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The first utilization of acidic ionic liquid for preparation of tetraarylporphyrins

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A phase-separated acidic ionic liquid affords to catalyze a reaction of pyrrole with benzaldehyde in dichloromethane, forming porphyrins in a comparable yield to the Lindsey method and is reusable at least ten times without loss of catalytic activity.

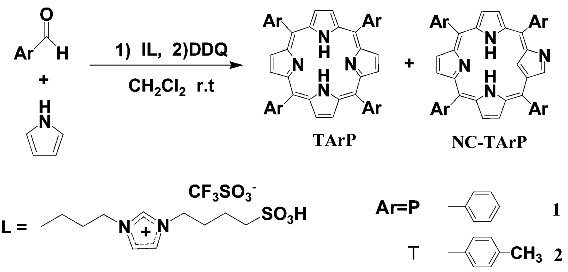
Tetraphenylporphyrin, TPP, offers attractive features in a wide variety of model studies.[1] Condensation of benzaldehyde with pyrrole followed by oxidation generally provides TPP in a one-flask synthesis. Heated pyridine and refluxing propionic acid open to air allowed Rothemund[2] and Adler *et al.*,[3] respectively, to have obtained TPP in less than 20% yield. Instead of these heated solvents, Lindsey *et al.* selected dichloromethane with an appropriate acid as the reaction medium, having improved the yield up to around 50%.[4] Due to its mild conditions, good yield and convenience, the Lindsey method has come into widespread use for numerous preparations of porphyrins. By the method using dichloromethane, *N*-confused tetraphenylporphyrin, NC-TPP was firstly isolated in *ca.* 5% yield by Furuta *et al.*[5] and Latos-Grazynski *et al.*,[6] and what is more, Lindsey *et al.* again optimized the reaction condition to yield the NC-TPP in 39 %.[7] In a series of the Lindsey methods, the halogenated solvent and harmful acids can be recognized to be prerequisite because of their superior solubility for porphyrins and the catalytic activity for the ring condensation, respectively. To keep using these materials because of their efficiency, however, is likely to become more undesirable than ever particularly in green chemistry. The need both for reducing the use of the halogenated solvent and for increasing the reusability of acid catalyst will increase rather than decrease. The two requirements, we believe, become indispensable to developing a successful green chemistry for porphyrin.

Room temperature ionic liquids (ILs) could be suitable and environmentally safer replacements for the volatile, toxic, and flammable organic solvents currently used in synthetic and catalytic reactions.[8a] There are various reports, in fact, about using ILs as reaction media,[8a] for instance, nucleophilic[8b] reactions, esterification[8c] and epoxidation with a manganese(III) porphyrin as a catalyst.[8d] However, no progress has been made in using IL for porphyrin preparations. Herein we study usage of IL as a new medium for porphyrin preparation aiming at being as green a reaction as possible throughout.

To begin with, the Lindsey method, [bmim][X],[9] where [bmim] and [X] denote 1-butyl-3-methylimidazolium cation and an arbitrary anion, respectively, is tested to see if the replacement with the halogenated solvent is able to afford the porphyrin formation. Standing [bmim][TFSI] solution of benzaldehyde (10 mM) and pyrrole (10 mM) in the presence of methanesulfonic acid, MSA (7 mM) at 22 °C for 10 min followed by addition of powder DDQ (10 mM) provides TPP in 41%, NC-TPP in 7% and black tarry byproducts estimated from HPLC analysis.[10] It is true that the IL(TFSI) shows similar yield to dichloromethane solvent as to porphyrin formation. However, the used IL is unlikely to be reused for the reaction due to the difficulty of removing the dissolved tarry byproducts away from the IL. Unlike the porphyrins, the tar emerged from the oxidation step could not be extracted with a halogenated medium from the nonvolatile IL. To avoid the tar contamination of the IL without losing productivity of the porphyrins, we devise a biphasic reaction arising from the interface between dichloromethane and an IL possessing an acid moiety (Scheme 1). Following Davis *et al.*,[8c] we prepared the Brønsted acidic IL, 3-butyl-1-(butyl-4-sulfonyl)imidazolium trifluoroethanesulfonate R–SO_3H, with which the dichloromethane phase is in fact immiscible.

Dichloromethane solution of pyrrole (14.5 mM, 10mL) was placed on the acidic IL (3 mL) in a test tube, having formed the interface (∅ 1.6 mm, 200 mm^2) at room temperature. Adding neat benzaldehyde (150 μL, 14.5 mM) onto the upper solution immediately brought a color into the dichloromethane phase. The color stemming from precursors of the porphyrins heightened on standing, as shown in Fig. 1. As opposed to the dichloromethane solution, the IL phase was not colored at all for the reaction period. After 20 min, the dark brown dichloromethane solution was separated from the acidic IL phase and then oxidized by addition of powder DDQ (342 mg, 14.5 mM) at room temperature. Into the black solution formed, triethylamine (100 μL) was added to quench the dissolved acid. The subsequent treatments for isolation of the porphyrins were conducted according to the literature. Recrystallized TPP and NC-TPP were obtained in yields of 43 % and 10 %, respectively. Also when *p*-tolualdehyde was applied in place of benzaldehyde, the interface of the acidic IL produced porphyrins in similar yields, 41% tetra-*p*-tolylporphyrin, TTP and 8 % *N*-confused tetra-*p*-tolylporphyrin, NC-TTP. Table 1 compares the present biphasic reaction with the Lindsey method using MSA as catalyst. It is obvious that the biphasic procedure is broadly comparable in yield to the Lindsey method apart from selectivity[11] for the ordinal and *N*-confused porphyrins.

Increasing concentration of the acid and/or the reactants generally results in low yield of the porphyrins due to oligomer



Scheme 1 Biphasic reaction of porphyrins.

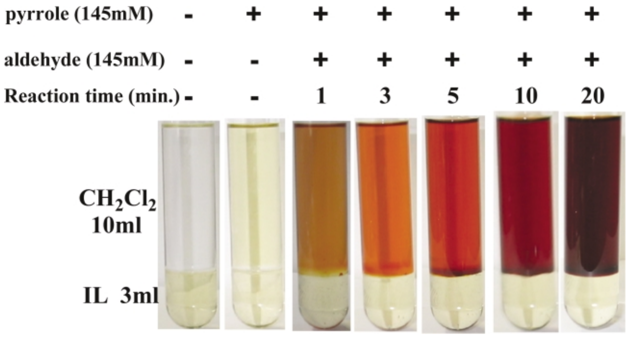


Fig. 1 Photograph showing colour change due to condensation reaction at interface between CH_2Cl_2 and Brønsted acidic IL.

formation as also shown in Table 1. This feature obliges us to use large amounts of the halogenated solvent, particularly in preparative scale syntheses.[12] The biphasic system is to suppress dissolution of the acidic IL into the halogenated phase, so that accelerated porphyrin formation would be conceivable even at high concentration of the reactants. In fact, when dichloromethane solution of the acidic IL[13] was applied without the interface, the poor porphyrin productivity, 7–11% TPP and 2–4% NC-TPP, was similar to the dichloromethane solution of the concentrated MSA. To minimize the amount of dichloromethane solvent, we examined the formation of the porphyrins at tenfold higher reactant concentration, 145 mM, on the interface. The isolated yield of TPP at 145 mM on the IL interface is as little as 16% less than that at 14.5 mM, but 2 to 11 times larger than that at 100 mM of the homogeneous condensation employing MSA.[7] This fact means, in spite of losing some of the efficiency, the biphasic reaction is suitable for the case of the high reactant concentration compared to the homogeneous reaction. Separating the acid catalysis from the reaction medium becomes useful enough to be productive in the porphyrin formation, particularly in the high concentration. This knowledge leads to a reduction in the amount of the halogenated solvent used.

In addition to the above superiority, another advantage of devising the separated phase of the acidic IL is the reusability. Table 2 shows the relation between the repeated use of the acidic IL and the preparation of TTP and NC-TTP. To reduce the amount of dichloromethane, the reactant concentration is set to be 145 mM, which is more than ten times what had been explored for the optimum concentration in the Lindsey method.[4] After the condensation of the two reactants in the biphasic system, the upper phase was taken away from the acidic IL phase. Onto the remained acidic IL being as a single phase in the test tube, fresh dichloromethane solution of the reactants was added to start again the biphasic reaction. On the other hand, powder DDQ was added into the taken-out dichloromethane solution and the formed porphyrins were isolated. This procedure was repeated ten times at room temperature without supplying any acid catalysts. From the first entry through the tenth final trials, the yields for isolated TTP and NC-TTP range from 27% to 31% and from 3.9% to 6.4%, respectively. It can be safety said, that is, the continually recycled usage of the acidic IL does not affect the porphyrin productivity at all.

Table 1 Influence of acid state on yields of TArP and NC-TArP[a]

Acid/mm^2 or mM		[reactant]/ mM	Time/ min	Por- phyrin	Yield (%) TArP	Yield (%) NC-TArP
R–SO$_3$H[b] interface 200 mm^2 at IL(RSO$_3$H)/CH$_2$Cl$_2$		14.5	20	1	43	10
		14.5	20	2	41	8.3
		145	**10**	**2**	**30**	**5.9**
		145	**10**	**1**	**27**	**4.2**
R–SO$_3$H in CH$_2$Cl$_2$		**145**	**10**	**1**	**7**[c] **11**[d]	**2**[c] **4**[d]
CH$_3$SO$_3$H in CH$_2$Cl$_2$	0.32[e]	10	480	1	43	10
	7[e]	10	30	1	5	39
	50[e]	100	8	1	12	12
	100	100	10	1	2.4	6.8

[a] *Reaction conditions*; room temperature, [aldehyde] = [pyrrole], [oxidant] = [reactant]. [b] this work; yields were determined after recrystallization. [c] CH$_2$Cl$_2$ having placed on the acidic IL phase for 10 min without shaking. [d] CH$_2$Cl$_2$ pre-equilibrated with the acidic IL by shaking for 5 min with a vortex mixer. [e] Lindsey method; data from ref. 7, yields were determined by HPLC analysis without recrystallization.

Table 2 Influence of reuse of the acidic IL on the isolated yield[a]

Cycle	1	2	3	4	5	6	7	8	9	10
TTP (%)	30	31	30	28	27	28	28	29	28	31
NC-TTP (%)	5.9	4.1	3.9	6.2	7.1	6.1	6.4	5.8	6	5.4

[a] [pyrrole] = [*p*-tolualudehyde] = [DDQ] = 145mM, room temperature, reaction time 10 min.

In conclusion, an acidic IL provides a new methodology for porphyrin preparation. The acidic IL phase separated with dichloromethane becomes quite instrumental for reducing the amount of the halogenated solvent used in porphyrin preparation. More important than the superior productivity in the high reactant concentration is the reusability of the acidic IL to catalyze the formation of porphyrinogens without deterioration of the activity.

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10 Yields of the obtained porphyrins are relevant to what kind of X is selected as the counter anion: TPP 11% (PF$_6$), 7% (AlCl$_4$), 0.1% (Br).

11 Investigation of a trade-off relation[7] between the yields of NC-TTP and of TTP in the biphasic reaction is currently under progress.

12 Preparing 1.0 g TPP and 1.0g NC-TPP require 2 L and 5 L dichloromethane, respectively, under the optimal condition of the Lindsey method employing MSA at room temperature.

13 Pure dichloromethane was pre-equilibrated with the acidic IL by shaking vigorously or just placing on the interface as described in Table 1.