**, **13a,b**, **14**, **15**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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