Direct mono-N-alkylation of amines in ionic liquids: chemoselectivity and reactivity†

Cinzia Chiappe* and Daniela Pieraccini

Dipartimento di Chimica Bioorganica e Biofarmacia, via Bonanno 33, 56126 Pisa, Italy

Received 15th November 2002
First published as an Advance Article on the web 25th February 2003

A simple method for the N-alkylation of primary amines was developed using ionic liquids as solvent in order to prepare secondary amines selectively. In ionic liquids overalkylation of the initially produced secondary amines is in general markedly reduced. Various amines, alkyl halides and sulfonates were examined. The observed selectivities between mono- and dialkylation are typically on the order of 9 : 1, or higher. Only in the cases of allyl or benzyl bromides does the reaction give the corresponding tertiary amines exclusively. The relative nucleofugality of chloride, bromide, iodide and tosylate with several primary amines was also evaluated, as well as the effect of caesium hydroxide.

Introduction

Amines and their derivatives are important functionalities in various natural products and unnatural synthetic targets. Because of their biological properties,[1] the synthesis of secondary amines has long been of interest and general methods for their preparation include direct N-alkylation,[2] amide reduction,[3] or reductive amination.[4] Although these methods are quite reliable, the possibility to control the concomitant overalkylations, when amine is employed as the limiting substrate, often reduces the application of these procedures. Direct N-alkylation is therefore generally used to convert primary and secondary amines to quaternary ammonium salts, although recently a novel method, using caesium bases in DMF, for the mono-N-alkylation of primary amines has been reported.[5] Room temperature ionic liquids (IL) are emerging as alternative recyclable, environmentally benign reaction media for various chemical transformations, due to their unique physical and chemical properties.[6] In continuation of our effort to explore new applications of ILs and in order to obtain information about the correlation between the physical properties of these solvents and the ability to affect reactivity, we have investigated the direct N-alkylation of amines in ionic liquids.

Cinzia Chippe graduated in Pharmaceutical Sciences in 1985 and obtained her Ph.D. degree in Chemical Sciences in 1989. In 1992 she joined the Department of "Chimica Bioorganica e Biofarmacia" at the University of Pisa where she is currently Full Professor of Organic Chemistry. Her research interests include the physical organic chemistry of electrophilic addition reactions, reactive intermediates, bioorganic chemistry and biocatalysis, and development of stereoselective biotransformations.

† This work was presented at the Green Solvents for Catalysis Meeting, held in Bruschal, Germany, 13–16 October 2002.

Here we present a highly efficient method for the synthesis of secondary amines from alkyl tosylates or alkyl halides by a nucleophilic substitution reaction using primary amines in an ionic liquid. 1-Butyl-3-methylimidazolium hexafluorophosphate, [bmim][PF_6], 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide, [bmim][NTf_2], hexylpyridinium bis(trifluoromethylsulfonyl)imide, [hpyr][Tf_2N], and 1-butyl-2,3-dimethylimidazolium hexafluorophosphate, [bdmim][PF_6] have been used as solvents. In this method the ionic liquid plays an important role in enhancing reactivity as well as reducing overalkylation.

Results and discussion

To establish the potential of ionic liquids as solvents for direct N-alkylation of amines we began our investigation by screening a variety of different primary and secondary alkyl halides with benzylamine and 2-phenylethylamine. The reactions were carried out in [bmim][PF_6], at the temperatures reported in Table 1 and 2, under stirring.

Furthermore, since caesium hydroxide was found[5] to be the most successful base to increase chemoselectivity in molecular solvents, the reactions were also carried out in the presence of an equivalent of this base with the aim of improving the yield in the mono-N-alkylation product. Finally, CsOH in the presence of activated powdered molecular sieves (4 Å) was also probed since, at least in molecular solvents, the inclusion of a drying agent accelerates alkylation as well as improves the selectivity.

Green Context

Ionic liquids continue to be the focus of a large volume of research work. Their ultra-low volatility provides an obvious advantage over volatile organic solvents and their almost infinite flexibility in structure and anionic character enables their use in a wide range of reactions. Here they are applied as reaction media for the very selective mono-N-alkylation of amines. Overalkylation products are minimised. Mild reaction conditions enable the chemistry to be applied to complex subtrates with other labile functionalities. ***JHC***

DOI: 10.1039/b211340f

Table 1 N-Alkylation of primary amines with variuos primary halogenides and tosylates at room temperature in [bmim][PF_6]

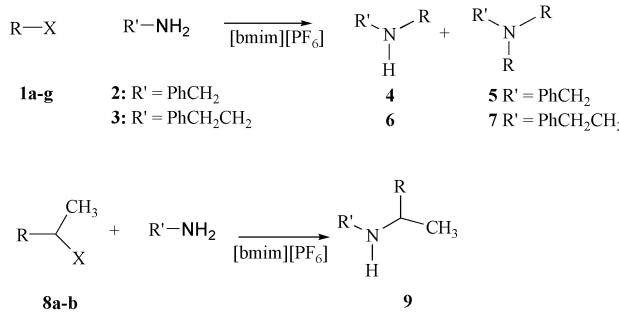
Substrate		Amine	$CsOH·H_2O$	Time/h	Conversion[a] (%)	Product ratio **4**	**5**
$C_8H_{17}Cl$	**1a**	**2**	1 eq	24	0	n.d.	
$C_8H_{17}Br$	**1b**	**2**	—	24	49	100	0
$C_8H_{17}Br$	**1b**	**2**	1 eq	18	55	100	0
$C_8H_{17}Br$	**1b**	**2**	1 eq	24	70	100	0
$C_8H_{17}Br$	**1b**	**2**	1 eq + 4 Å MS	24	100	100	0
$C_8H_{17}I$	**1c**	**2**	—	18	40	87	13
$C_8H_{17}I$	**1c**	**2**	1 eq	18	50	80	20
$C_8H_{17}I$	**1c**	**2**	1 eq	24	60	84	16
$C_8H_{17}OTs$	**1d**	**2**	—	24	87	100	0
$C_8H_{17}OTs$	**1d**	**2**	1 eq	18	50	100	0
$C_8H_{17}OTs$	**1d**	**2**	1eq	24	100	100	0
$(CH_3)_3CCH_2Br$	**1e**	**2**	1 eq	24	0	n.d.	
$PhCH_2Br$	**1f**	**2**	—	4	100	0	100
$PhCH_2Br$	**1f**	**2**	0.1 eq	1	100	0	100
CH_2=$CHCH_2Br$	**1g**	**2**	—	4	100	0	100
CH_2=$CHCH_2Br$	**1g**	**2**	0.1 eq	1	100	0	100
						6	**7**
$C_8H_{17}Cl$	**1a**	**3**	—	24	0	n.d.	
$C_8H_{17}Cl$	**1a**	**3**	1 eq	24	0	n.d.	
$C_8H_{17}Br$	**1b**	**3**	—	24	40	88	12
$C_8H_{17}Br$	**1b**	**3**	1 eq	24	70	81	19
$C_8H_{17}I$	**1c**	**3**	—	18	48	82	18
$C_8H_{17}I$	**1c**	**3**	1 eq	24	64	66	34
$C_8H_{17}OTs$	**1d**	**3**	—	24	57	80	20
$C_8H_{17}OTs$	**1d**	**3**	1 eq	24	70	75	25
$PhCH_2Br$	**1f**	**3**	—	4	100	44	56
$PhCH_2Br$	**1f**	**3**	1 eq	1	100	27	73
CH_2=$CHCH_2Br$	**1g**	**3**	—	4	100	5	95
CH_2=$CHCH_2Br$	**1g**	**3**	1 eq	1	100	19	81

[a] The extraction yield was always > 85–90%. The remaining products were identified as the unreacted reagents. n.d. = not detected.

Table 2 N-Alkylation of amine **2** with secondary bromides and tosylates in [bmim][PF_6]

Substrate		$CsOH·H_2O$	Time/h	*T*/°C	Product **9** Yield (%)[a]
sec-$C_7H_{15}Br$	**8a**	1 eq	18	25	0
sec-$C_7H_{15}Br$	**8a**	1 eq	24	45	48
sec-$C_8H_{17}OTs$	**8b**	—	24	45	43
sec-$C_8H_{17}OTs$	**8b**	1 eq	18	25	50
sec-$C_8H_{17}OTs$	**8b**	1 eq	24	45	> 95

[a] The remaining products were identified as the unreacted reagents.



Reactions were typically carried out by addition of the alkyl halide or tosylate (0.7 M), under stirring, to the ionic liquid containing the amine (0.6 M). After 18–24 h at room temperature, or at 45 °C, the reactions were stopped by addition of a aqueous solution of $NaHCO_3$ followed by extraction of the products with Et_2O (extraction yields always > 85–90%). The reaction mixtures were analyzed by NMR and the products identified on the basis of the ^1H and ^{13}C NMR spectra. Generally, the residue IL was washed with water, dried and reused at least two times without any significant modification in yields and selectivity.

As shown by the data reported in Table 1 and 2 the conversion, *i.e.* the reaction rate, and the selectivity depend both on the nature of the reagents and on the type of leaving group, while the presence of caesium hydroxide, as well as of molecular sieves, only affects the reaction rate. Activate halides (allyl bromide, **1g**, and benzyl bromide, **1f**) react in relatively short times with benzylamine, a reactive amine, to give exclusively the tertiary amine **5**. 2-Phenylethylamine gives with the same bromides mixtures of tertiary and secondary amines. The addition of CsOH, even in a catalytic amount,[7] is not able to improve the selectivity. Primary alkyl chloride **1a** practically does not react with benzylamine or 2-phenylethylamine, also in the presence of CsOH. At variance, the primary bromide, iodide and tosylate, **1b**–**d**, undergo substitution easily to provide, after 24 h at room temperature, the expected secondary amine with high selectivity (ranging from 82 to 100%). The observed selectivity is similar (sometimes higher) to that recently reported for the reaction of primary and secondary bromides with 2-phenylethylamine or benzylamine in aprotic solvents (DMF, DMSO and DMAC) in the presence of CsOH, where the ratio between mono- and di-N-alkylation products ranges from 6:1 to 9:1.

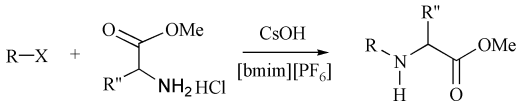
The reactivity scale of the leaving groups in [bmim][PF_6] is therefore the following: $TsO^- > I^- \cong Br^- >> Cl^-$. The addition of CsOH decreases the reaction times reducing the importance of the leaving group; similar conversions were obtained under comparable conditions.

Interestingly, the secondary, more demanding, bromide and tosylate **8a** and **8b** give exclusively the mono-N-alkylation product (Table 2). In this case, also with the more reactive tosylate, and in the presence of CsOH, slightly higher temperatures (around 45 °C) are necessary to obtain complete conversion in 24 h. These data suggest that the introduction of

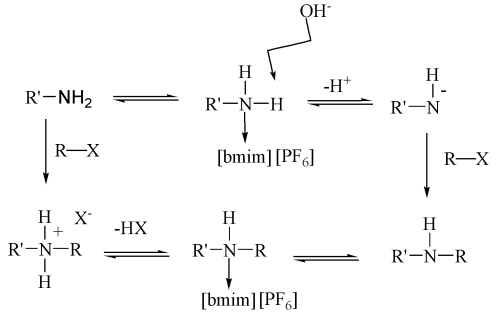
steric elements suppresses overalkylation. It is finally worthy of note that, as expected for a nucleophilic substitution, no reaction was observed when neopentyl bromide was used as substrate.

Based on these results, we maintain that the simple procedure, without addition of CsOH, is the most clean to obtain mono-N-alkylation products. Indeed caesium hydroxide is not able to affect chemoselectivity and the 2-H proton of the imidazolium cation is sufficiently acidic that in the presence of a strong base it might be deprotonated to form a carbene.

Encouraged by the generally good performance of this simple method, *i.e.* that only using an liquid ionic as reaction medium gives mono-N-alkylation products with yields and selectivities comparable to those obtained[5] in DMF, in the presence of caesium salts, the feasibility to use amino acid derivatives as substrates was also investigated. Alanine methyl ester hydrochloride was converted into the corresponding monoalkylated product (46% yield) by reaction with **1f** in [bmim][PF_6], at room temperature, in the presence of two equivalents of CsOH which was necessary in this case to transform the chlorohydrate into the corresponding free base and to increase the reaction rate.



Although, at variance with molecular solvents, only few data about nucleophilic displacement reactions have been reported in ionic liquids,[8] the results obtained in this work further confirm that ionic liquids are suitable solvents for this type of reaction and are able to affect positively the reaction chemoselectivity. Related to this latter feature, it is worthy of note that the product distribution obtained in [bmim][PF_6] seems to indicate that in this medium the reactivity of primary and secondary amines is opposite to that normally observed in molecular solvents. This behaviour may be rationalized, taking into account the explanation given[5] for the effect of CsOH in DMF, on the basis of a possible interaction between the amino group and the imidazolium ring. A stronger affinity of the secondary amine for [bmim][PF_6] over that of primary amine, which may be attributed to the higher basicity, may account for the observed selectivity. The interaction between the primary amine and the imidazolinium cation could give a weakly coordinated complex which, however, increases the acidity of the amine protons. They may become sufficiently acidic to be removed by the hydroxide anion when the reactions are carried out in the presence of CsOH. This feature may explain the shorter reaction times when CsOH was added. The reaction with the halide or tosylate gives the secondary amine, which should be more strongly coordinated to the imidazolium cation. The stronger interaction suppresses further alkylation by reducing the nucleophilicity of the secondary amine, thereby allowing complete transformation of the primary amine. Furthermore, the sterically more hindered complex of the secondary amine should be less prone to undergo proton abstraction by the eventually added base.



In agreement with this hypothesis recent NMR experiments and studies related to the selective transport of amines by using ionic liquids as supported liquid membranes have shown[9,10] a stronger interaction of the secondary amines, compared to primary and tertiary amines, with [bmim][PF_6]. In particular, on the basis of the ^{1}H NMR experiments the interactions of the imidazolium ring with the electron-donating group have been mainly attributed[9] to hydrogen bonding and ring stacking effects. To further investigate the nature of the interaction between amine and ionic liquid, alkyl bromide **1b** was added to benzylamine, **2**, in three different ILs; 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide, [bmim][NTf_2], hexylpyridinium bis(trifluoromethylsulfonyl)imide, [hpyr][Tf_2N], and 1-butyl-2,3-dimethylimidazolium hexafluorophosphate, [bdmim][PF_6]. It has been indeed recently shown[8c] that, for example, halide nucleophilicity depends on the used ionic liquid, being determined by a combination of cation and anion properties. Furthermore, it is well known that the anion structure plays an important role in the nature of the ionic liquids and on their interaction capabilities; the most dominant interaction constants are dipolarity/polarizability, hydrogen bond basicity and dispersion forces, although some ionic liquids also show hydrogen bond acidity.[11] The anion has a great influence on the overall hydrogen bond basicity of ionic liquids, but also affects the hydrogen bond acidity. It is well established[6] that ionic liquids having as the cation the [bmim] structure are able to take part in hydrogen bonding. More in particular, [bmim][Tf_2N] exhibits[11] the highest hydrogen bond acidity, therefore, under our reaction conditions [bmim][Tf_2N] should hydrogen bond more strongly to amines than [bmim][PF_6].[11] On the other hand, the introduction of a methyl group at the C-2 position of the imidazolium ring ([bdmim]) reduces this ability, as well as a reduced ability to undergo hydrogen bonding is generally attributed to pyridinium salts.

The data reported in Table 3 show that, although the natures of the cation and anion of the ionic liquid are able to affect significantly the reaction rate, they only moderately affects the chemoselectivity. In particular, although on going from [bmim][PF_6] to [bdmim][PF_6] the chemoselectivity decreases, in agreement with a possible role of the hydrogen bonding, this effect is very low and it is in contrast with the data related to the same reaction in [hpyr][Tf_2N], showing high chemoselectivity, and in [bmim][Tf_2N]. In this latter ionic liquid we find the lowest ratio between **4** and **5** although [bmim][Tf_2N] should be the more prone among the examined ionic liquids to give hydrogen bonding. Therefore, the data clearly show that the chemoselectivity is not dependent on the hydrogen bond acidity of the ionic liquid alone. Probably, factors and/or interaction(s) different from hydrogen bonding between the secondary amine and the solvent determine the apparently reduced nucleophilicity of the formed secondary amine.

Table 3 N-Alkylation of amine **2** with **1b** in ionic liquids at room temperature

IL	Time/h	Conversion[a] (%)	Product ratio **4**	**5**
[bmim][PF_6]	24	49	100	0
[bmim][Tf_2N]	24	66	94	6
[hpyr][Tf_2N]	24	30	99	1
[bdmim][PF_6]	24	90	96	4

[a] The remaining products were identified as the unreacted reagents.

In conclusion, we have demonstrated the possibility to perform the nucleophilic mono-N-alkylation of primary amines using simply alkyl halides or tosylates in an ionic liquid. The ionic liquid not only promotes N-alkylation but often also reduces or eliminates the formation of overalkylation products. High chemoselectivities involved in amine and amino acid derivative alkylations have been clearly shown. Furthermore,

the mild reaction conditions (room temperature or slightly higher, short reaction times, absence of caesium bases in the reaction medium) allow the application of this procedure even in the presence of labile functionalities. Further studies on the development of this protocol are in progress in our laboratory. Investigations on the nature of the interaction between amines and ionic liquids are also progressing.

Experimental

General remarks

^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC 200 instrument. 1-Bromooctane (Fluka ≥98%), 1-iodooctane (Aldrich ≥98%), 1-chlorooctane (Janssen ≥99%), 1-bromo-2,2-dimethylpropane (Aldrich ≥98%), benzylbromide (Aldrich ≥98%), allylbromide (Aldrich ≥98%), 2-phenylethylamine (Aldrich 99+%), benzylamine (Aldrich ≥98%), caesium hydroxide monohydrate (Fluka), were used as supplied. 1-Butyl-3-methylimidazolium hexafluorophosphate and bis(trifluoromethylsulfonyl)imide, [bmim][PF_6] and [bmim][NTf_2], were prepared following the reported[12] procedures: attention was paid to the elimination of Cl^- present in the solvent as impurity. 1-Butyl-2,3-dimethylimidazolium hexafluorophosphate, [bdmim][PF_6], (Solvent Innovation, 98%) was used as supplied. Recycling of ILs was accomplished by washing with water. The uncoloured recovered ILs were dried, analyzed by NMR and reused at least two times.

Synthesis of [hpyr][Tf_2N]

To a sample of 1-hexylpyridinium chloride (15.85 g, 0.08 mol) in 30 ml of H_2O a solution of lithium bis((trifluoromethyl)sulfonyl)amide (Fluka puriss.) (22.78 g, 0.08 mol) in 30 ml of H_2O was added under stirring. The anion exchange was immediate, leading to the formation of a biphasic system, in which the lower phase was represented by the desired product. The ionic liquid was decanted in a separatory funnel and washed with water until no chloride was detectable. The organic layer was then dried over anhydrous $MgSO_4$, filtered and analyzed by NMR.

^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 0.86 (t, 3H, J = 6.8 Hz, CH_3); 1.31 (br, 6H, 3 CH_2); 1.96 (m, 2H, CH_2); 4.58 (t, 2H, J = 7.5 Hz, N-CH_2); 8.05 (m, 2H, aromatic proton); 8.49 (m, 1H, aromatic proton); 8.83 (m, 2H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, δ/ppm): 13.62 (CH_3); 22.09 (CH_2); 25.41 (CH_2); 30.76 (CH_2); 31.35 (CH_2); 62.43 (N-CH_2); 128.55 (2 CH aromatic); 144.25 (2 CH aromatic); 145.43 (1 CH aromatic).

Synthesis of compound 1d

To a solution of *p*-toluenesulfonyl chloride (5.0 g, 0.027 mol) in 25 ml of dichloromethane, 1-octanol (2.3 g, 0.018 mol) was added. The reaction was performed using a catalytic amount of pyridine (0.5 ml). At the end of the reaction, the pyridinium chloride (visible as long white needles) was removed by filtration and the resulting filtrate was washed with 0.1 M HCl, then with $NaHCO_3$(aq) and finally with water until neutralisation. The organic layer was then dried ($MgSO_4$), filtered and the solvent was removed by distillation at reduced pressure. ^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 0.79 (t, 3H, J = 6.8 Hz, CH_3); 1.14–1.30 (br, 10H, 5 CH_2); 1.55 (m, 2H, CH_2-CH_2O); 2.37 (s, 3H, Ph-CH_3); 3.94 (t, 2H, J = 6.8 Hz, CH_2OTs); 7.26 (m, 2H, aromatic protons); 7.71 (m, 2H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, δ/ppm): 14.00 (CH_3); 21.55 (CH_3); 22.53 (CH_2); 25.25 (CH_2); 28.79 (2 CH_2); 28.97 (CH_2); 31.62 (CH_2); 70.65 (CH_2OSO_2); 127.80 (2 =CH); 129.73 (2 =CH); 133.10 (> C <); 144.57 (> C <).

Synthesis of compound 8b

The procedure was the same as for **1d**. ^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 0.85 (t, 3H, CH_3, J = 6.3 Hz); 1.15 (br, 8H, 4 CH_2); 1.25 (d, 3H, CH_3-CH, J = 6.2 Hz); 1.48–1.57 (m, 2H, CH_2); 2.43 (s, 3H, $PhCH_3$); 4.59 (m, 1H, CHOTs); 7.32 (m, 2H, aromatic protons); 7.79 (m, 2H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, δ/ppm): 13.93 (CH_3); 20.76 (CH_2); 21.48 (CH_3); 22.38 (CH_2); 24.73 (CH_2); 28.70 (CH_2); 31.49 (CH_2); 36.40 (CH_3); 80.58 (CH_2OSO_2); 127.62 (2 =CH); 129.59 (2 =CH); 134.60 (> C <); 144.57 (> C <).

General procedures for N-alkylation in ionic liquids

To a solution of amine (0.6 mmol) in the ionic liquid (1 ml), the required alkyl halide or tosylate (0.7 mmol) was added and the mixture was stirred at room temperature for 24 hours. The reaction mixture was washed with $NaHCO_3$(aq) and then extracted with Et_2O (1 ml × 5). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The solvent was removed by distillation *in vacuo* and the crude mixture was analysed by NMR. The products were identified on the basis of NMR spectra (^{1}H, ^{13}C, DEPT), by comparison with data reported in literature.[5]

General procedures for N-alkylation in ionic liquids using caesium hydroxide

To a solution of amine (0.6 mmol) in [bmim][PF_6] (1.37 g, 1 ml) caesium hydroxide monohydrate (0.6 mmol) was added and the mixture was vigorously stirred for 30 minutes. During this period the suspension became yellow. The alkyl halide or tosylate (0.7 mmol) was then added to the suspension and the reaction was allowed to proceed at the temperature reported in Tables 1 and 2 for 24 hours. The reaction mixture was washed with $NaHCO_3$(aq) and then extracted with Et_2O (1 ml × 5). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The solvent was removed by distillation *in vacuo* and the crude mixture was analysed by NMR.

From amine 2

Dialkylamine 4 (R = C_8H_{17}, R′ = $PhCH_2$). ^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 0.88 (t, 3H, J = 7.0 Hz, CH_3); 1.25 (br, 10H, 5CH_2); 1.47–1.52 (m, 2H, CH_2); 1.68 (s, NH); 2.61 (t, 2H, J = 7.2 Hz, CH_2NH-); 3.78 (s, 2H, $PhCH_2$); 7.24–7.40 (m, 5H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, δ/ppm): 13.94 (CH_3); 22.50 (CH_2); 27.21 (CH_2); 29.13 (CH_2); 29.38 (2CH_2); 31.65 (CH_2); 48.52 (CH_2NH); 53.62 (CH_2NH); 127.39 (2 =CH); 127.92 (=CH); 128.41 (2 =CH); 137.68 (> C <).

Trialkylamine 5 (R = C_8H_{17}, R′ = $PhCH_2$). ^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 0.88 (t, 6H, J = 6.8 Hz, 2CH_3); 1.25 (br, 20H, 10 CH_2); 1.43–1.47 (m, 4H, 2 CH_2); 2.41 (t, 4H, J = 7.2 Hz, CH_2NCH_2); 3.56 (s, 2H, $PhCH_2$); 7.24–7.40 (m, 5H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, δ/ppm): 14.07 (CH_3); 22.65 (CH_2); 27.01 (CH_2); 27.42 (CH_2); 29.32 (CH_2); 29.53 (CH_2); 31.86 (CH_2); 53.79 (CH_2N); 58.63 (CH_2N); 126.49-128.50 (5 =CH aromatic); 140.15 (> C <).

Trialkylamine 5 (R = benzyl, R′ = $PhCH_2$). ^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 3.48 (s, 6H, 3 $PhCH_2$N); 7.11–7.41, (m, 15H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, δ/ppm): 57.86, (NCH_2); 126.86 (=CH); 128.20 (2 =CH); 128.75 (2 =CH); 139.44 (> C <).

Trialkylamine 5 (R = allyl, R′ = $PhCH_2$). ^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 3.09 (d, 4H, J = 6.4 Hz, 2 =$CHCH_2$N); 3.54 (s, 2H, $PhCH_2$N); 5.12 (d, 2H, J = 10.3 Hz,

2 CH_2=); 5.18 (d, 2H, *J* = 17.2 Hz, 2 CH_2=); 5.76–5.95 (ddt, 2H, 2 =CH, *J* = 17.05 Hz, *J* = 10.3 Hz, *J* = 6.4 Hz); 7.17–7.40 (m, 5H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, *δ*/ppm): 56.30 (NCH_2); 57.45 ($PhCH_2$); 117.71 (2 =CH_2); 126.91 (=CH); 128.18 (2 =CH); 128.98 (2 =CH); 135.44 (2 =CH); 138.97 (> C <).

Dialkylamine 9a (R = C_5H_{11}, R′ = $PhCH_2$). ^{1}H NMR ($CDCl_3$, *δ*/ppm relative to TMS): 0.81 (t, 3H, *J* = 6.8 Hz, CH_3); 0.99 (d, 3H, *J* = 6.2 Hz, CH_3); 1.20–1.45 (br, 6H, 3CH_2); 1.73–1.85 (m, 2H, CH_2); 1.78 (s, NH); 2.55 (m, 1H, CHNH); 3.62 (d, 1H, *J* = 12.5 Hz, $PhCH_2$); 3.79 (d, 1H, *J* = 12.5 Hz, $PhCH_2$); 7.18–7.30 (m, 5H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, *δ*/ppm): 13.84 (CH_3); 20.06 (CH_3); 22.34 (CH_2); 27.27 (CH_2); 30.99 (CH_2); 36.82 (CH_2); 51.21 (CH_2N); 51.74 (CHNH); 126.91 (2 =CH); 128.21 (2 =CH); 128.36 (=CH); 139.80 (> C <).

Dialkylamine 9b (R = C_6H_{13}, R′ = $PhCH_2$). ^{1}H NMR ($CDCl_3$, *δ*/ppm relative to TMS): 0.89 (t, 3H, *J* = 6.8 Hz, CH_3); 1.09 (d, 3H, *J* = 6.3 Hz, CH_3); 1.17–1.40 (br, 8H, 4CH_2); 1.55 (m, 2H, CH_2); 2.14 (s, NH); 2.55 (m, 1H, CHNH); 3.75 (d, 1H, *J* = 12.5 Hz, $PhCH_2$); 3.89 (d, 1H, *J* = 12.5 Hz, $PhCH_2$); 7.27–7.82 (m, 5H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, *δ*/ppm): 13.80 (CH_3); 19.92 (CH_3); 22.36 (CH_2); 25.66 (CH_2); 29.23 (CH_2); 31.56 (CH_2); 36.73 (CH_2); 51.04 (CH_2N); 52.20 (CHNH); 126.91 (2 =CH); 128.21 (2 =CH); 128.36 (=CH); 139.80 (> C <).

From amine 3

Dialkylamine 6 (R = C_8H_{17}, R′ = $PhCH_2CH_2$). ^{1}H NMR ($CDCl_3$, *δ*/ppm relative to TMS): 0.80 (t, 3H, *J* = 6.7 Hz, CH_3); 1.18 (br, 10H, 5CH_2); 1.38 (m, 2H, CH_2); 1.94 (s, NH); 2.55, (t, 2H, *J* = 7.4 Hz, NCH_2); 2.65 (m, 2H, $PhCH_2$-); 2.84 (m, 2H, CH_2N); 7.07–7.20 (m, 5H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, *δ*/ppm): 13.84 (CH_3); 22.42 (CH_2); 27.11 (CH_2); 29.02 (CH_2); 29.26 (CH_2); 29.64 (CH_2); 31.60 (CH_2); 35.97 ($PhCH_2$); 49.56 (CH_2NH); 50.86 (CH_2NH); 125.90 (=CH); 128.20 (2 =CH); 128.45 (2 =CH); 139.75 (> C <).

Trialkylamine 7 (R = C_8H_{17}, R′ = $PhCH_2CH_2$). ^{1}H NMR ($CDCl_3$, *δ*/ppm relative to TMS): 0.80 (t, 6H, *J* = 6.8 Hz, 2CH_3); 1.18 (br, 20H, 10 CH_2); 1.38 (m, 4H, 2CH_2); 1.94 (s, NH); 2.45, (m, 4H, 2CH_2); 2.76 (m, 4H, $PhCH_2CH_2$N); 7.07–7.20 (m, 5H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, *δ*/ppm): 13.84 (CH_3); 22.42 (CH_2); 27.11 (CH_2); 29.02 (CH_2); 29.26 (CH_2); 29.64 (CH_2); 31.60 (CH_2); 35.97 ($PhCH_2$); 53.93 (CH_2N); 55.91 (CH_2NH); 125.90 (=CH); 128.20 (2 =CH); 128.45 (2 =CH); 139.75 (> C <).

Dialkylamine 6 (R = allyl, R′ = $PhCH_2CH_2$). ^{1}H NMR ($CDCl_3$, *δ*/ppm relative to TMS): 2.82–2.91 (m, 4H, $PhCH_2CH_2$); 3.27 (d, 2H, *J* = 5.9 Hz, CH_2N); 5.13 (m, 2H, CH_2=); 5.88 (m, 1H, =CH); 7.18–7.31 (m, 5H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, *δ*/ppm): 36.06 ($PhCH_2$); 50.29 (NCH_2); 52.08 (NCH_2); 116.19 (=CH_2); 126.16 (=CH); 128.26 (2 =CH); 128.43 (=CH); 135.51 (2 =CH); 139.80 (> C <).

Trialkylamine 7 (R = allyl, R′ = $PhCH_2CH_2$). ^{1}H NMR ($CDCl_3$, *δ*/ppm relative to TMS): 2.70–2.80 (m, 4H, $PhCH_2CH_2$); 3.17 (d, 2H, *J* = 6.5 Hz, CH_2N); 5.13 (d, 2H, *J* = 10.8 Hz, CH_2=); 5.18 (d, 2H, *J* = 17.2 Hz, CH_2=); 3.79 (d, 1H, *J* = 12.5 Hz, $PhCH_2$); 5.86 (ddt, 2H, *J* = 17.2, 10.8, 6.5 Hz, 2 =CH); 7.18–7.31 (m, 5H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, *δ*/ppm): 33.23 ($PhCH_2$); 55.04 (NCH_2); 56.76 (NCH_2); 117.44 (2 =CH_2); 125.86 (2 =CH); 128.26 (2 =CH); 128.66 (=CH); 135.51 (2 =CH); 140.49 (> C <).

Dialkylamine 6 (R = benzyl, R′ = $PhCH_2CH_2$). ^{1}H NMR ($CDCl_3$, *δ*/ppm relative to TMS): 1.87 (s, NH); 2.60–2.82 (m, 4H, $PhCH_2CH_2$); 3.68 (s, 2H, $PhCH_2$); 7.07–7.49 (m, 10H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, *δ*/ppm): 36.22 ($PhCH_2$); 50.40 (NCH_2); 53.71 (NCH_2); 126.06 (=CH); 126.84 (=CH); 128.07 (=CH); 128.36 (2 =CH); 128.60 (=CH); 139.61 (> C <).

Trialkylamine 7 (R = benzyl, R′ = $PhCH_2CH_2$). ^{1}H NMR ($CDCl_3$, *δ*/ppm relative to TMS): 2.60–2.82 (m, 4H, $PhCH_2CH_2$); 3.53 (s, 4H, $PhCH_2$); 7.07–7.49 (m, 15H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, *δ*/ppm): 33.43 (CH_2); 55.01 (NCH_2); 58.13 (NCH_2); 125.71 (=CH); 126.68; 126.84 (=CH); 128.07 (2 =CH); 128.60 (2 =CH); 128.72 (=CH); 140.06 (> C <).

From alanine methyl ester chlorohydrate

Dialkylamine (R = $PhCH_2$, R′ = $CH(CH_3)COOCH_3$). ^{1}H NMR ($CDCl_3$, *δ*/ppm relative to TMS): 1.14 (d, 3H, CH_3, *J* = 7.10 Hz); 3.39 (q, 1H, CHN, *J* = 7.05 Hz); 3.55 (d, 1H, CH(H)Ph, *J* = 14 Hz); 3.65 (s, 3H, OCH_3); 3.76 (d, 1H, CH(H)Ph, *J* = 14 Hz); 7.13–7.33 (m, 5H, aromatic protons). ^{13}C NMR and DEPT ($CDCl_3$, *δ*/ppm): 16.39 (CH_3); 52.65 (CHN); 55.80 (CH_2N); 57.47 (CH_3O); 126.90–128.23 (aromatic carbons); 139.95 (> C <); 173.88 (OC=O).

Acknowledgement

Financial support for this research was provided by MIUR and Università di Pisa.

References

1 I. S. Blagbrough, S. Carrington and A. J. Geall, *Pharm. Sci.*, 1997, **3**, 223; R. J. Bergeron, Y. Feng, W. R. Weimer, J. S. McManis, H. Dimova, C. Porter, B. Raisler and O. Phanstiel, *J. Med. Chem.*, 1997, **40**, 1475.

2 J. A. O'Meara, N. Gardee, M. Jung, R. N. Ben and T. Durst, *J. Org. Chem.*, 1998, **63**, 3117; F. Valot, F. Fache, R. Jacqot, M. Sagnol and M. Lemaire, *Tetrahedron Lett.*, 1999, **40**, 3689.

3 S. Salomaa, in *The Chemistry of Carbonyl Group*, ed. S. Patai, Wiley, New York, 1966, vol. 1, pp. 177–210.

4 A. K. Szardening, T. S. Burkoth, G. C. Look and D. A. Campbell, *J. Org. Chem.*, 1996, **61**, 6720; T. Rische, B. Kitsos-Rzychon and P. Eibracht, *Tetrahedron Lett.*, 1998, **54**, 2723.

5 R. N. Salvatore, A. S. Nagle and K. W. Jung, *J. Org. Chem.*, 2002, **67**, 674.

6 J. D. Holbrey and K. R. Seddon, *Clean Prod. Process.*, 1999, **1**, 223; M. J. Earle and K. R. Seddon, *Pure Appl. Chem.*, 2000, **72**, 1391; T. Welton, *Chem. Rev.*, 1999, **99**, 2071; P. Wasserscheid and M. Keim, *Angew. Chem., Int. Ed.*, 2000, **39**, 3773; J. Dupont, R. F. de Suaza and P. A. Z. Suarez, *Chem. Rev.*, 2002, **102**, 3667.

7 It has been reported (ref. 5) that, at least in molecular solvents, if more that a catalytic amount of CsOH is used with allyl and benzyl bromide overalkylation becomes more prominent due to the highly reactive nature of these electrophiles.

8 (*a*) C. Wheeler, K. N. West, C. L. Liotta and C. A. Eckert, *Chem. Commun.*, 2001, 887; (*b*) N. L. Lancaster, T. Welton and G. B. Young, *J. Chem. Soc. Perkin Trans. 2*, 2001, 2267; (*c*) N. L. Lancaster, P. A. Salter, T. Welton and G. B. Young, *J. Org. Chem.*, 2002, **67**, 8855; (*d*) D. W. Kim, C. E. Song and D. Y. Chi, *J. Am. Chem. Soc.*, 2002, **124**, 10278; (*e*) Z. M. A. Judeh, H.-Y. Shen, B. C. Chi, L.-C. Feng and S. Selvasothi, *Tetrahedron Lett.*, 2002, 9381.

9 L. C. Branco, J. G. Crespo and C. A. M. Afonso, *Chem. Eur. J.*, 2002, **8**, 17.

10 L. C. Branco, J. G. Crespo and C. A. M. Afonso, *Angew. Chem., Int. Ed.*, 2002, **41**, 2771.

11 J. L. Anderson, J. Ding, T. Welton and D. W. Armstrong, *J. Am. Chem. Soc.*, 2002, **124**, 14247.

12 J. Fuler, R. T. Carlin, H. C. De Long and D. Haworth, *J. Chem. Soc., Chem. Commun.*, 1994, 299.