ACTA CHEMICA IASI, **18**, 77-88 (2010)

New Phenothiazine Derivatives with Ionic Liquid Structure

Gina Dumitriu,[a] Liliana Lucescu,[a] Elena Bicu,[a] and Dalila Belei[a*]

[a]*Departament of Chemistry, "Al. I. Cuza" University Iasi, 11 Carol I Bd, Iasi 700506, Romania*

Abstract: By alkylation of 1-methylimidazole with *N*-alkyl- and *N*-acylphenothiazines, we obtained some new imidazolium salts. The new compounds have ionic liquid structure.

Keywords: ionic liquid, imidazolium, phenothiazine, 2-chlorophenothiazine

Introduction

According to a common definition, ionic liquids (ILs) are a diverse group of ionic compounds that have a melting point below 100 °C. Many of them are even liquids at room temperature (RTILs – room temperature ionic liquids). The discovery date of the first ionic liquid is disputed, along with the identity of the ones that discovered it. Ethanolammonium nitrate was reported in 1888 by S. Gabriel and J. Weiner[1] having a melting point 52–55 °C. One of the earliest true room temperature ionic liquids was ethylammonium nitrate $(C_2H_5)\ NH_3^+ \cdot NO_3^-$ with a melting point of 12 °C, synthesized in 1914 by Paul Walden[2].

* Dr. Dalila Belei, tel: +40 232 201349, fax: +40 232 201313, e-mail: dalila@uaic.ro

Ionic liquids have a very low vapor pressure, high boiling points and their polarity can be varied widely depending on the nature of both the anions and the cations[3,4]. Thus they can be used as preferable solvents in a number of cases. In addition, it is possible to recycle and re-use ionic liquids, as well as the so called "working solutions", which are solutions of catalysts in ionic liquids[5-9]. Some of the ionic liquids are referred to as 'Green Solvents'[10,11]. Ionic liquids have gained a wide interest and broad applications[4,10,12-15].

The ionic liquid cation is generally an organic structure of low symmetry. Figure 1 shows some five-membered cations including imidazolium, pyrazolium, triazolium, thiazolium and oxazolium.

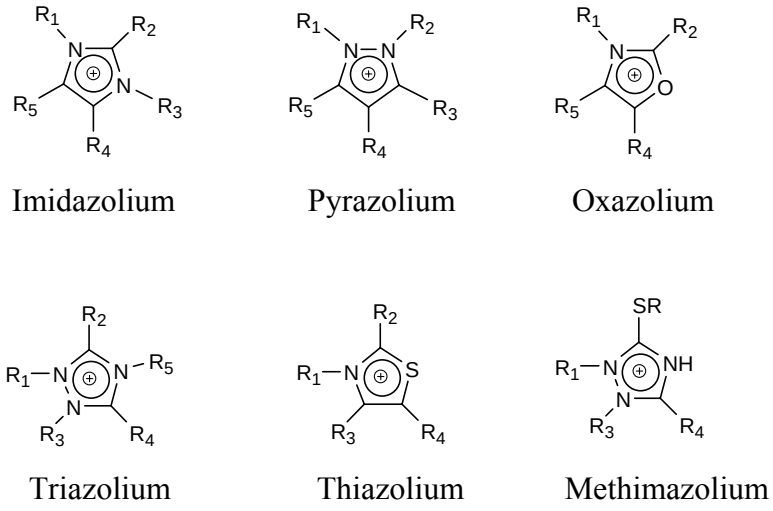


Figure 1. Five membered heterocyclic cations

The most common anions found in ionic liquid structures are: halides, BF_4^-, PF_6^-, NO_3^-, $AlCl_4^-$, $Al_2Cl_7^-$, etc.

While the halide salts are usually solids at room temperature, there are many anions that lower the melting points of the salts below room temperature.

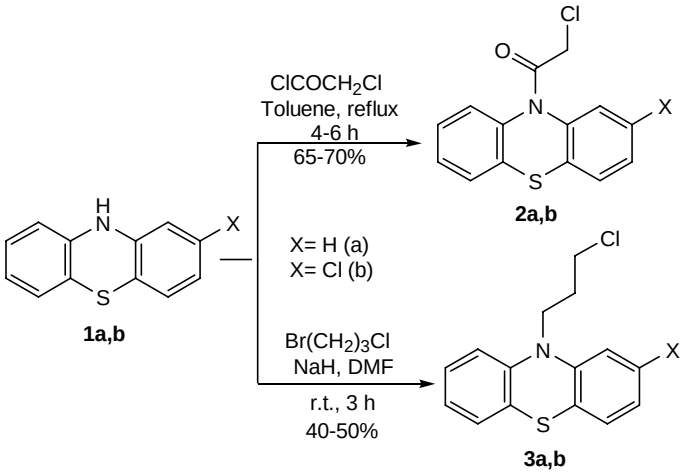
It is generally assumed that non-symmetrical *N*, *N'*-alkyl-imidazolium cations yield salts that have the lowest melting points. However, dibutyl, dioctyl, dinonyl and didecylimidazolium hexafluorophosphates are also liquid at room temperature.

Of the many known ionic liquids, 1-butyl-3-methyl- and 1-ethyl-3-methylimidazolium are probably the most investigated structures of this class.

Results and discussions

Analyzing the information presented above regarding the use of 1-substituted-3-methylimidazolium derivatives as ionic liquids, we set the goal to synthesize new phenothiazin-imidazolium type **4a,b** and **6a,b** hybrids.

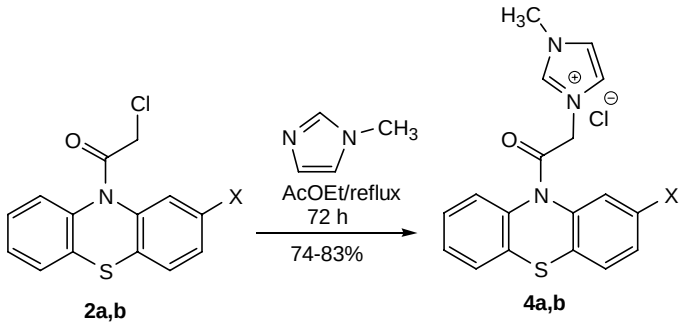
Thus, the first step in our study was the synthesis of phenothiazine derivatives by alkylation and acylation of the nitrogen atom of phenothiazine or 2-chlorophenotiazine (Scheme 1):



Scheme 1

After obtaining and characterizing of the precursors described above, the imidazolium salts were obtained by alkylation of 1-methylimidazole in ethyl acetate, at reflux.

Using *N*-acylphenothiazine derivatives **2a,b**[16] as alkylating agents, imidazolium chlorides **4a** and **4b** were obtained with a yield of 74-83% (scheme 2):

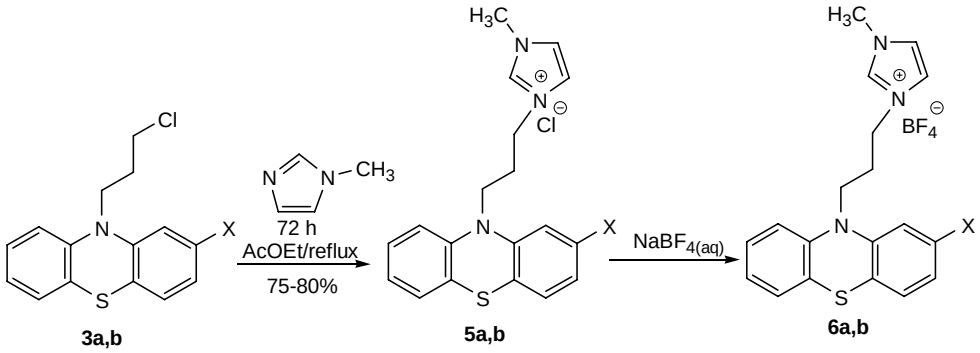


Scheme 2

Both compounds were characterized by spectral (IR, ^{1}H and ^{13}C NMR, and MS) and analytical data. The most important signals in the IR spectra of compounds **4a,b** are the characteristic absorption bands at 1680-1685 cm^{-1} and 1445-1442 cm^{-1}, which are due to –NCO- group and

C-N vibration. The absorption bands associated with other functional groups also appeared in the expected region. The ^{1}H NMR spectra of these compounds showed a characteristically low field absorption of an imidazolium proton at C2 (δ= 9.4 ppm). The methylene protons adjacent to the quaternary nitrogen were also deshielded, showing signals at δ= 5.3-5.6 ppm.

Then, using 10-(3-chloropropyl)-10*H*-phenothiazine and 2-chloro-10-(3-chloropropyl)-10*H*-phenothiazine **3a,b**[17] as alkylation agents, the imidazolium chlorides **5a,b** were obtained and subsequently transformed in the corresponding tetrafluoroborate **6a,b** by treating them with aqueous solution of sodium tetrafluoroborate (scheme 3):



Scheme 3

The structure of the new organic compounds **6a,b** was established by spectroscopic analysis: IR, ^{1}H NMR, ^{13}C NMR and MS. Thus, in the IR spectra the C-N vibration occurs at 1450-1456 cm^{-1}. The ^{1}H and ^{13}C NMR spectra also confirmed the proposed structures. For example, in ^{1}H NMR spectrum of compound **6a**, the signal for the methyl group appeared at δ= 3.8 ppm and the imidazolium proton from C2 at δ= 9 ppm respectively (Figure 2):

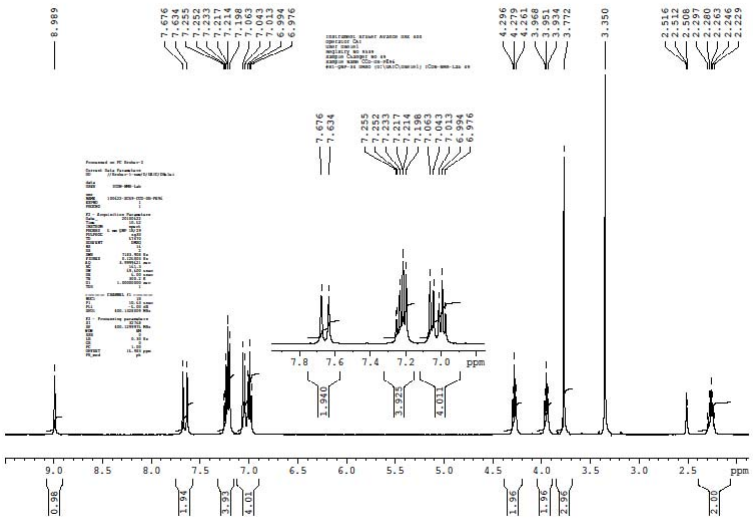


Figure 2. ^{1}H NMR of compound **4a**

In terms of physical properties, compounds **5a,b** are liquids, while the other compounds that have been obtained are stable crystalline white solid substances. Whereas the melting point of 1-sustituted-3-methyl-imidazolium chlorides **4a,b** is high, the compounds **6a,b** have a much lower melting point, confirming our expectations.

Experimental

Melting points were obtained on a Mel-Temp II apparatus. IR spectra were recorded on a Bruker Tensor 27 instrument. NMR spectra were recorded on a Bruker DPX-300 spectrometer. Chemical shifts are reported in ppm downfield from TMS. Mass spectra were recorded on a Finnigan MAT 90X spectrometer.

10-(Chloroacetyl)-10H-phenothizine (**2a**)

General procedure: To a solution of phenothizine (2 g, 10 mmol) in toluene (40 mL), chloroacetyl chloride (1.7 g, 15 mmol) was added in portions. The mixture was refluxed for five hours. After cooling, the reaction product was separated and recrystallised from ethanol (25 mL) giving colourless crystals; yield 1.65 g (60%).

Mp 118-119 °C [lit. 115-116.5]. IR (ATR): 1668, 1549, 1421, 1317, 1201, 1128, 1116 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 4.50 (s, $2H_{phen}$, CH_2), 7.30 (dt, $2H_{phen}$, J= 7.7 Hz), 7.39 (dt, $2H_{phen}$, J= 7.6 Hz), 7.54 (dd, $2H_{phen}$, J= 7.7 Hz), 7.69 (dd, $2H_{phen}$, J= 7.4 Hz). ^{13}C NMR (DMSO-d_6): δ = 43.0 (CH_2), 127.1, 127.7, 128.2, 132.5, 137.8 (CH and C), 165.2 (NCO). MS (ESI): *m/z* = 275 [M^+].

2-Chloro-10-(chloroacetyl)-10H-phenothizine (**2b**)

Colourless crystals; yield 2 g (65%). Mp 117-118 °C. IR (ATR): 1678, 1575, 1402, 1331, 1236, 1129, 1094, 803, 737 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.18 (d, 2H, CH_2), 7.19-7.64 (m, 7 H, 7 x CH_{ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.6 (CH_2), 126.2, 127.0, 127.4, 127.6, 127.7, 128.2, 128.5, 132.9, 137.3, 138.8 (CH and C), 165.3 (NCO). MS (ESI): *m/z* = 310 [M^+].

10-(3-Chloropropyl)-10H-phenothiazine (**3a**)

General procedure: To a solution of phenothizine (2 g, 10 mmol) in dimethylformamide (25 mL), sodium hydride (0.83 g, 21 mmol, 60% dispersion in mineral oil) was added in portions, at 0-5 °C. After 15 minutes of vigorous stirring 1-bromo-3-chloropropane (3 mL, 30 mmol) was added.

The reaction mixture was stirred at room temperature for three hours and then poured into cold water. The solid thus obtained was recrystallized from etahnol : acetone= 7:3, giving colourless crystals; yield 1.35 g (50%).

Mp 67-69 °C [lit. 63-64 °C]. IR (ATR): 3064, 2954, 1591, 1569, 1455, 1440, 1331, 1249, 1124, 754, 535 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.27 (m, 2H, –CH_2–, J= 6.4 Hz, J= 6.8 Hz), 3.51 (t, 2H, –CH_2Cl, J= 6.8 Hz, J= 6.4 Hz), 4.07 (t, 2H, NCH_2–, J= 6.4 Hz, J= 6.8 Hz), 6.86-7.24 (m, 8 H, 8 x CH_{ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.7 (CH_2), 42.4 (CH_2), 49.3 (CH_2), 115.6, 122.7, 125.7, 127.3, 127.6, 145.0 (CH and C). MS (ESI): *m/z(%)* = 275.1 (25) [M^+].

2-Chloro-10-(3-chloropropyl)-10H-phenothiazine (**3b**)

Mp 69-71 °C. IR (ATR): 3057, 2948, 1569, 1454, 1325, 1279, 1251, 1117, 756, 547 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (m, 2H, –CH_2–, J= 6.5 Hz, J= 6.9 Hz), 3.48 (t, 2H, –CH2Cl, J= 6.9 Hz, J= 6.5 Hz), 4.12 (t, 2H, NCH2–, J= 6.5 Hz, J= 6.9 Hz), 6.81-7.21 (m, 7 H, 7 x CHar). 13C NMR (75 MHz, CDCl3): δ = 29.4 (CH2), 42.1 (CH2), 48.9 (CH2), 115.2, 122.4, 126.1, 127.1, 127.3, 131.2, 145.4 (CH and C). MS (ESI): m/z(%) = 310.1 (20) [M^+].

1-[2-Oxo-2-(10H-2-phenothiazin-10-yl)etyl]-3-methylimidazolium chloride (4a)

General procedure: 1-methylimidazole (1 mL, 12 mmol) was added to a solution of 10-(chloroacetyl)-10*H*-phenothizine (2.75 g, 10 mmol) in ethyl acetate. The reaction mixture was stirred at reflux for 72 hour and then cooled. Separation of imidazolium chloride occurs, resulting a white solid.

The raw product was filtered in vacuum and then recrystallised from ethanol. The pure product is white, with mp = 239-242°C.

IR (ATR): 3368, 1682, 1566, 1461, 1312, 1260, 1170, 749 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.92 (s, 3H, CH_3), 5.62-5.79 (broad, 2 H, CH_2), 7.39-7.56 (m, 8 H, CH_{phen}), 7.76 (s, 1 H, $CH_{imidazole}$), 7.90 (s, 1 H, $CH_{imidazole}$), 9.27 (s, 1 H, $CH_{imidazole}$); ^{13}C-NMR (DMSO-d_6): δ 35.7 (CH_3), 50.7 (CH_2); 107.3, 122.7, 123.9, 126.9, 127.6, 128.1, 132.8, 135.7, 137.9 (CH and C), 164.6 (CON). MS (ESI): m/z(%) = 322 (100) $[M-Cl]^+$.

1-[2-Oxo-2-(2-chloro-10H-2-phenothiazin-10-yl)etyl]-3-methyl-imidazolium chloride (4b)

Mp 227-230°C. IR (ATR): 3356, 1674, 1543, 1478, 1314, 1258, 1163, 758 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.68 (s, 3H, CH_3), 5.43-5.61 (broad, 2 H, CH_2), 7.35-7.66 (m, 7 H, CH_{phen}), 7.63 (s, 1 H, $CH_{imidazole}$), 7.85 (s, 1 H, $CH_{imidazole}$), 9.31 (s, 1 H, $CH_{imidazole}$); ^{13}C-NMR (DMSO-d_6): δ 35.0 (CH_3), 51.2 (CH_2); 107.6, 122.4, 122.9, 126.6, 127.4, 128.3, 132.9, 135.2, 137.6 (CH and C), 164.4 (CON). MS (ESI): m/z(%) = 357 (100) $[M-Cl]^+$.

*1-[3-(10H-Phenothiazin-10-yl)propyl]-3-methyl-imidazolium tetrafluoroborate (**6a**)*

A mixture consisting of 10-(3-chloropropyl)-10H-phenothiazine (2.75 g, 10 mmol) and 1-methylimidazole (1 mL, 12 mmol) was dissolved in ethyl acetate. The reaction mixture was refluxed for 72h, then 1-[3-(10*H*-phenothiazin-10-yl)propyl]-3-methyl-imidazolium chloride was isolated as a yellow viscous liquid which by treating with aqueous solution of sodium

tetrafluoroborate allowed to obtain imidazolium tetrafluoroborate. The pure product is white, with mp = 157-160°C.

IR (ATR): 3156, 3101, 1573, 1560, 1456, 1325, 1256, 1211, 1166, 1028, 854, 753, 652, 625, 519 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.26 (m, 2H, CH_2, J= 6.8 Hz; J= 6.8 Hz), 3.77 (s, 3 H, CH_3), 3.95 (t, 2 H, CH_2, J= 6.8 Hz; J= 6.8 Hz), 4.28 (t, 2 H, CH_2, J= 6.8 Hz; J= 7.2 Hz), 6.98-7.06 (m, 4 H, CH_{Pheno}), 7.20-7.26 (m, 4 H, CH_{Pheno}), 7.63 (s, 1 H, $CH_{imidazole}$), 7.68 (s, 1 H, $CH_{imidazole}$), 8.99 (s, 1 H, $CH_{imidazole}$); ^{13}C-NMR (DMSO-d_6): δ 29.7 (CH_2), 35.6 (CH_3), 43.3 (CH_2), 46.7 (CH_2), 115.9, 122.2, 122.8, 123.6, 127.2, 127.7, 132.8, 135.7, 136.6, 144.4 (CH and C). MS (ESI): m/z(%) = 322 (100) $[M\text{-}BF_4]^+$.

*1-[3-(2-Chloro-10H-phenothiazin-10-yl)propyl]-3-methyl-imidazolium tetrafluoroborate (**6b**)*

Mp = 157-160°C. IR (ATR): 3144, 3095, 1562, 1459, 1331, 1262, 1204, 1183, 1032, 851, 749, 657, 524 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.31 (m, 2H, CH_2, J= 6.8 Hz; J= 6.8 Hz), 3.81 (s, 3 H, CH_3), 4.01 (t, 2 H, CH_2, J= 6.8 Hz; J= 6.8 Hz), 4.21 (t, 2 H, CH_2, J= 6.8 Hz; J= 7.2 Hz), 6.98-7.34 (m, 7 H, CH_{Pheno}), 7.59 (s, 1 H, $CH_{imidazole}$), 7.71 (s, 1 H, $CH_{imidazole}$), 9.01 (s, 1 H, $CH_{imidazole}$); ^{13}C-NMR (DMSO-d_6): δ 29.2 (CH_2), 36.1 (CH_3), 42.9 (CH_2), 46.4 (CH_2), 116.2, 121.9, 122.5, 123.8, 126.9, 127.5, 132.6, 136.1, 136.3, 144.7 (CH and C). m/z(%) = 357 (100) $[M\text{-}BF_4]^+$.

Conclusions

Using *N*-acetyl- and *N*-alkylphenothiazines, a new series of imidazolium salts was obtained and their structure was confirmed by analytical and spectral methods (IR, ^{1}H-NMR, ^{13}C-NMR and MS).

We expect some of the imidazolium derivatives presented above to show ionic liquid properties.

Acknowledgements

This work was supported by the Romanian CNCSIS-UEFISCSU, project number PNII-IDEI 2643/2008.

References

1. Gabriel, S. and Weiner, J., *Chem. Ber.*, **21**, 2669 (1888).
2. Walden, P., *Bull. Acad. Sci.*, 405 (1914).
3. Holbrey, J. D., Rogers and R. D., '*Ionic Liquids in Synthesis'*, Wasserscheid, P., Welton, T. (Eds.); Wiley-VCH: Weinheim, 2nd ed., vol. 1, p. 57, 2008.
4. Anthony, J. L., Brennecke, J. F., Hollberg, J. D., Maginn, E. J. et al. in '*Ionic Liquids in Synthesis'*, Wasserscheid, P.; Welton, T. (Eds.); Wiley VCH: Weinheim, 1st ed., vol. 1, p. 41, 2003.
5. Wasserscheid, P. and Keim, W., *Angew. Chem., Int. Ed. Engl.*, **39**, 3773 (2000).
6. Joerger, J. M., Paris, J. M., and Vaultier, M., *Arkivoc*, **(iv)**, 152 (2006).
7. Sheldon, R., *Chem. Commun.*, **23**, 2399 (2001).
8. Gayet, F., Marty, J. D., and Lauth-de Viguerie, N., *Arkivoc*, **(xvii)**, 61 (2008).

9. Mital, A., Lad, R., Thakur, A., Negi, V. S., and Ramachandran, U., *Arkivoc*, **(xi)**, 99 (2006).
10. Earle, M. J. and Seddon, K. R., *Pure Appl. Chem.*, **72**, 1391 (2000).
11. Jain, N., Kumar, A., Chauhan, S., and Chauhan, S. M. S., *Tetrahedron*, **61**, 1015 (2005).
12. Vallette, H., Ferron, L., Coquerel, G., Guillen, F., and Plaquevent, J. C., *Arkivoc*, **(iv)**, 200 (2006).
13. Chiappe, C., ,*Ionic Liquids in Synthesis'*, Wasserscheid, P.; Welton, T. (Eds.); Wiley-VCH: Weinheim, 2nd ed., vol. 1, p. 265, 2008.
14. Wasserscheid, P. and Schulz, P., ,*Ionic Liquids in Synthesis'*, Wasserscheid, P.; Welton, T. (Eds.); Wiley-VCH: Weinheim, 2nd ed., vol. 2, p. 369, 2008.
15. Ludley, P. and Karodia, N., *Arkivoc*, **(iii)**, 172 (2002).
16. (a) Dahlbom, R., *Acta. Chem. Scand.*, **7**, 873 (1953); (b) Gritsenko, A. N., Zhuravlev, S. V., and Skorodumov, V. A., *Kimioterapii Akad. Med. Nauk U.S.S.R.*, **1**, 13 (1958).
17. (a) Wunderlich, H., Lugenheim, W., Stark, A. and Detrekoei, G., *Pharmazie*, **21**, 57 (1966); Gozlon, I., Ladkani, D., Halpern, M., Rabinovitz, M., and Avnir, D., *J. Heterocyclic Chem.*, **21**, 613 (1984).