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# The first example of the Schmidt reaction in ionic liquids

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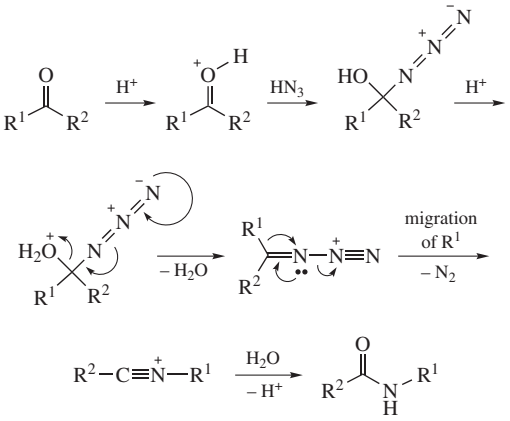
**The Schmidt reaction of aryl methyl ketones in ionic liquids (optimally in 1-ethyl-3-methylimidazolium triflate with $CF_3SO_3H$ additive) proceeds at 40 °C within 10–30 h to give the corresponding acetanilides in good yields.**

A reaction of hydrazoic acid with ketones in the presence of strong acids is known as the Schmidt reaction yielding corresponding carboxamides.[1] The proposed reaction mechanism[2] includes the protonation of carbonyl oxygen followed by addition of $HN_3$ molecule (Scheme 1). After the second protonation and water elimination, one of the substituents R migrates to the nitrogen atom causing the nitrogen molecule split-off. Finally, the nitrilium ion formed during this migration step reacts with water to give the amide. Typically, in the case of unsymmetrical ketones, the largest substituent undergoes migration. For instance, alkyl aryl ketones are usually converted into corresponding carboxamides (aryl fragment migration).



**Scheme 1**

The disadvantage in the classical Schmidt reaction realizing is the use of strong inorganic acids, which have to be neutralized upon the product isolation. The alternative of these conditions can be the use of ionic liquids (ILs) as a reaction medium. ILs have been widely employed over the past years as promising substitutes for common organic solvents.[3–5] ILs have considerable advantages over routine organic solvents: they are fire-resistant and have limited vapor pressure thereby allowing efficient recovery of organic products from the reaction mixture. Moreover, many reactions gain acceleration in ILs due to the stabilization of intermediates in ionic media.[5–7] The implementation of organic reactions in ILs pertains to a certain extent to the concept of 'green chemistry'.

Here, we report the first example of the Schmidt reaction of aryl methyl ketones in ILs. To find out the optimal conditions, the influence of the ionic liquid nature, $NaN_3$ excess and variations in the process parameters (catalyst, temperature and reaction time) on the product yield have been studied. Among all investigated ILs 1-ethyl-3-methylimidazolium hydrogen sulfate [emim][$HSO_4$] and trifluoromethane-sulfonate [emim][$CF_3SO_3$] provided the best reaction outcome. These ionic liquids serve as reaction media and support the catalytic activity of acid added to the reaction mixture.

Our attempts to carry out the Schmidt reaction in [emim][$HSO_4$] with a small excess of $NaN_3$ (1.2 mol per 1.0 mol **1a**) at 20 °C and at 100 °C (Table 1, entries 1 and 3) without the addition of any acidic catalyst were unsuccessful: only traces of target acetanilide **2a** were found in the reaction mixture (TLC monitoring). The replacement of $NaN_3$ with $Me_3SiN_3$ (Table 1, entry 2) does not significantly improve its yield. However, it was increased to ~30% by using of 2 moles of $NaN_3$ per 1 mol of **1a** and addition of $H_2SO_4$ (2.5 mol per 1.0 mol **1a**) as a catalyst (Table 1, entries 5 and 6). The results were much better in another ionic liquid, [emim][$CF_3SO_3$], with the application of $CF_3SO_3H$ as a catalyst (Table 1, entry 7). The yield of **2a** reached 74% at 40 °C and 30 h reaction duration. We have successfully employed other aryl methyl ketones **1b–k** in the Schmidt reaction under these optimized conditions. The reaction time was varied in between 10–30 h depending on the nature of starting ketone **1** (Scheme 2, Table 1, entries 7–17).† The corresponding acetanilides **2b–k** were obtained in 47–90% yields. The electronic nature of substituents in the aromatic ring of starting compounds **1b–k** strongly influenced the yield of products **2b–k**. All synthesized compounds **2** have melting points and spectral characteristics identical to those described in literature.

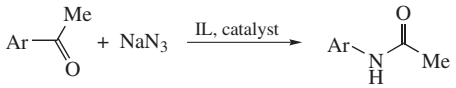
ILs were regenerated after the extraction of obtained products **2** and reused not less than 3 times (see entries 8–8-3 by the example of compound **1b**) that allowed one to avoid

† *The synthesis of acetanilides* **2a–k** *(general procedure).* Trifluromethanesulfonic acid or sulfuric acid (2.5 mmol) was added to the mixture of 1 mmol of aryl methyl ketone **1** and 2 mmol of $NaN_3$ in 2–3 g of corresponding ionic liquid. The reaction mixture (protected from air moisture with a drying tube) was stirred at the temperature given in Table 1 for the specified time. The reaction completion was monitored by TLC [the disappearance of starting ketones **1**; Silufol $UV_{254}$ plates; eluent, $CHCl_3$–ethyl acetate (10:1)]. The reaction mixture was extracted with diethyl ether (10×3 ml). The extract was washed with water (10×2 ml), dried with $MgSO_4$ and the solvent was evaporated *in vacuo*. The yields and melting points of acetanilides **2** are given in Table 1. After the extraction of obtained products **2**, ionic liquids were kept *in vacuo* at 50–60 °C for 2 h and reused in the next syntheses.

**Table 1** Synthesis of acetanilides **2** by the Schmidt rearrangement of aryl methyl ketones **1** in ILs.

| Entry | Starting ketone[a] | $NaN_3$ (equiv.) | IL | IL quantity/g | Catalyst (2.5 equiv.) | Time/h | *T*/°C | Yield of **2** (%) | Mp[c]/°C (lit., mp) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | | [emim][$HSO_4$] | 1.0 | — | 50 | 20 | Traces (TLC) | |
| 2 | **1a** | 1.2[b] | [emim][$HSO_4$] | 1.0 | — | 50 | 20 | ~20 (TLC) | |
| 3 | **1a** | 1.2 | [emim][$HSO_4$] | 1.0 | — | 30 | 100 | Traces (TLC) | |
| 4 | **1a** | 1.2 | [emim][$HSO_4$] | 1.0 | $H_2SO_4$ | 90 | 20 | Traces (TLC) | |
| 5 | **1a** | 2.0 | [emim][$HSO_4$] | 1.0 | $H_2SO_4$ | 30 | 100 | 32 | 111–113 (113–114)[8] |
| 6 | **1a** | 2.0 | [emim][$HSO_4$] | 1.0 | $H_2SO_4$ | 60 | 40 | 29 | 111–113 (113–114)[8] |
| 7 | **1a** | 2.0 | [emim][$CF_3SO_3$] | 3.0 | $CF_3SO_3H$ | 30 | 40 | 74 | 111–113 (113–114)[8] |
| 8 | **1b** | 2.0 | [emim][$CF_3SO_3$] | 3.0 | $CF_3SO_3H$ | 20 | 40 | 88 | 151–153 (153)[9] |
| 8-1 | **1b** | 2.0 | 1st recycle | 3.0 | $CF_3SO_3H$ | 22 | 40 | 85 | |
| 8-2 | **1b** | 2.0 | 2nd recycle | 3.0 | $CF_3SO_3H$ | 25 | 40 | 82 | |
| 8-3 | **1b** | 2.0 | 3rd recycles | 3.0 | $CF_3SO_3H$ | 25 | 40 | 80 | |
| 9 | **1c** | 2.0 | [emim][$CF_3SO_3$] | 2.0 | $CF_3SO_3H$ | 16 | 40 | 55 | 92–94 (92–93)[10] |
| 10 | **1d** | 2.0 | [emim][$CF_3SO_3$] | 3.0 | $CF_3SO_3H$ | 25 | 40 | 55 | 127–128 (129.5–130.5)[11] |
| 11 | **1e** | 2.0 | [emim][$CF_3SO_3$] | 2.5 | $CF_3SO_3H$ | 18 | 40 | 64 | 92–94 (82–83.5)[12] |
| 12 | **1f** | 2.0 | [emim][$CF_3SO_3$] | 3.0 | $CF_3SO_3H$ | 11 | 40 | 74 | 177–179 (179–180)[13] |
| 13 | **1g** | 2.0 | [emim][$CF_3SO_3$] | 2.0 | $CF_3SO_3H$ | 14 | 40 | 47 | 86–87 (87)[14] |
| 14 | **1h** | 2.0 | [emim][$CF_3SO_3$] | 3.0 | $CF_3SO_3H$ | 10 | 40 | 90 | 168–169 (169–170)[15] |
| 15 | **1i** | 2.0 | [emim][$CF_3SO_3$] | 2.5 | $CF_3SO_3H$ | 10 | 40 | 78 | 152–153 (152)[16] |
| 16 | **1j** | 2.0 | [emim][$CF_3SO_3$] | 3.0 | $CF_3SO_3H$ | 27 | 100 | 70 | 127–128 (132–134)[17] |
| 17 | **1k** | 2.0 | [emim][$CF_3SO_3$] | 3.0 | $CF_3SO_3H$ | 15 | 40 | 78 | 190–191 (192)[18] |

[a]1 mmol of the starting ketone was used. [b]$Me_3SiN_3$ was used. [c]Melting points were measured on a Boetius RNMK 05 apparatus.




**1a–k** **2a–k**

**a** Ar = Ph
**b** Ar = 4-$MeC_6H_4$
**c** Ar = 4-$EtC_6H_4$
**d** Ar = 2,4-$Me_2C_6H_3$
**e** Ar = 3-$MeOC_6H_4$
**f** Ar = 4-$ClC_6H_4$
**g** Ar = 3-$BrC_6H_4$
**h** Ar = 4-$BrC_6H_4$
**i** Ar = 3-$O_2NC_6H_4$
**j** Ar = 2-naphthyl
**k** Ar = 2-fluorenyl

**Scheme 2**

neutralization of acid after every run. In addition, a danger of the overall process is significantly decreased since the forming toxic and explosive $HN_3$ is fixedly solvated by ILs and does not evolve as in common organic solvents.

In conclusion, the Schmidt reaction of aryl methyl ketones was performed for the first time in ILs and a series of acetanilides was successfully prepared in moderate to high yields. The optimum conditions (IL = [emim][$CF_3SO_3$] and catalyst $CF_3SO_3H$) were found and IL was regenerated and reused in the next syntheses. Moreover, the use of ILs as reaction medium for the Schmidt reaction significantly increases the safety and manufacturability of the overall process.

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