Pergamon

Tetrahedron Letters 39 (1998) 8955–8958

TETRAHEDRON
LETTERS

Novel organic ionic liquids (OILs) incorporating cations derived from the antifungal drug miconazole.

James H. Davis, Jr.*†, Kerri J. Forrester, and Travis Merrigan

Department of Chemistry, University of South Alabama, Mobile, Alabama 36608-0002 USA

Received 3 September 1998; revised 18 September 1998; accepted 21 September 1998

Abstract

The imidazole-ring containing antifungal drug miconazole reacts with a variety of alkyl iodides to form imidazolium cations. After anion metathesis with $NaPF_6$, organic ionic liquids (OILs) are obtained. These new ionic liquids are believed to be the first to be derived from a bioactive molecule. One of the new OILs also exhibits lyotropic liquid crystalline behavior while inducing the gelation of benzene.

Keywords: ionic liquids; liquid crystals; antifungals; imidazoles

Organic ionic liquids (OILs), may be defined as materials which incorporate at least one organic ion in an ion pair which is liquid at temperatures of ~150°C or lower [1-3]. Because of a number of useful properties which they possess, OILs are of interest for development in several areas, including catalysis, electrochemistry and as solvents for "green" chemistry [2-4]. Most of the OILs described to date are combinations of a 1-butyl-3-methylimidazolium $[bmim]^+$, 1-ethyl-3-methylimidazolium $[emim]^+$ or *N*-butylpyridinium cation and a charge-diffused inorganic anion [4].

In connection with an ongoing project involving the use of azolium ions as carbene ligand precursors, we have prepared several novel imidazolium cations derived from drugs and natural products [5]. The side chains of these cations are structurally complex and functionally diverse compared to those commonly used in OILs. As an adjunct to our carbene work, we deemed it worthwhile to determine if these or related imidazolium ions might be utilized as the cation component of OILs. We now report the initial results of one of these studies, in which

---

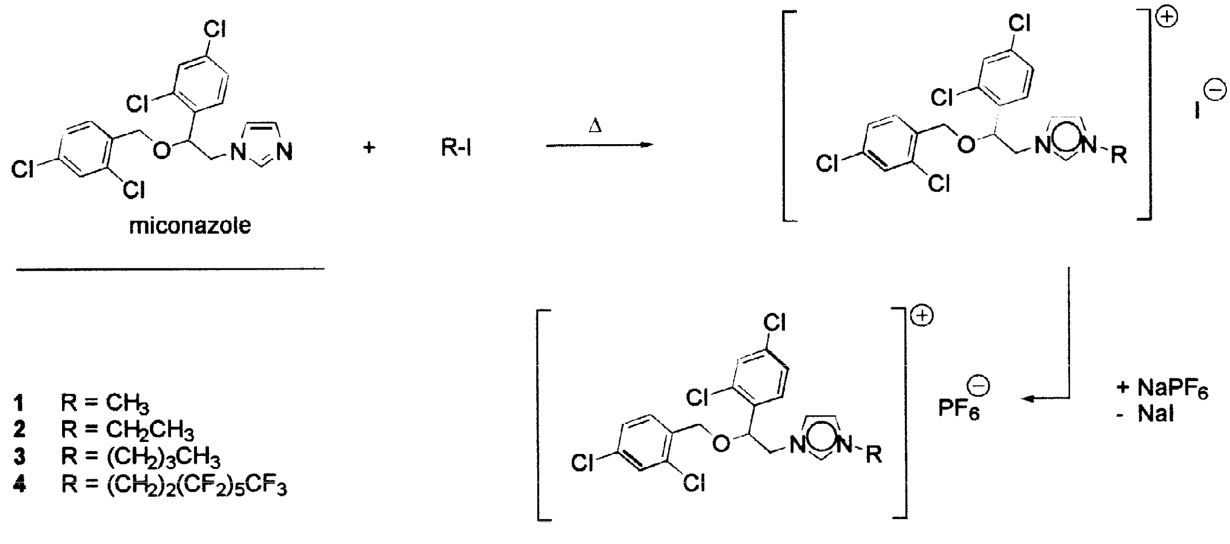
† jdavis@jaguar1.usouthal.edu

PII: S0040-4039(98)02070-X

we have utilized cations derived from the antifungal drug miconazole in the formulation of new OILs. To our knowledge, these new OILs are the first to be derived from a biologically active molecule.

Overnight reaction of miconazole with neat methyl-, ethyl- or n-butyliodide at reflux results in the quantitative formation of the corresponding N(3)-alkylmiconazolium iodides. Similarly, overnight reflux of miconazole with a 1.5 molar excess of 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-8-iodooctane in THF gives the expected salt in 52% yield. The miconazolium iodides are readily isolated as pale yellow solids by the removal of volatiles in vacuo and the repeated washing of the residue with ether then hexanes. Subsequent anion metathesis with $NaPF_6$ in THF or MeOH results in the formation of the miconazolium-based ionic liquids 1-4 [Scheme]. These species are isolated as straw-colored liquids by filtratration to remove NaI, followed by vacuum evaporation of the solvent. Straightforward verifications of the cation structures and the overall compositions and purities of 1-4 have been accomplished by acquisition of clean ^{1}H- and ^{13}C-NMR spectra as well as by FT-IR [6] and FAB-MS.

Scheme

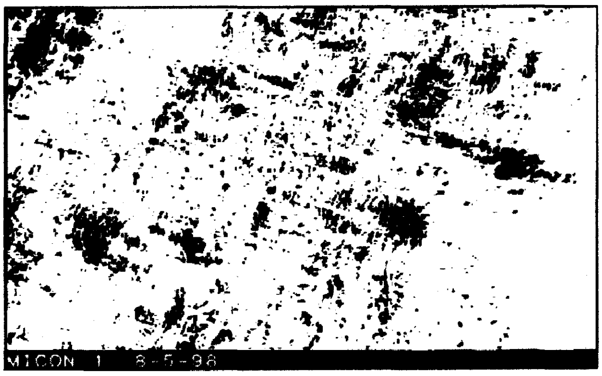


1 $R = CH_3$
2 $R = CH_2CH_3$
3 $R = (CH_2)_3CH_3$
4 $R = (CH_2)_2(CF_2)_5CF_3$

Compounds 1 and 3 remain liquid for weeks; 1 gradually crystallizes while 3 slowly glassifies, suggesting that relatively stable, room-temperature supercooled phases exist for each. Both compounds are reversibly reliquified by heating. Compound 1 undergoes observable phase transitions to gelatinous states at 68°-72°C and 130°-140°C before fully liquefying between 158° and 163°C. Compound 3, by comparison, transitions directly to a liquid between 86°- 89°C. Alone among the new compounds, 2 remains a mobile liquid indefinitely at room temperature. Over a period of hours, 4 becomes a soft yellow wax which is readily reliquified by heating to 92°-96°C. All four organic ionic liquids appear to be stable in air to temperatures ≥ 150°C.

Notably, in addition to being a low-melting salt compound 4 exhibits the capacity to selectively and reversibly gel benzene at modest mass percentages. Optical microscopic examination of one such gel, prepared by adding five mass percent of 4 to benzene, reveals the former to exhibit lyotropic liquid crystalline behavior within this matrix [Figure]. While the capacity of certain lipophilic quaternary ammonium ions to gel organic liquids has been noted, this behavior has not been specifically reported for species also described as ionic liquids [7-8].

Figure



Digitized, color-inverted optical micrograph (500x) of a gel composed of five mass percent of **4** in benzene, examined under polarizing light. The structure of this gel is strikingly similar to those formed by certain long-chained tetraalkylammonium salts in hydrocarbons.

As in one prior case, the presence in these ionic liquids of putative hydrogen-bonding sites, e.g., ether oxygen and imidazolium C(2)-H, suggest that ionic liquids may be somewhat tolerant of incorporated functional groups [9]. It is also apparent that a fine balance exists in the combinations of imidazole ring side chains which control the liquidus range of these compounds. For example, miconazole derivative 1, with a C_1 chain appended to N(3), eventually crystallizes at ambient temperatures. In contrast, N(3)-ethyl derivative 2 gives a persistent room-temperature liquid. The two longer-chain homologues 3 and 4 exist as a room-temperature glass and as a waxy semi-solid. Further experiments designed to probe the effects of alkyl chain size, structure and composition on ionic liquid properties are underway in our group. Studies of possible practical applications of these new drug-based materials are also being actively pursued. The results of these and related studies will be reported in due course.

Acknowledgments

We wish to thank Dr. Andrzej Wierzibicki and Mr. Travis Rutland for obtaining optical micrographs for us. We also wish to thank Dr. N. Dale Ledford for recording NMR spectra of our product cations, and Dr. Ann Abraham of the University of South Alabama College of Medicine for performing the FAB-MS experiments.

References

[1] Hussey, C. L. *Pure Appl. Chem.*, **1988**, *60*, 1763.

[2] Chauvin, Y.; Olivier-Bourbigou, H. *CHEMTECH*, **1995**, *25*, 26.

[3] Chauvin, Y.; Einloft, S.; Olivier, H. *Ind. Eng. Chem. Res.*, **1995**, *34*, 2698.

[4] Freemantle, M. *Chem. Eng. News* **1998**, *76* (13), 32.

[5] Davis, J. H., Jr.; Lake, C. M.; Bernard, M. A. *Inorg. Chem*, **1998**, *37*, in press.

[6] Elaiwi, A.; Hitchcock, P. B.; Seddon, K. R.; Srinivasan, N.; Tan, Y.-M.; Welton, T.; Zora, J. A. *J. Chem. Soc., Dalton Trans.* **1995**, 3467; and references therein.

[7] Lu, L.; Weiss, R. G. *J. Chem. Soc., Chem. Commun.* **1996**, 2029.

[8] Bowles, C. J.; Bruce, D. W.; Seddon, K. R. *J. Chem. Soc., Chem. Commun.* **1996**, 1625.

[9] Bonhote, P.; Dias, A.; Papageorgiou, N.; Kalyanasundaram, K.; Gratzel, M. *Inorg. Chem.* **1996**, *35*, 1168.