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Synthesis and preliminary use of novel acrylic ester-derived task-specific ionic liquids

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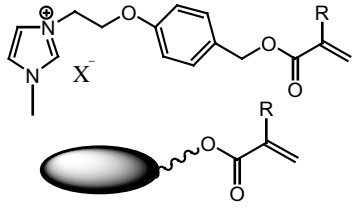
Abstract—Novel electrophilic alkenes bearing an ionic liquid-type appendage have been prepared and used in Diels–Alder cycloadditions, 1,4-additions, Heck couplings and Stetter reactions; this new type of support allows easy monitoring of the reactions by NMR and MS as well as simple and efficient work-up and isolation procedures.

Room temperature ionic liquids (RTILs) are the subject of current interest as novel reaction media.[1] This is mainly due to their unique physical properties, which makes them attractive solvents for organic synthesis,[2] organometallic catalysis[3] as well as for biotransformations.[4] In parallel to these uses a new class of reagents designed as task-specific ionic liquids (TSILs) have been developed: such derivatives combine an ionic liquid-type part (in order to maintain the corresponding physical properties) with an attached extra function designed for the specific property.[1,5] Excellent representative examples include co-ordination and extraction of metal ions,[6] CO_2 capture[7] and transition metal catalysts supported on ionic liquids.[8] Very recently a polymerizable ionic liquid has been used to increase the hardness of materials.[9]

Another very attractive possibility is to develop such TSILs as alternatives to classical solid and soluble polymeric supports used in parallel, as well as for multistep synthesis. The general principle is similar to those used in such methods with the RTILs replacing the polymeric support.[10] The main potential advantages of such derivatives are the following: (i) due to the insolubility properties induced by the RTIL part of the molecule, it is anticipated that simple washing with the appropriate solvents should remove the excess of reagents at each step of the synthesis, (ii) these derivatives are low molecular weight supports and therefore they should maintain good mobility at the attached function making their reactivity very close to solution chemistry and (iii) last, but not the least, this should greatly assist the spectral analysis of such small molecules for instance by NMR and MS. The first examples validating this concept have been reported recently in the cases of the Knoevenagel condensation and 1,3-dipolar cycloadditions, as well as for the preparation of a small library of thiazolidinones.[11]

As an extension of our programme dealing with chemistry on soluble supports,[12] we have selected as the first model the structures of type **1** and **2** with an imidazolium core in order to be as close as possible to classic RTILs and retain the corresponding physical properties (Fig. 1). A Wang-type linker was chosen since it is also



1a R=H, X=BF_4, **2a** R=Me, X=BF_4
1b R=H, X=NTf_2, **2b** R=Me, X=NTf_2

Figure 1. New task-specific ionic liquids.

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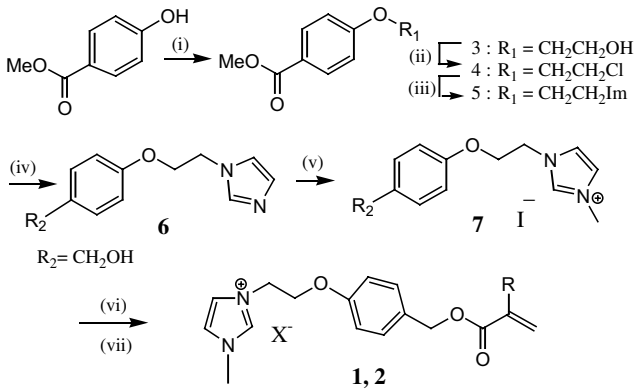


Scheme 1. Reagents and conditions: (i) 2-Chloroethanol (2 equiv), KOH (2 equiv), [Bmim][PF_6], 80 °C, 12 h, 87%; (ii) $SOCl_2$ (2 equiv), Py (2 equiv), reflux, 3 h, 80%; (iii) NaH (1.2 equiv), Im., DMF, 100 °C, 16 h, 60%; (iv) LAH (1.2 equiv), THF, reflux, 17 h, 88%; (v) MeI (2 equiv), CH_2Cl_2, reflux, 24 h, 90%; (vi) NH_4BF_4 (1.2 equiv), CH_3CN, 60 °C, 24 h, 95% or $LiNTf_2$ (1.2 equiv), CH_3CN, 60 °C, 24 h, 92%; (vii) acryloyl chloride (2 equiv), DIEA (2 equiv), CH_3CN, rt, 20 h, **1a** 85%, **1b** 90% or methacryloyl chloride (2 equiv), DIEA (2 equiv), CH_3CN, rt, 20 h, **2a** 92%, **2b** 90%.

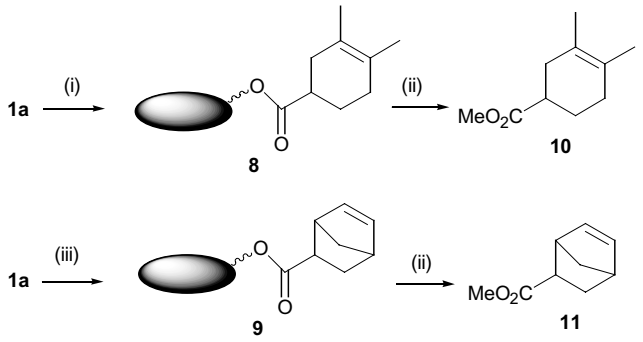
versatile in combinatorial chemistry with flexible lability. Finally electrophilic alkenes have been selected as functional groups since they offer a wide range of possible reactions such as cycloadditions, nucleophilic additions or transition metal-catalyzed reactions.

The purpose of this communication is to report an efficient synthesis of the new TSILs **1** and **2** and describe preliminary results of their use in different types of organic reactions. These compounds **1** and **2** have been prepared from commercially available methyl 4-hydroxybenzoate as shown in Scheme 1. A classical sequence afforded in four steps and 30% overall yield the imidazole bearing the Wang-type linker **6**. Alkylation followed by ion exchange gave the corresponding salts, and final esterification steps using the corresponding acid chloride in the presence of Hunig's base gave the key intermediates **1** and **2**. It should be noted that, while intermediates before quaternization were purified by classical chromatography, compounds **1** and **2** were isolated in pure form by simple extraction and washing procedures.[13]

A Diels–Alder cycloaddition was chosen as the first model reaction, wherein addition of 2,3-dimethylbutadiene to **1a** gave quantitatively the adduct **8**; similarly cyclopentadiene afforded the compound **9**.

After removal of excess reagents under vacuum and washing with ether, the products were obtained in pure form and fully characterized by NMR and MS (Scheme 2). Furthermore transesterification of adducts **8** or **9** gave respectively the cyclohexene derivatives **10** and **11**, which were identical to authentic samples.

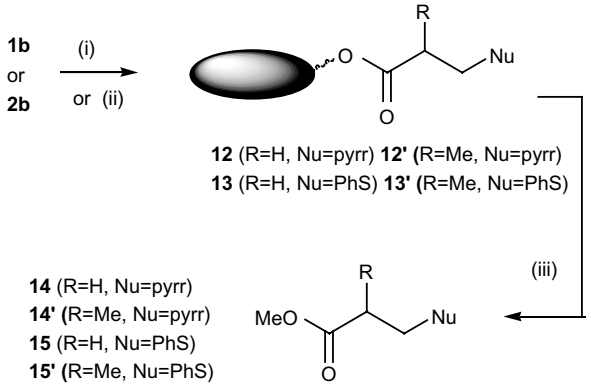
Nucleophilic additions were next studied and pyrrolidine and thiophenol were selected as models. In both cases the reaction afforded quantitatively the desired products **12**–**13′**, which were purified and characterized



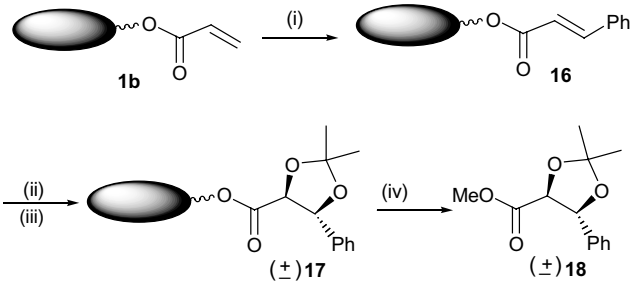
Scheme 2. Reagents and conditions: (i) 2,3-dimethylbutadiene (50 equiv), 70 °C, 72 h, 95%; (ii) NaOMe, THF, MeOH, reflux, 4 h, 75%; (iii) cyclopentadiene (3 equiv), 120 °C, 4 h, 90%.

as previously described. In the same way transesterification led to compounds **14**–**15′** (Scheme 3).

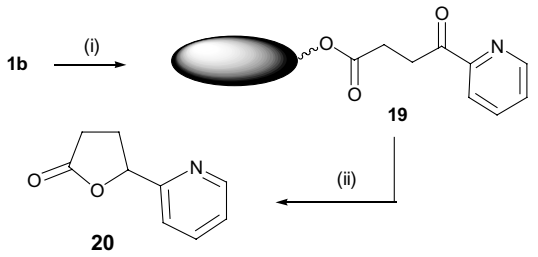
The Heck reaction has become a very important method for C–C bond formation[14] therefore it was logical to extend our study to such Pd-catalyzed reactions. The acrylate **1b** underwent a smooth coupling with PhI to give, as expected, compound **16** (Scheme 4).



Scheme 3. Reagents and conditions: (i) pyrrolidine (1.5 equiv), 24 h, rt, 90%; (ii) PhSH (1.5 equiv), TEA, 20 h, rt, 96%; (iii) NaOMe, THF, MeOH, reflux, 70%.



Scheme 4. Reagents and conditions: (i) PhI (1.5 equiv), cat. $Pd(OAc)_2$, TPP (0.2 equiv), TEA (2 equiv), 120 °C, 1 h, 75%; (ii) cat. OsO_4, NMO (1.2 equiv), acetone, water, rt 12 h, 87%; (iii) 2,2-dimethoxypropane (10 equiv), cat. PPTS, reflux, 97%; (iv) NaOMe, THF, MeOH reflux, 60%.



Scheme 5. Reagents and conditions: (i) pyridine-2-carboxaldehyde (2 equiv), 80 °C, 12 h, 87%; (ii) $NaBH_4$, MeOH, rt, 50%.

Dihydroxylation of the latter derivative using OsO_4 was also uneventful affording, after acetonide formation, compound **17**. Transesterification afforded the desired product **18** in 35% overall yield from **1b**.

The Stetter reaction is also a very useful method for the preparation of 1,4-dicarbonyl compounds.[15] Reaction of **1b** with pyridine-2-carboxaldehyde led to compound **19**, which after reaction with $NaBH_4$ afforded lactone **20** in a process equivalent to the cyclorelease strategy (Scheme 5).

In conclusion, these preliminary results clearly demonstrate that new families of TSILs with electrophilic alkene-type appendages are easily prepared and used in synthesis. Their development in asymmetric synthesis, as well as in multistep and/or parallel synthesis, is under active study in our laboratories.

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13. All new compounds have spectral (NMR and MS) data in full agreement with the indicated structures. All molecules having the ionic liquid-type appendage are viscous oils. **1a**,**b** and **2a**,**b** were found to be soluble in CH_2Cl_2, CH_3CN, THF and insoluble in water and ether. The nature of the counter anion X^- was established by LSIMS/MS through the presence of the $[2C^+, X^-]$ anion.
Representative procedure for **1a**: To a stirred solution of **7** (1.00 g, 2.77 mmol) in acetonitrile (10 mL) was added NH_4BF_4 (0.395 g, 3.32 mmol) in one portion. The reaction mixture was heated under stirring at 60 °C for 24 h. After cooling to room temperature it was filtered through Celite and the solvent removed under vacuum. The crude product was used directly for the next step: after dissolution in acetonitrile (10 mL) were added Hunig's base (0.81 g, 6.28 mmol) and acryloyl chloride (0.56 g, 6.28 mmol) at 0 °C. The reaction mixture was stirred for 20 h at room temperature then diluted with water and extracted with CH_2Cl_2 (2 × 50 mL), dried and concentrated under vacuum to give **1a** (0.828 g, 80% yield).
1a: ^{1}H NMR (400 MHz, $CDCl_3$): 3.99 (s, 3H), 4.35 (t, $J = 4.8$ Hz, 2H), 4.74 (t, $J = 4.8$ Hz, 2H), 5.09 (s, 2H), 5.82 (dd, $J = 10.4$ Hz, $J = 1.2$ Hz, 1H), 6.14 (dd, $J = 17.2$ Hz, $J = 10.4$ Hz, 1H), 6.38 (dd, $J = 17.2$ Hz, $J = 1.2$ Hz, 1H), 6.98 (m, 2H), 7.27 (m, 2H), 7.4 (m, 1H), 7.62 (m, 1H), 9.35 (s, N–CH–N). ^{13}C NMR (100 MHz, $CDCl_3$): 36.24, 42.27, 48.94, 54.01, 65.28, 65.52, 114.02, 122.70, 122.78, 127.65, 128.69, 129.53, 130.69, 136.38, 156.90, 165.48. HRMS/LSIMS; C^+ calcd for $C_{16}H_{19}N_2O_3$: 287.1396, found: 287.1391; $[2C^+, BF4^-]^+$ calcd for $C_{32}H_{38}N_4O_6F^{411}B$: 661.2821, found: 661.2830.
2b: ^{1}H NMR (400 MHz, $CDCl_3$): 1.92 (s, 3H), 3.91 (s, 3H), 4.57 (t, $J = 5.0$ Hz, 2H), 4.60 (t, $J = 5.0$ Hz, 2H), 5.09 (s, 2H), 5.55 (m, 1H), 6.10 (m, 1H), 6. 87 (m, 2H), 7.26–7.35 (m, 3H), 7.5 (m, 1H), 8.81 (1H, N–CH–N). ^{13}C NMR, (100 MHz, $CDCl_3$): 18.67, 36.75, 49.84, 66.24, 66.29, 114.83, 118.57, 121.77, 122.70, 122.78, 127.83, 130.33, 130.69, 136.57, 136.95, 157.70, 167.69. HRMS/ESIMS; C^+ calcd for $C_{17}H_{21}N_2O_3$: 301.1552, found: 301.1550; $[2C^+, NTf_2]^+$: 882.
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