ORGANIC
LETTERS

2007
Vol. 9, No. 25
5247−5250

Ionic Liquids as Designer Solvents for Nucleophilic Aromatic Substitutions

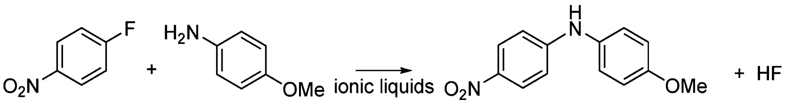
Ian Newington,[†] Juan M. Perez-Arlandis,[‡] and Tom Welton*,[‡]

GE Healthcare Bio-Sciences, The Grove Centre, White Lion Road Amersham,
HP7 9LL, and Imperial College of Science Technology and Medicine,
South Kensington, London SW7 2AZ, UK

t.welton@imperial.ac.uk

Received October 5, 2007

ABSTRACT



Ionic liquids were designed to optimize the nucleophilic aromatic substitution reaction of an activated aniline with an activated arylhalide. The design was achieved by selecting the anions on the basis of calculations of the gas-phase basicity of their conjugate acids.

Ionic liquids have attracted much attention recently as solvents for chemicals synthesis.[1] They have various useful properties, often being nonflammable, noncorrosive, and nonvolatile under atmospheric conditions. Consequently, they have been used as solvents for a wide range of organic reactions. Although controversial,[2] much of the work in the area has been based on the possibility that they might offer an environmentally benign alternative to conventional VOC solvents. Our interest has largely focused on the possibility that they may substantially alter the reactivity of dissolved solutes. This potential has led to ionic liquids being described as "designer solvents".[3] However, although there is extensive literature describing the diversity of ionic liquids available,[1] we know of no example to date of when this has been applied to designing an ionic liquid for a particular reaction, which we report here.

First it is necessary to define what we mean by solvent design. This should be separated from the task-specific ionic-liquid concept, in which a functional group that takes part in a reaction is introduced to one of the ionic-liquid species.[1,4] Also, for the process to be truly one of design, it is necessary to identify some fundamental property of the solvent that predictably determines the macroscopic outcome that one is trying to control, then manipulate that property to achieve the desired outcome. The aim of this paper is to demonstrate how knowledge of a combination of experimental and theoretical understandings of ion properties can be used to design an ionic-liquid solvent to maximize the efficiency of a nucleophilic aromatic substitution (S_NAr) reaction.

Arylamines are versatile intermediates with widespread use in polymers, pharmaceuticals, and photography. These are usually prepared by nucleophilic aromatic substitution, which is one of the fundamental reactions in traditional synthetic organic chemistry.[5] Classical methods for the synthesis of arylamines typically require a large excess of amine, addition of base and highly polar solvents such as DMSO[6] and DMF[7] at high temperatures with highly activated arylhalides.[8,9] In this paper we report the use of the designer approach to the selection of ions for ionic liquid solvents for a model "base-free" nucleophilic aromatic substitution reaction.

[†] GE Healthcare Bio-Sciences.

[‡] Imperial College of Science Technology and Medicine.

(1) Wasserscheid, P., Welton, T., Eds. *Ionic Liquids in Synthesis*, 2nd ed.; VCH-Wiley: Weinheim, Germany, 2007.

(2) (a) Scammells, P. J.; Scott, J. L.; Singer, R. D. *Aust. J. Chem.* **2005**, *58*, 155. (b) Clark, J. H.; Tavener, S. J. *Org. Process Res. Dev.*, **2007**, *11*, 149.

(3) Freemantle, M. *Chem. Eng. News* **1998**, *76*, 32.

(4) Wierzbicki, A.; Davis, J. H., Jr. In *Proceedings of the Symposium on Advances in Solvent Selection and Substitution for Extraction*, March 5−9, 2000, Atlanta, Georgia; AIChE: New York, 2000.

(5) Smith, M. B.; March, J. *Advanced Organic Chemistry*, 5th ed.; Wiley-VCH: New York, 2001.

(6) Brown, G. R.; Foubister, A. J.; Ratcliffe, P. D. *Tetrahedron Lett.* **1999**, *40*, 1219.

(7) Cho, Y. H.; Park, J. C. *Tetrahedron Lett.* **1997**, *38*, 8331.

(8) Shaw, J. E.; Kunerth, D. C.; Swanson, S. B. *J. Org. Chem.* **1976**, *41*, 732.

(9) Kulagowsky, J. J.; Rees, C. W. *Synthesis* **1980**, 215.

10.1021/ol702435f CCC: $37.00 © 2007 American Chemical Society
Published on Web 11/15/2007

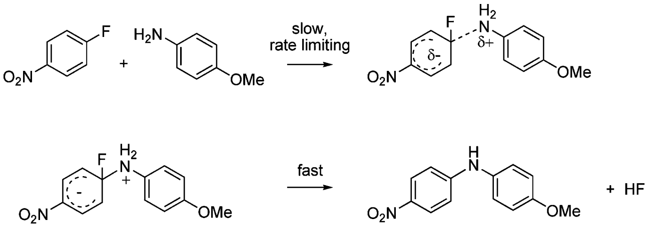
Previous investigations of nucleophilic aromatic substitutions in ionic liquids include the N-arylation of secondary cyclic amines[10] and the substitution of some 2-substituted-5-nitrothiophenes with cyclic amines.[11] In the latter, significantly greater rates of the reactions were observed in the ionic liquids [C_4C_1im][BF_4], [C_4C_1im][PF_6], and [$C_4C_1C_1$-im][BF_4] (where [C_4C_1im]$^+$ is the 1-butyl-3-methylimidazolium cation and [$C_4C_1C_1$im]$^+$ is the 1-butyl-2,3-dimethylimidazolium cation) than in methanol or benzene. The effects of the ionic liquids were found to be complex and to be dependent upon both the cation and anion.

Our initial studies involved the use of nine of the more commonly used ionic liquids, four molecular solvents with suitable boiling points for the established experimental conditions, and reaction with no added solvent. The reactions were monitored by measuring the yields after 24 h.

Clearly the nature of the solvent has a dramatic effect on the reaction (Table 1). Toluene (nonpolar, aprotic solvent) gives an exceptionally poor result, as does propylene carbonate {PC, polar, moderate donor (i.e., hydrogen-bond acceptor) solvent}. *N,N′*-Dimethylpropylene urea {DMPU, polar, strong donor (i.e., hydrogen-bond acceptor) solvent} provides the best solvent for this reaction. Hence, it can be concluded that the yields of this reaction after 24 h are greatly increased by using a solvent that is a strong donor. This is in good agreement with previous investigations of solvent effects and mechanistic predictions.[12]

Nucleophilic aromatic substitution reactions involving activated substrates and good leaving groups are known to proceed through an addition−elimination mechanism[13] (Scheme 1) involving the formation of an intermediate Meisenheimer complex.[14,15]

Scheme 1



During the first step of this reaction, the nucleophilic anisidine attacks the 1-fluoro-4-nitrobenzene and bonds to the carbon that bears the halogen. This step, involving the loss of aromaticity, generally proceeds slowly. In the second step, the complex formed loses the halide in a fast step, where the aromaticity of the ring is restored. The solvent can affect the rates of these reactions by interaction with starting materials, transition states, and/or the intermediate. In addition to simple dipole interactions between the transition state and the solvent, it is important to consider the hydrogen-bonding interactions that can occur between the amine/solvent, transition state/solvent, and Meisenheimer complex/solvent.

Solvents with hydrogen-bond accepting properties can interact with the protons on the aniline, increasing the electron density on the nitrogen atom and therefore its nucleophilic character. This increase has been shown when DMSO is used as the solvent for primary and secondary amines.[16] Also, the similarity between the transition state in these S_NAr reactions and the Meisenheimer complex intermediate predicts that factors that contribute to the stabilization of the transition state will also tend to stabilize the complex. Investigations on the stability of Meisenheimer complexes[17] in various solvents have shown the formation of more stable complexes in dipolar aprotic solvents relative to protic solvents. Hence, this reaction should be accelerated by polar, hydrogen-bond accepting solvents.

The reaction in DMF appears at first glance to contradict this analysis. Although DMF is in many ways similar to DMPU comparable yields were not obtained. However, in this reaction it was observed that the amount of unreacted *p*-fluoronitrobenzene was much lower than expected (only 30%) and the formation of *p*-dimethylaminonitrobenzene was noted in HPLC results. Hence, formation of this byproduct competes too well with the primary reaction for this, or closely related solvents, to be useful.

The effects of some of the most common ionic liquids used in the literature on this reaction were also studied (Table 1). Since its rate determining step involves the formation of a dipolar activated complex in which, compared to the initial state, there are considerable differences in charge distribution,

Table 1. Nucleophilic Aromatic Substitution of *p*-Fluorobenzene and *p*-Anisidine in Molecular Systems and Ionic Liquids[a]

solvent	yield %
toluene	0.1
PC	0.9
DMF	22.1
DMPU	41.4
solventless[b]	2.4
[C_4C_1pyrr][TfO]	5.2
[C_4C_1im][TfO]	4.9
[$C_4C_1C_1$im][TfO]	3.4
[C_4C_1im][BF_4]	2.4
[$C_4C_1C_1$im][BF_4]	2.1
[$C_4C_1C_1$im][N(Tf)$_2$]	0.4
[C_4C_1im][PF_6]	0.4
[C_4C_1im][N(Tf)$_2$]	0.4
[C_4C_1pyrr][N(Tf)$_2$]	0.4

[a] Conditions: slight excess *p*-anisidine (1:1.05 molar ratio), 100 °C, 24 h, under dry N_2. Yield determined by HPLC using internal standard. [b] The starting materials were mixed together and the reaction was heated to 100 °C and stirred for 24 h. In this case the *p*-anisidine was added in 50% excess.

---

[10] Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Venkat Narsaiah, A. *Tetrahedron Lett.* **2003**, *44*, 2217.

[11] D'Anna, F.; Frenna, V.; Noto, R.; Pace V.; Spinelli, D. *J. Org. Chem.* **2006**, *71*, 5144.

[12] (a) Terrier, F. *Nucleophilic Aromatic Displacement;* VHC: Weinheim, Germany, 1991. (b) Nudelman, N. S.; *The Chemistry of Amino, Nitroso, and Related Groups;* Patai S., Ed.; Wiley: Winchester, 1996; Chapter 26.

we proposed that ionic liquids could be suitable solvents in which to conduct the reaction of *p*-fluoronitrobenzene and *p*-anisidine. We have also previously noted the ability of ionic liquids to accelerate nucleophilic substitution reactions of amines.[19] However, none of the ionic liquids gave a synthetically useful yield for the reaction under the conditions used. Even with these very low yields some trends could be identified. Between the ionic liquids, the nature of the anion appears to be the factor that has more effect on the yields of the reaction. We have previously shown that the ability of these ionic liquids to act as hydrogen bond acceptors is a property of the anions.[20] Hence, this is in accord with the results for the molecular solvents. Higher yields were achieved for triflate ($[TfO]^-$) ionic liquids, while those based on the bis(trifluoromethylsulfonyl)-imide ($[N(Tf)_2]^-$) anion and $[PF_6]^-$ provided the lowest. For ionic liquids based on $[TfO]^-$ and $[N(Tf)_2]^-$, $[C_4C_1im]^+$ gave slightly lower yields than $[C_4C_1pyrr]^+$ (where $[C_4C_1pyrr]^+$ is the 1-butyl-1-methylpyrrolidinium cation) ionic liquids. However, $[C_4C_1C_1im]^+$ gave the lowest yield of the $[TfO]^-$ ionic liquids, whereas for the $[N(Tf)_2]^-$ ionic liquids it gave the highest. Given the very low yields of these reactions, it is possible that these differences arise from experimental error.

So, the reaction yield after 24 h in ionic liquids is increased by more hydrogen bond accepting anions. The question is, can an ionic liquid be designed such that it provides a higher yielding solvent for the reaction than any of the molecular solvents that have been used? The huge range of potential ionic liquids means that this may be possible, but the task of ion selection is not straightforward.

We have shown previously that good correlations were obtained between the theoretical Gibbs free energy change upon deprotonation of the conjugate acid of the anion in the gas phase (ΔG_H) and the hydrogen bond basicity of the ionic liquids.[20] Koppel et al.[21] have published an extended list of calculated ΔG_H values for some neutral Brønsted superacids. Therefore, we opted to select candidate anions from this list. The highest values of ΔG_H in this study were obtained for CH_3SO_3H and CF_3COOH. This led us to the prediction that ionic liquids based upon $[CH_3SO_3]^-$ and $[CF_3COO]^-$ anions should be effective solvents for this reaction. For this reason the $[CH_3SO_3]^-$ and $[CF_3COO]^-$ versions of the $[C_4C_1im]^+$ and $[C_4C_1pyrr]^+$ ionic liquids were prepared.[18]

A considerable improvement was achieved through the use of these more basic anions (see Table 2). Both conversions and yields were increased, with a yield of 78% for the best ionic liquid, which is almost twice as good as the best molecular solvent tested (DMPU) for the same reaction time and temperature. The $[CF_3COO]^-$-based ionic liquids gave marginally lower conversions than the $[CH_3SO_3]^-$ ionic liquids. Although this difference is small, it is consistent with the expectations from the ΔG_H values. The difference was more pronounced when comparing the yields of the reactions. For the $[CH_3SO_3]^-$ ionic liquids the difference between the yields and conversions was small, but it was much larger for the $[CF_3COO]^-$ ionic liquids. The most likely explanation for this is that the $[CF_3COO]^-$ anion is sufficiently nucleophilic that at the high concentrations that it is present (as a component of the solvent) it reacts with the 1-fluoro-4-nitrobenzene.[22]

Table 2. Nucleophilic Aromatic Substitution of *p*-Fluorobenzene and *p*-Anisidine in "Designed" Ionic Liquids[a]

solvent	yield %	conversion %	difference %
$[C_4C_1pyrr][CH_3SO_3]$	76.0	77.8	1.8
$[C_4C_1im][CH_3SO_3]$	76.7	77.6	0.9
$[C_4C_1pyrr][CF_3COO]$	69.1	74.3	5.2
$[C_4C_1im][CF_3COO]$	67.6	73.0	5.4

[a] Conditions slight excess *p*-anisidine (1:1.05 molar ratio), 100 °C, 24 h, under dry N_2. Yield determined by HPLC using an internal standard.

The small cation effect for those ionic liquids sharing the same anion was also noted. The yields and conversions were found to be slightly higher for those based in the pyrrolidinium cation. This is probably attributable to the slowing of the reaction by the better hydrogen-bond donor cation, $[C_4C_1im]^+$, interacting more strongly with the nitrogen of the anisidine. We have seen similar behavior in our studies of S_N2 reactions in ionic liquids.[19]

Traditional methods for synthesising nitrophenylamines often require severe conditions and yields are often unsatisfactory.[22] An improved preparation for 2-nitrodiphenylamines was reported by Rees et al. in 1980.[9] The substrates for this improved reaction involved the use of *o*-fluoronitrobenzene and substituted aniline. The starting materials were mixed in a ratio 1:2, respectively, and were allowed to react at 180 °C for 48 h in the presence of 1 equiv of solid anhydrous potassium fluoride. Improvements in these reactions were attributed to the presence of KF, which was a particularly good base when hydrogen fluoride was generated. In an attempt to improve the reaction in ionic liquids still further, we investigated the effect of the addition of F^- and other

---

(13) Brunnet, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273.

(14) Meisenheimer, J. *Justus Liebigs Ann. Chem.* **1902**, *323*, 205.

(15) For a review on rate and mechanism involving the formation of Meisenheimer complexes see: Terrier, F. *Chem. Rev.* **1982**, *62*, 78.

(16) (a) Mancini, P. M. E.; Terenzani, A.; Adam, C.; Vottero, L. R. *J. Phys. Org. Chem.* **1997**, *10*, 849. (b) Crampton, M.; Robotham, I. A. *J. Chem. Res., Synop.* **1997**, 22.

(17) Cox, B. G.; Parker, A. *J. Am. Chem. Soc.* **1973**, *95*, 408.

(18) First these ionic liquids were heated to 100 °C for 24 hours to ensure that there was no evidence of decomposition.

(19) Crowhurst, L.; Lancaster, N. L.; Pérez Arlandis, J. M.; Welton, T. *J. Am. Chem. Soc.* **2004**, *126*, 11549.

(20) Crowhurst, L.; Mawdsley, P. R.; Perez-Arlandis, J. M.; Salter, P. A.; Welton, T. *Phys. Chem. Chem. Phys.* **2003**, *5*, 2790.

(21) Koppel, I. A.; Burk, P.; Koppel, I.; Leito, I.; Sonoda, T.; Mishima. M. *J. Am. Chem. Soc.* **2000**, *122*, 5114.

(22) Lewis, E. S.; Douglas, T. A.; McLaughlin, M. L. *Adv. Chem.* **1987**, *215*, 35.

(23) (a) John, H. G. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1331. (b) Lindley, J. M.; McRobbie, I. M.; Cohn, O. M.; Suschitxky, H. *Chem. Soc., Perkin Trans. 1* **1977**, 2194.

bases to this reaction system. Owing to it excellent performance above we selected the [C_4C_1pyrr][CH_3SO_3] ionic liquid for this experiment. In all cases, the base was added in 10% molar ratio relative to the starting materials. We used a variety of F^- sources (KF, CsF, Bu_4NF), strong neutral bases (1,8-diazabicyclo[5.4.0]undec-7-ene, 1,1,3,3-tetramethylguanidine), Cs_2CO_3, ^{t}BuONa, and NaOH, but in no case was the yield of the reaction greater than that for the reaction without added base. This is presumably due to the ionic-liquid anion being sufficiently basic to play this role.

In conclusion, we have used calculated theoretical parameters, ΔG_H for the conjugate acid of the anion of the ionic liquid, to design an optimum ionic liquid to be used as a solvent for a reaction, namely the nucleophilic aromatic substitution of *p*-fluorobenzene and *p*-anisidine. This has provided dramatic increases in yield above that possible to achieve in the best available molecular solvents. It has also provided reaction conditions that can be used without the addition of a base. This is the first demonstration of ionic liquids as truly “designer solvents”.

Acknowledgment. We would like to thank the Kodak Foundation for a scholarship (J.M.P.A.) and Merck for the kind donation of the trifluoroacetate ionic liquids.

Supporting Information Available: Detailed experimental procedures and spectroscopic data (^{1}H and ^{13}C NMR, MS). This material is available free of charge via the Internet at http://pubs.acs.org.

OL702435F