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The regiospecific Fischer indole reaction in choline chloride·2ZnCl$_2$ with product isolation by direct sublimation from the ionic liquid†

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The Fischer indole synthesis occurs in high yield with one equivalent of the ionic liquid choline chloride·2ZnCl$_2$; exclusive formation of 2,3-disubstituted indoles is observed in the reaction of alkyl methyl ketones, and the products readily sublime directly from the ionic liquid.

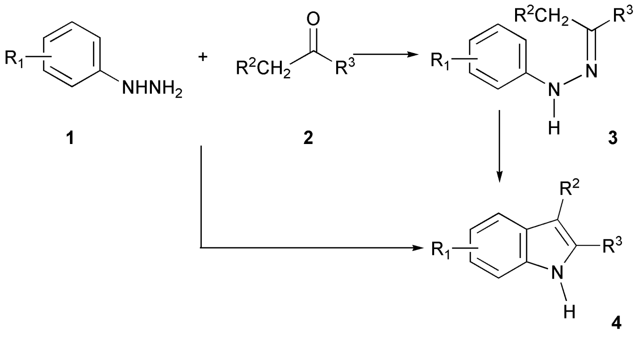
The alkylimidazolium–aluminium chloride mixtures have been studied extensively for use in acid catalysed reactions, particularly in Friedel–Crafts reactions.[1] However, chloroaluminate(III) ionic liquids are moisture sensitive and the product isolation from these liquids can be difficult. Similarly, ionic liquids formed using zinc chloride with pyridinium[2a] and imidazolium salts,[2b] have also been reported.

Recent studies at Leicester have demonstrated that quaternary ammonium salts may be used to produce moisture-stable Lewis acidic ionic liquids.[3] The combination of choline chloride, a cheap readily-available quaternary ammonium salt, and ZnCl$_2$ or SnCl$_2$ can be used as a Lewis acidic solvent for the Diels–Alder reaction.[4] More recently, the novel solvent properties of choline chloride–urea ionic liquids have been reported.[5]

In seeking new applications for the choline chloride·2ZnCl$_2$, some recent publications on the synthesis and reactions of heterocyclic compounds in ionic liquids have attracted our attention; these included the Bischler–Napieralski cyclisation,[6] the formation of 2-phenylimidazo[1,2-*a*]pyridine,[7] and the acylation[8] and electrophilic fluorination[9] of indoles. There was also one report of the Fischer indole synthesis in an ionic liquid using 1-butylpyridinium chloride–AlCl$_3$ (*n*-BPC-AlCl$_3$) ionic liquid.[10] This reaction is a good candidate for performing in ionic liquids as it is normally carried out in hot polyphosphoric acid, product isolation is by addition to water followed by filtration of the product, and disposal of the phosphoric acid residues can have a considerable environmental impact.

In our initial studies we prepared the phenylhydrazone of acetophenone and heated it with 3 eq. of the choline chloride·2ZnCl$_2$ ionic liquid for 4 h. Product isolation by addition of water and filtration of the product gave a 91% yield of 2-phenylindole **4aa** at 95 °C (Scheme 1). Yields were rather more modest with the phenylhydrazones of butanone and cyclohexanone, with 2,3-dimethylindole **4ab** (56%) and 1,2,3,4-tetrahydrocarbazole **4ac** (38%) as the products.

The isolated products of these reactions were finally purified by vacuum sublimation. It occurred to us that it may be possible to isolate the indole product directly from the ionic liquid by vacuum sublimation. Since an ionic liquid has little or no vapour pressure, then the vapour pressure of the solution of the indole product in the ionic liquid would be expected to be about the same as the vapour pressure of the indole itself. In the case of 2-phenylindole **4aa** a 91% yield of product could be obtained by direct vacuum sublimation of the ionic liquid reaction mixture. For 2,3-dimethylindole **4ab** a 56% yield was obtained using this method. In the reaction with the cyclohexanone hydrazone **3ac**, the product 1,2,3,4-tetrahydrocarbazole **4ac** was sublimed directly from the reaction without a vacuum and could be isolated by scraping it from the ionic liquid surface and from the glass of the reaction vessel. A key factor in determining the efficiency of the product sublimation is that we are going from a hydrazone which is basic to a product which is a weak base as the lone pair on the indole nitrogen is part of the aromatic system and not available for coordination to ZnCl$_2$.



Scheme 1

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† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b3/b313655h/

Table 1 One-pot reaction with product isolation by sublimation

Hydrazine R^1, **1**	Ketone **2**	Indole **4**	Ionic liquid (eq.)	Time/h	*T*/°C	Yield (%)	Mp/°C Found	Mp/°C Reported
H, **1a**	Butanone **2b**	2,3-Dimethylindole **4ab**	3	1	95	80	105–107	107
2,5-Cl$_2$, **1b**	Butanone **2b**	4,7-Dichloro-2,3-dimethylindole **4bb**	3	4	95	72	89–90	90–91
4-Cl, **1c**	Butanone **2b**	5-Chloro-2,3-dimethylindole **4cb**	1	2	120	88	142–143	141–142
2-Me, **1d**	Butanone **2b**	2,3,7-Trimethylindole[a] **4db**	1	3	120	71	75–76	76–77
H, **1a**	2-Pentanone **2d**	3-Ethyl-2-methylindole **4ad**	3	4	95	48	43–44	44–45
4-Cl, **1c**	2-Pentanone **2d**	5-Chloro-3-ethyl-2-methylindole **4cd**	1	2	120	64	74–75	76
H, **1a**	Cyclohexanone **2c**	1,2,3,4-Tetrahydrocarbazole[a] **4ac**	3	4	95	82	117–119	118–119
2,5-Cl$_2$, **1b**	Cyclohexanone **2c**	5,8-Dichloro-1,2,3,4-tetrahydrocarbazole **4bc**	3	4	95	59	90–91	91–93
4-Cl, **1c**	Cyclohexanone **2c**	6-Chloro-1,2,3,4-tetrahydrocarbazole **4cc**	1	2	120	84	147–148	146–147
2-Me, **1d**	Cyclohexanone **2c**	8-Methyl-1,2,3,4-tetrahydrocarbazole* **4dc**	1	3	120	76	93–94	93–95

[a] Vacuum sublimation direct from the ionic liquid was incomplete, the unsublimed product was isolated by aqueous work-up and sublimation of the isolated product. Yields quoted are based on the total weight of the isolated product.

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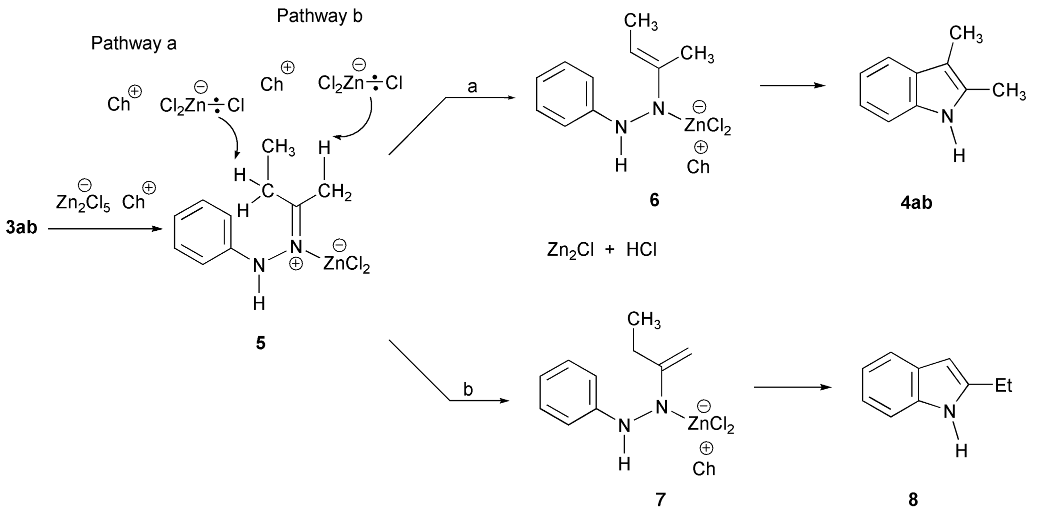

Scheme 2

We further reasoned that it may be possible to carry out a series of reactions in the same ionic liquid. To this end when we had sublimed the 2-phenylindole **4aa** in 91% yield from the ionic liquid we added a further quantity of acetophenone hydrazone and carried out a second reaction. This time the yield was 72% and a third repetition gave a 34% yield. During the Fischer indole reaction 1 eq. of ammonia is produced which coordinates to $ZnCl_2$. In the repeated use of the choline chloride·$2ZnCl_2$ for a series of reactions ammonia will accumulate and reduce the efficiency of the reaction as observed by the fall in yield.

In seeking further improvements in the reaction we next attempted a one-pot conversion of the phenylhydrazine and the ketone to the indole. This worked well with yields in the range of 48–88%, Table 1.

Another important issue in the Fischer indole synthesis is the selectivity when an unsymmetrical dialkyl ketone is used. In previous studies on the Fischer indole synthesis[11] of the phenylhydrazone of butanone a 4 : 1 mixture of 2,3-dimethylindole **4ab** and 2-ethylindole **8** was obtained. In order to explain this selectivity we first have to consider the actual species present in the ionic liquid choline chloride·$2ZnCl_2$. The FAB mass spectrum of choline chloride·$2ZnCl_2$ shows the presence of $[ZnCl_3]^-$ (*m*/*z*, 171), $[Zn_2Cl_5]^-$ (*m*/*z*, 307) and $[Zn_3Cl_7]^-$ (*m*/*z*, 443).[3] We believe that these species arise from the following equilibria where Ch^+Cl^- is choline chloride.[12]

$$2ZnCl_2 + Ch^+Cl^- \rightleftharpoons Zn_2Cl_5^- + Ch^+ \qquad (1)$$

$$2Zn_2Cl_5^- \rightleftharpoons ZnCl_3^- + Zn_3Cl_7^- \qquad (2)$$

$$Zn_2Cl_5^- \rightleftharpoons ZnCl_2 + ZnCl_3^- \qquad (3)$$

If we consider eqn. (3), the reaction of the hydrazone **3ab**, a Lewis base, with $Zn_2Cl_5^-$ will produce iminium cation **5** and $ZnCl_3^-$ (Scheme 2). $ZnCl_3^-$ can now act as a base and remove a proton in one of two ways. In pathway a, the proton is removed by $ZnCl_3^-$ to produce the zinc enamine **6**, which is the thermodynamic product, $ZnCl_2$ and HCl. Under the published reaction conditions[11] pathway b is also observed in which a proton is lost from the methyl group to give the less substituted zinc enamine **7**, which is the kinetic product. The reaction here is under kinetic control as there is no special stability of the iminium cation **5** and pathways a and b are irreversible processes leading to two products **4ab** and **8**. We propose that in the ionic liquid choline chloride·$2ZnCl_2$ the iminium cation is stabilised and pathway b becomes a reversible reaction hence the less substituted zinc enamine **7** can reprotonate, return to the iminium cation **5** and follow pathway a to the more stable zinc enamine **6** and hence form exclusively the 2,3-dimethylindole **4ab**. This explanation is bourne out by four examples using butanone and two using pentanone, in all cases a single indole arising from the more substituted enamine intermediate is observed, Table 1.

Finally we reduced the amount of ionic liquid used in the reaction to 1 eq. to obtain between 64 and 88% of directly sublimed product as shown in Table 1 for the synthesis of 5-chloro-2,3-dimethylindole **4cb** and 2,3,7-trimethylindole **4db**, 5-chloro-3-ethyl-2-methylindole **4cd**, and 6-chloro- and 8-methyl-1,2,3,4-tetrahydrocarbazole **4cc** and **4dc**.

In conclusion we have carried out the Fischer indole synthesis using 1 eq. of the ionic liquid choline chloride·$2ZnCl_2$ with direct product isolation by vacuum sublimation. In unsymmetrical cases regiospecific formation of a single product arising from the formation of the more substituted enamine intermediate is observed.

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12 We have carried out a full electrochemical study of these equilibria including mole fraction measurements of the ions $ZnCl_3^-$, $Zn_2Cl_5^-$ and $Zn_2Cl_5^-$ using potentiometry. These results are the subject of a manuscript in preparation.