JOC Note

Selective N,N-Dibenzylation of Primary Aliphatic Amines with Dibenzyl Carbonate in the Presence of Phosphonium Salts

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Abstract: In the presence of catalytic amounts of tetraalkylphosphonium salts and under solventless conditions, primary aliphatic amines (RNH_2: R = $PhCH_2$, $Ph(CH_2)_2$, n-decyl, and 1-naphthylmethyl) are efficiently N-benzylated to the corresponding $RN(CH_2Ph)_2$, using dibenzyl carbonate as the benzylating reagent. Compared to the reaction run without salt, where the competitive formation of the benzyl carbamate is favored, the phosphonium salt promotes high selectivity toward the benzylated amine and an increase of the reaction rate as well. However, in a single case explored for an amino acidic compound, namely 4-(aminomethyl)benzoic acid [4-(NH_2CH_2)$C_6H_4CO_2H$], both N,N-dibenzylation and esterification of the acid group were observed. Analysis of the IR vibrational modes of benzylamine in the presence of tetrabutylphosphonium bromide supports the hypothesis that this enhanced selectivity may be due to an acid–base interaction between the salt and the amine, which increases the steric bulk of the amine and favors attack of the nucleophile on the less hindered alkyl terminus of dibenzyl carbonate.

The benzylation reaction is widely used in organic synthesis, most often as a protection protocol.[1] The reaction is frequently carried out with benzyl halides, which although efficient for a number of N-, O-, and S-nucleophiles,[2] pose concerns because of their toxicity/carcinogenicity and/or lachrymatory properties. To develop *green* methodologies with a reduced impact on health and environment, dibenzyl carbonate ($PhCH_2OCO_2CH_2Ph$, DBnC, **1**) offers a valid alternative as a benzylating reagent. DBnC, in fact, prepared by transesterification of the nontoxic dimethyl carbonate (DMC),[3] is a low-melting and easy-to-handle solid whose reactivity can be summarized as indicated (Scheme 1).[4]

Around room temperature, DBnC reacts exclusively through a $B_{Ac}2$ mechanism and only the carboxybenzylation reaction takes place.[5] At higher temperatures ($T \geq 130$ °C), $B_{Ac}2$ and $B_{Al}2$ mechanisms are competitive, and the outcome depends on the nature of the nucleophile and of the catalyst. For example, in the presence of K_2CO_3 at 180–200 °C, methylene-active compounds ($ArCH_2X$, X = CN, CO_2Bn) react with **1** to give both C-benzyl and C-carboxybenzyl derivatives [$ArCH(Bn)X$ and $ArCH(CO_2$-

Bn)X, respectively, eqs 1 and 2, Scheme 2]; however, because of the reversibility of the $B_{Ac}2$ pathway, the benzylated compound can be obtained as the sole product (eq 3).[3]

The use of stronger nitrogen bases results in a similar competitive alkylation/acylation sequence through a nucleophilic catalysis.[6] This reaction, however, yields ultimately only benzylated derivatives: at 135 °C, indoles and carboxylic acids react with DBnC in the presence of DABCO (or DBU) as a base to give N-benzylindoles and benzyl esters, respectively.[7] It is notable that the same reactions can be dramatically accelerated through the combined use of microwave irradiation and of ionic liquids.[8]

A different situation occurs with zeolite catalysts such as MY faujasites (M = Na, K): at 130–150 °C, DBnC reacts with primary aromatic amines through a direct $B_{Al}2$ pathway, and because of the amphoteric/steric properties of the zeolite, only mono-N-benzylanilines (XC_6H_4NHBn, X = H, p-NO_2, p-Cl) are observed.[9]

In all cases, DBnC-mediated benzylation reactions produce only $PhCH_2OH$ as a coproduct, which is recyclable to the synthesis of DBnC itself.

With the aim of exploring new applications of dibenzyl carbonate as a green alkylating agent, we decided to investigate its reactivity with other N-nucleophiles, particularly with primary aliphatic amines (**2**), and in the presence of tetraalkylphosphonium or 1,3-dialkylimidazolium salts (**3**). These low-melting salts—sometimes referred to as ionic liquids (IL)—represent an alternative class of recyclable environmentally benign reaction media and catalysts:[10] in fact, they possess weak-to-moderate Lewis-acidic properties, high ionic conductivity, negligible vapor pressure, and moderate-to-high thermal stability.[11]

The Reaction of Benzylamine with DBnC. Benzylamine (**2a**) was initially chosen as a model compound. It was made to react with DBnC (the molar ratio **1**/**2a** was of 2.1) at 145–170 °C, in the presence of the following salts: hexadecyltributylphosphonium bromide (**3a**); tetrabutylphosphonium bromide (**3b**), ethyltriphenyl phosphonium iodide (**3c**), cetylpyridiunium chloride (**3d**), and 1-butyl-3-methylimidazolium tetrafluoroborate (**3e**). Compounds **3a**–**e** were added in the range of 0.05–0.5 molar equiv with respect to **2a**. The reaction of **2a** with DBnC was also run without added salts. Results are reported in Table 1.

Without added salt (entry 1), the conversion of the substrate reaches 76 and 93%, after 5 and 3 h at 145 °C and at 170 °C, respectively. In both cases, along with the formation of dibenzyl- and tribenzylamine (compounds

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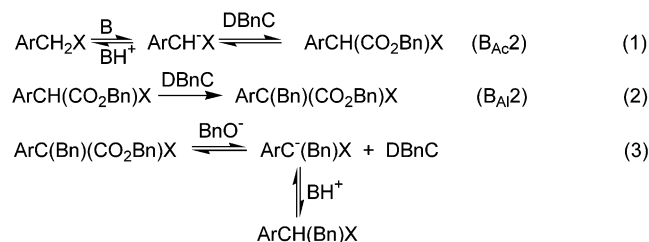**SCHEME 1. Synthesis and Reactivity of DBnC**[a]
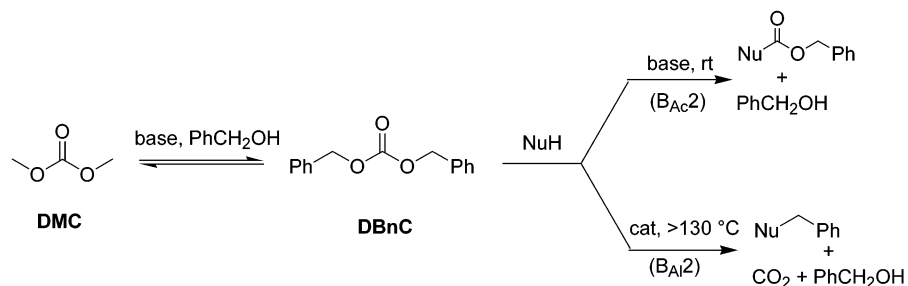
[a] NuH: generic nucleophile.

SCHEME 2. Mono-C-benzylation of Active Methylenes with DBnC and K_2CO_3

$$ArCH_2X \underset{BH^+}{\overset{B}{\rightleftharpoons}} ArCH^-X \overset{DBnC}{\rightleftharpoons} ArCH(CO_2Bn)X \quad (B_{Ac}2) \quad (1)$$

$$ArCH(CO_2Bn)X \overset{DBnC}{\longrightarrow} ArC(Bn)(CO_2Bn)X \quad (B_{Al}2) \quad (2)$$

$$ArC(Bn)(CO_2Bn)X \overset{BnO^-}{\rightleftharpoons} ArC^-(Bn)X + DBnC \quad (3)$$

$$\Big\updownarrow BH^+$$

$$ArCH(Bn)X$$

TABLE 1. Reaction of Benzylamine (2a) with DBnC (1) in the Presence of Salts (3)

entry	added salt	molar ratio (2a:1:3)	T (°C)	t (h)	conv (%)	products (%, GC)[a] 4a	5a	6a	Y^b (5a, %)
1	none	1:2	145	5	76	21	5	45	
			170	3	93	22	29	33	
2a	3a:	1:2:0.05	170	2	100	19	58	13	
2b	C₁₆H₃₃-			4	100	13	64	14	
3	PBu₃Br	1:2:0.1	170	2	100	3	81	9	80[c]
4		1:2:0.21	170	1	100	11	75	7	
				1.75	100	1	85	6	81[c]
5		1:2:0.3	170	1	100		86	9	
6	3b:	1:2:0.3	170	2	100	<1	80	10	
7	Bu₄PBr	1:2:0.5	170	0.75	100	1	82	7	82[c] (78[d])
8	3c: Ph₃PEtI	1:2:0.26	170	1.75	100	5	80	7	79[c]
9	3d:	1:2:0.3	145	2	100	31	34	28	
10	CetyPy[e]		170	2	100	5	58	18[f]	
11	3e: BmImBF₄	1:2:0.5	145	3.5	100	28	39	25	

[a] **4a**: dibenzylamine; **5a**: tribenzylamine; **6a**: benzyl *N*-benzylcarbamate (PhCH₂NHCO₂CH₂Ph); [b] Y: isolated yield of tribenzylamine. [c] Product purified by flash chromatography. [d] Product purified by recrystallization. [e] CetyPy: cetylpyridinium chloride monohydrate. [f] Byproducts (10%).

4a and **5a**), sizable amounts (33−45%) of benzyl *N*-benzylphenylcarbamate (**6a**) are observed. The overall alkylation to carbamation selectivity ($S_{A/C}$) does not exceed 61%.[12]

The presence of a phosphonium salt has a dramatic influence on the reaction rate and most importantly, on the reaction selectivity. At 170 °C, when hexadecyltributylphosphonium bromide (**3a**) is used—even in a very low amount (molar ratio **3a/2a** = 0.05; entry 2a)—the conversion is quantitative after only 2 h, and the alkylation reaction takes over, yielding tribenzylamine as the primary product (58%). The $S_{A/C}$ ratio is enhanced to 86%.

The catalytic effect is well evident for both compounds **3a** and **3b**. For example, as the **3a:2a** molar ratio is increased from 0.05 to 0.3, the time for the complete

conversion of benzylamine decreases from 4 to 1 h (compare entries 2−5). A similar behavior is observed in the experiments run with tetrabutylphosphonium bromide (**3b**) (entries 6−7). It should be noted, however, that the larger amount of salts **3a**,**b** produces only modest variation of the alkylation-to-carbamation selectivity, from 86 to a maximum of 92% (entries 2a and 4).

Also, ethyltriphenylphosphonium iodide (**3c**) is effective for the reaction of benzylamine and DBnC: at 170 °C, tribenzylamine is obtained in 80% GC-yield with only 7% of the carbamate **6a** (entry 8).

In all cases, the use of compounds **3a**−**c** allows isolated yields of the wanted product **5a** in the range of 79−82%.

Ammonium as well as imidazolium salts do not show the satisfactory performance of the phosphonium compounds. When cetylpiridinium chloride and 1-butyl-3-methylimidazolium tetrafluoroborate are employed, both the reaction rate (in relation to the amount of the used salt) and, mostly, the selectivity ratio $S_{A/C}$ (not over 77%, entry 10) drop with respect to **3a**−**c** (compare entries 2−8 and 9−11). Under the same conditions of entry 10, the use of Aliquat 336 (methyltricaprylammonium chloride)—not reported in Table 1—becomes impracticable because the salt decomposes during the reaction and a complex mixture of products forms.

Reaction of Primary Aliphatic Amines with DBnC. A second set of experiments was undertaken to examine the reactivity of different primary aliphatic amines. At 170 °C, phenethyl-, *n*-decyl-, and 1-naphthylmethylamines (**2b**−**d**, respectively) and 4-(aminomethyl)benzoic acid (**2e**) were made to react with DBnC in the presence of tetrabutylphosphonium bromide (**3b**) (the molar ratio **2/1/3b** was of 1:2.1:0.25).[13] Results are reported in Table 2.

Data show that under the investigated conditions amines **2b**−**d** react quantitatively with DBnC to afford the corresponding *N,N*-dibenzyl derivatives (**5b**−**d**) in comparable times (at 100−150 °C) and with isolated yields in the range of 74−86%. Moreover, the selectivity $S_{A/C}$ is always very high (86−100%), especially in the case of compounds **2d** whose reaction, perhaps due to steric reasons, does not show the formation of the corresponding carbamate at all (entry 3).

In the case of compound **2e**, benzyl 4-(*N,N*-dibenzylaminomethyl)benzoate (**5e**) is obtained in a 85% isolated

(12) $S_{A/C}$ is defined as the ratio: $([4a] + [5a])/([4a] + [5a] + [6a]) \times 100$.

(13) Under the conditions used for amines **2a**−**d**, compound **2e** was not completely soluble. A higher amount of DBnC was used: the molar ratio **2e/1/3b** was 1:3.5:0.25.
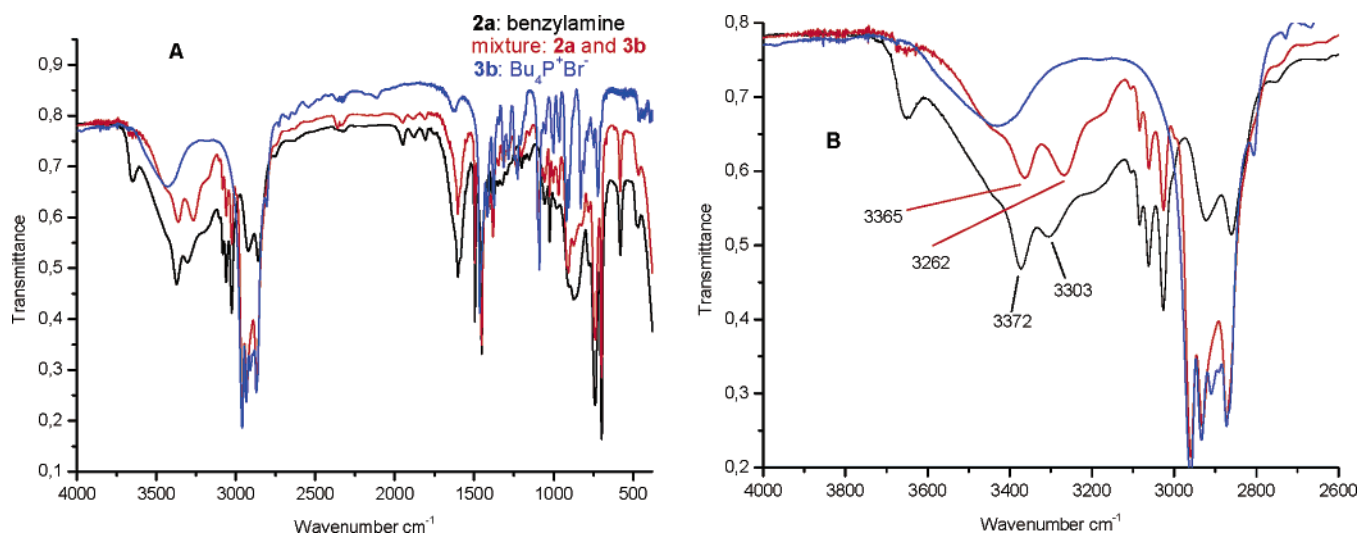
FIGURE 1. (A) IR spectra of pure benzylamine (**2a**, black), pure tetrabutylphosphonium bromide (**3b**, blue), and a mixture of **2a** and **3b** (red), recorded at room temperature. (B) enlargement of Figure 1A between 2600 and 4000 cm^{-1}.

TABLE 2. Reaction of Aliphatic Amines (2b−d) with DBnC (1) in the Presence of Bu₄PBr (3b)[a]

entry	Substrate, RNH₂ R	t / min	Conv. 'n (%)	Products RN(CH₂Ph)₂	RNHCO₂CH₂Ph	Y [b] (%)
1	**2b**: Ph(CH₂)₂	100	100	**5b**: 86	**6b**: 7	86[c] (88[d])
2	**2c**: n-C₁₀H₂₁	150	100	**5c**: 81	**6c**: 13	74[c] (83[d])
3	**2d**: (naphthalene-CH₂)	100	100	**5d**: 95	-	82 [c]
4	**2e**: (benzene with CH₂ and CO₂H)	120	100	(CH₂N(CH₂Ph)₂ / CO₂CH₂Ph benzene) **5e**	nd [e]	85 [c]

[a] All reactions were performed at 170 °C and at atmospheric pressure: the molar ratio **2/1/3b** was of 1:2:0.25. [b] Y: isolated yield of *N,N*-dibenzylated amine **5**. [c] Product purified by flash chromatography; [d] Product purified by distillation. [e] nd: not determined.

SCHEME 3. Reaction of Amines with Dimethyl Carbonate in Ionic Liquids

$$RR`NH + MeOCO_2Me \xrightarrow{\text{Ionic Liquid}} RR`NCO_2Me + MeOH$$
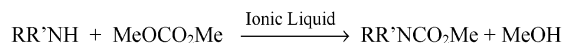
yield (entry 4). The simultaneous esterification of the acid group (either with DBnC or the coproduct PhCH₂OH) is reasonably catalyzed by the salt **3b**:[14] this reaction could not be avoided even when DBnC was used in less than 2 equiv with respect to the reagent **2e**.

It should be noted here that these results are distinctly different from those reported for the similar reaction of aliphatic amines with dimethyl carbonate in the presence of ionic liquids: in that case in fact, working at 170 °C in a sealed vessel (autoclave), only traces of methylation products are observed and methyl urethanes are formed with up to 99% selectivity (Scheme 3).[15]

Such a striking difference is most likely due to the presence of small amounts of CO₂—formed by the competitive methylation reaction and confined in the auto-

clave—which is known to catalyze carbamate formation even in trace amounts.[16] This should also be helped by the high solubility of CO_2 in ionic liquids.[17] On the contrary, when reactions are performed in an open vessel (as for the case of DBnC), carbon dioxide can easily escape from the mixture so that alkylation takes place almost exclusively.

Possible Role of Phosphonium Salts. In the reaction of primary aliphatic amines with DBnC, data of Tables 1 and 2 showed that the presence of a catalytic amount of an onium salt, in particular of a phosphonium type, had a 2-fold effect: (i) it dramatically improved the rate and (ii) it favored a $B_{Al}2$ mechanism. These observations implied that the effect of the salt had to involve some kind of activation/interaction with the reagents **1** and **2**. To investigate this, IR spectra of pure compounds **1**, **2a**, and **3b** and of mixture thereof were recorded at both ambient temperature and at 150 °C. Results are reported in Figure 1.

The analysis of the N−H vibrational modes of benzylamine shows a relevant feature. The pure amine displays the two expected bands of asymmetrical and symmetrical stretching modes at 3372 and 3303 cm^{-1}, respectively (Figure 1, black curves), the latter being much less intense.[18] Instead, the IR spectrum of the mixture of benzylamine and the salt **3b** (red curve) shows that the weaker band (at 3303 cm^{-1}) of the pure compound is no longer present, and a new absorption peak appears at 3262 cm^{-1}. Interestingly, the two bands at 3365 and 3262 cm^{-1} possess the same intensity.

The evident shift to the right of a N−H stretching mode of the amine, which is visible at both ambient temperature and at 150 °C (Figures 1B and 2, respectively),[19] reflects a possible acid−base interaction between the amine and the phosphonium salt (Scheme 4).

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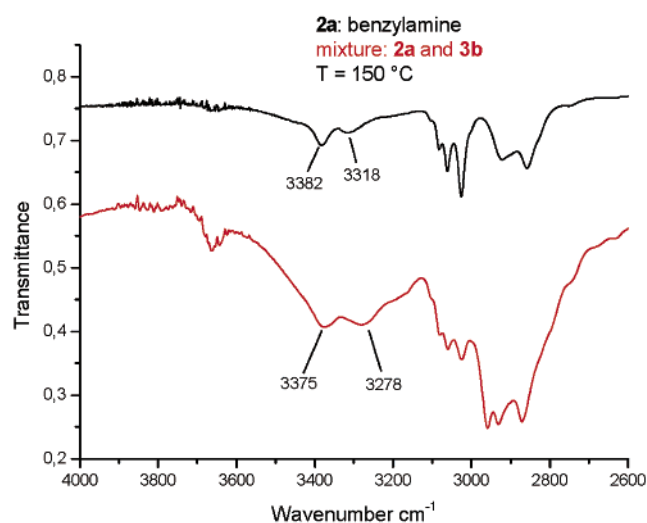(15) Siam, T.; Guo, S.; Shi, F.; Deng, Y. *Tetrahedron Lett.* **2002**, *43*, 8145−47.

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FIGURE 2. IR spectra—enlarged between 2600 and 4000 cm^{-1}—of pure benzylamine (**2a**, black) and a mixture of **2a** and **3b** (red), recorded at 150 °C.

SCHEME 4.   Interactions between the NH$_2$ Group of Benzylamine and a Tetraalkylphosphonium Bromide[a]
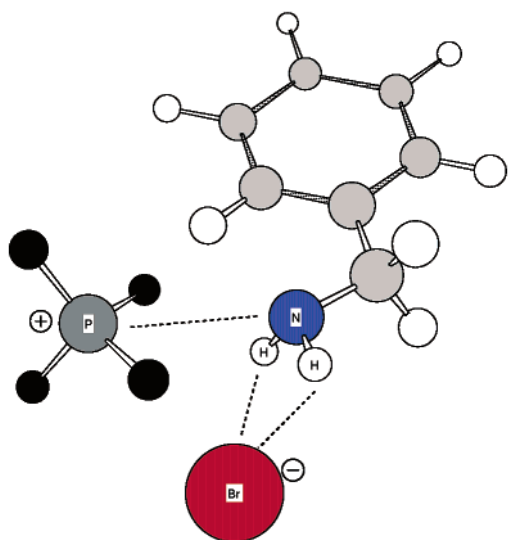
[a] ● : alkyl substituent.

The increased steric hindrance around the NH$_2$ group would plausibly facilitate the attack of the nucleophile on the alkyl rather than the carbonyl terminus of the organic carbonate **1**. The high reaction selectivity (S$_{A/C}$) could be explained accordingly. On the same basis however, a clear reason for the enhancement of the reaction rate cannot be presently accounted for.

It is noteworthy that a deformation of the OH stretching mode of phenol has also been reported in the IR analysis of a mixture of phenol and *n*-Bu$_4$N$^+$Br$^-$.[20]

By contrast, the IR spectrum—not shown—of the mixture of the carbonate **1** and the salt **3b** is merely the overlap of the IR spectra of the pure compounds, suggesting that the lack of any specific interaction between the two moieties.

The reaction here described is a new and direct methodology for the *N,N*-dibenzylation of primary ali-

phatic amines with dibenzyl carbonate as an alkylating agent. Although the reaction is quite energy intensive, it shows valuable synthetic and environmentally benign features: (i) DBnC allows the replacement of toxic benzyl halides and avoids the use of stoichiometric amount of base, (ii) the reaction takes place under solventless conditions, and (iii) a high alkylation selectivity is observed providing that a phosphonium salt be present as a catalyst. Under these conditions, a preliminary reaction of an amino acidic substrate, indicates that the N-alkylation cannot be discriminated over the esterfication of the acid functionality. IR data suggest that the role of the salt on the reaction outcome is primarily played through an interaction with the amine, while no effects seem to involve the organic carbonate.

Experimental Section

Reactions were carried out with the following procedure: a mixture of the amine (**2a**–**e**, 8.5 mmol) and DBnC (17.9 mmol for **2a**–**d**; 31.4 mmol for **2e**, see ref 13) was loaded in a 10-mL glass reactor (shaped as a test tube) equipped with condenser, a magnetic bar, and a side screw-capped neck for the withdrawal of samples. To this mixture, a salt of onium- or imidazolium-type (**3a**, hexadecyltributylphosphonium bromide; **3b**, tetra-butylphosphonium bromide; **3c**, ethyltriphenyl phosphonium iodide; **3d**, cetylpyridinium chloride; **3e**, 1-butyl-3-methyl-imidazolium tetrafluoroborate) was added (.0.05 to 0.5 molar equiv with respect to **2a**; see Tables 1 and 2). The reactor was then dipped in an oil bath preheated at the desired temperature (145−170 °C), with stirring. At intervals, samples of the reaction mixture were withdrawn and analyzed by GC and GC/MS.

The same procedure was also used for the reaction of **2a** with DBnC in the absence of the onium salt. In all cases, no additional solvents or co-solvents were employed.

Products **5a**–**e** were isolated either by flash-chromatography or recrystallization/distillation, and characterized by GC/MS, ^{1}H NMR, and ^{13}C NMR.

Further details on the reaction methodology, and on the isolation and characterization of products **5a**–**e**, are described in the Supporting Information.

Spectroscopic and physical properties were in agreement with those reported in the literature. **5a**: mp 90−92 °C (white solid) [lit.[21] mp 91−93 °C]. **5b**: colorless liquid [lit.[21] bp 180−185 °C/0.5 mm]. **5c**: colorless liquid [lit.[22] bp 216−217 °C/0.5 mm]. **5d**: mp 64−67 °C (white solid).[22] Product **5e** was a highly viscous oil.

Supporting Information Available: ^{1}H and ^{13}C NMR and GC/MS spectra for *N,N*-dibenzylamines **5a**–**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Probably because of the increase of the temperature, the NH-adsorption maxima of Figure 1B (25 °C: 3365 and 3262 cm^{-1}) are slightly different from the corresponding ones of Figure 2 (150 °C: 3375 and 3278 cm^{-1}).

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