

## Ultra-Easy Access to NH<sub>2</sub>-Functionalized TSILs, Their Potential as Highly Volume-Efficient Electrophile Scavengers, and Insights into the Electronics of Girard's Reagent T, A Venerable Chemical Work Horse

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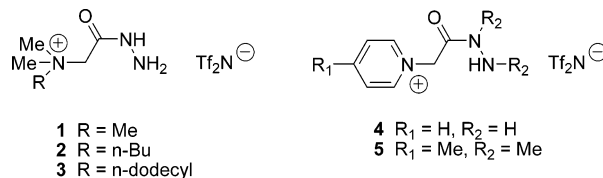
Received November 20, 2006

The development of nucleophilic scavengers is of importance to endeavors ranging from gas separation to solution-phase library synthesis. While most of the latter efforts are focused on polymer-based approaches,<sup>1,2</sup> we believe that task-specific ionic liquids (TSILs)<sup>3</sup> have much to offer in this regard. Indeed, one of our successes after introducing<sup>4</sup> the TSIL concept was the use of [*N*-methyl-*N'*-(3-aminopropyl)-imidazolium]BF<sub>4</sub><sup>-</sup> to capture heterocumulenes such as CO<sub>2</sub>, isocyanates, and isothiocyanates.<sup>5</sup>

Over time we found TSILs based on imidazolium amine cations to be tedious compounds with which to work. Their syntheses involve relatively expensive reagents, can require the use of large amounts of solvent, often entail extensive workups, and the ILs themselves can be unstable to prolonged storage. Except for the last, these difficulties frequently plague the synthesis and use of polymeric scavengers as well.<sup>1,2</sup> Consequently, we set out to create new NH<sub>2</sub>-bearing TSILs for nucleophilic capture applications which could be quickly, easily, and affordably prepared compared to our earlier TSILs or to reactive resins.

Here, we report a success in this regard, having created a new class of TSILs (Scheme 1) which are the first to incorporate a hydrazide group; while they do not constitute a library of compounds, *the new materials have the potential to be exploited as an enabling technology in library synthesis*. Specifically, the pseudo-amine functionality of the present TSILs makes them effective agents for the reactive capture of reagent types frequently used in excess in library synthesis (and does so with a degree of selectivity). Notably, the parent TSILs are prepared with remarkable ease because many commercial salts containing functional ions, such as (carboxymethyl)trimethylammonium chloride hydrazide and 1-(carboxymethyl)pyridinium chloride hydrazide, are prospectively “incognito-TSILs”.<sup>6</sup> Better known as Girard's reagents T and P, respectively, these salts have been widely used since the 1930s to facilitate various separations<sup>7–9</sup> and have recently been used by Lehn and Herrmann as platforms for the slow release of fragrance aldehydes.<sup>10</sup>

Scheme 1. New Hydrazide-Functionalized TSILs



The parent TSILs are prepared from the commercial salts in a *one-step, one-pot process*. The combination of aqueous solutions of Girard's reagent T chloride with NaTf<sub>2</sub>N results in the instantaneous formation of a second liquid (TSIL) phase. In contrast, the Girard's reagent P Tf<sub>2</sub>N salt is rather water soluble. Where isolation of the T-TSIL is accomplished by simple decantation, the P-salt is isolated by evaporation of water from the reaction mixture, followed by its extraction from the resulting residue using ethanol. Further, variants of the Girard's chloride salts with different head groups [e.g., (carboxymethyl)butyldimethylammonium, (carboxymethyl)-dimethyldodecylammonium, etc.] are suitable as TSIL presursors and are also easily prepared in a one-pot fashion per Girard's original approach.<sup>11</sup> The TSILs and their reaction products have been characterized using multiple techniques, including high-field multinuclear NMR, X-ray crystallography, and ESI-MS, -(MS)<sup>2</sup>, and -(MS)<sup>3</sup> (Table 1).

The innate potential of the TSILs to act as agents for reactive capture was assessed by screening their reactions in biphasic systems against THF, CHCl<sub>3</sub>, Et<sub>2</sub>O, and toluene solutions of various substrate molecules. Compound **1** served as our prototype and was therefore screened the most extensively, being assessed for reactivity with phenylisocyanate, ethylisocyanate, phenylisothiocyanate, isobutyraldehyde, and acetic anhydride. In all cases, treatment of these solutions with **1** (1.1–1.8 mequiv) resulted in the removal (to the NMR detection limits) of the substrate from the carrier solvent.<sup>12</sup>

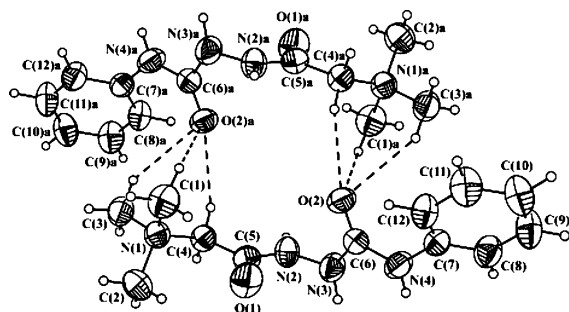
Given the inherent complexity<sup>13</sup> of the NMR spectra of hydrazides and their reaction products, we set out to independently make and isolate several of the cations as BPh<sub>4</sub><sup>-</sup> salts. We succeeded in doing so with the Girard's T parent cation, as well as its reaction products with phenylisocyanate, isobutyraldehyde, and acetic anhydride; single-crystal X-ray structures were obtained on each. We found that in the case of the isocyanate the condensation occurred as expected: the hydrazide –NH<sub>2</sub> group added to the isocyanate C atom to generate a ureido linkage in the same fashion as would an amine (Figure 1).<sup>14</sup> The reactions of the Girard's T cation with both isobutyraldehyde and acetic anhydride also proceeded as expected, the former giving rise to a hydrazone and the latter to an N-acetylated adduct (see Supporting Information for X-ray data). Further, we have been able to establish by ESI-MS that the conjugate cations formed by the TSILs share the same parent mass and fragmentation patterns as those formed in reactions in acetonitrile using the Girard's-T BPh<sub>4</sub><sup>-</sup> salt, allowing us to reasonably infer the nature of the cations present in the TSIL

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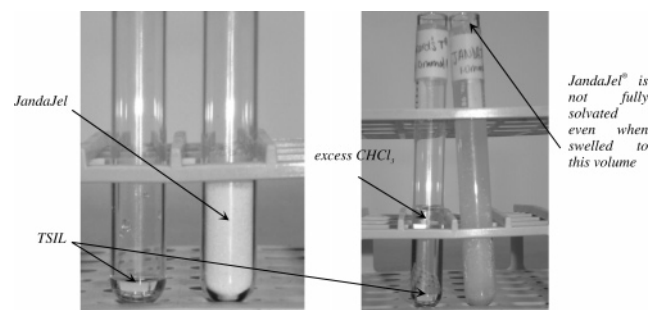
**Table 1.** Representative ESI-MS/(MS)<sup>2</sup>/(MS)<sup>3</sup> Data<sup>a</sup>

cation	anion	captured substrate	expected cation mass	observed cation mass	(MS) <sup>2</sup> fragments	(MS) <sup>3</sup> fragments
(CH <sub>3</sub> ) <sub>3</sub> NCH <sub>2</sub> CH <sub>2</sub> C(O)NHNH <sub>2</sub>	Tf <sub>2</sub> N		132	132	60	
	BPh <sub>4</sub> <sup>b</sup>		132	132	60	
	Tf <sub>2</sub> N	Ph-N=C=O	251	251	132	115, 73, 60 <sup>c</sup>
	BPh <sub>4</sub> <sup>b</sup>	Ph-N=C=O	251	251	132	115, 73, 60 <sup>c</sup>

<sup>a</sup> See the Supporting information for extensive additional MS data. <sup>b</sup> See the Supporting Information for the X-ray structure of this salt. <sup>c</sup> Fragments from 132.



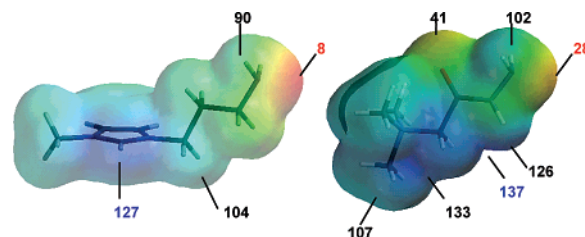
**Figure 1.** ORTEP<sup>14</sup> showing a dimer of the cationic product of the reaction between Girard's T BPh<sub>4</sub><sup>-</sup> and phenylisocyanate. Note the H-bonding between cations in the solid-state.



**Figure 2.** Solvent-swelling behaviors of TSIL **1** and JandaJel-NH<sub>2</sub>.

phases by relating them back to those structures determined through the X-ray studies (Table 1 and Supporting Information).

While the TSILs share a capacity for reactive scavenging with amine-functionalized resins, the former possess a key advantage over the latter in addition to their simple synthesis and relative economy. Scavenger polymers are normally heterogeneous in relation to the solvents with which they are used. Nevertheless, the two must interact to yield a solvent-swelled material to enable access to functional groups within the polymer. This commonly requires solvent volumes several times that of the dry polymer. Depending on the solvent, given ILs similarly form two-phase systems in which the salt incorporates solvent while remaining negligibly soluble in the latter.<sup>15</sup> As noted, this is the case with **1** and several aprotic organic solvents. In these instances the TSILs are swelled by solvent volumes that are a *fraction* of those required by commercial resins bearing equal numbers of -NH<sub>2</sub> groups. For example, treatment of **1** and JandaJel-NH<sub>2</sub> (1 mmol NH<sub>2</sub> each) with CHCl<sub>3</sub> results in two-phase systems in both cases (Figure 2). However, any TSIL volume change is imperceptible, while the expanded JandaJel occupies a volume 4–5 times that of the dry polymer. The results using an amine-functionalized Wang-type resin are similar. From a process standpoint, the potential advantages



**Figure 3.** Comparative electrostatic potentials of the *N*-methyl-*N'*-(3-aminopropyl)imidazolium (left) and Girard's T (right) cations. Note the clearly more positive (hence less nucleophilic) electrostatic potential of the -NH<sub>2</sub> group in the latter. See the Supporting Information for comparative potentials in the neutral isostere 3,3-dimethylbutanoic hydrazide.

of the TSIL systems with respect to solvent and reactor volumes are obvious and are a solid justification for screening them when nucleophilic scavenger systems are needed.

While the hydrazide TSILs were envisioned as surrogates for their synthetically cumbersome amine-imidazolium cousins, the reactivity of the two classes differs in one regard. Where the latter react indiscriminately with CO<sub>2</sub>, isocyanates, and isothiocyanates, we observed no reaction between the Girard-type TSILs and CO<sub>2</sub>. Puzzled by this, we performed calculations on the Girard's T cation and, for purposes of comparison, its neutral isostere 3,3-dimethylbutanoic hydrazide, as well as our own *N*-methyl-*N'*-(3-aminopropyl)imidazolium cation.<sup>5b,16</sup> The results were enlightening. First, the calculated electrostatic potentials (Figure 3) of the -NH<sub>2</sub> nitrogen atoms differed significantly within the group. With values of +28, -34, and +8 kcal mol<sup>-1</sup>, respectively, these calculations suggest that the Girard -NH<sub>2</sub> would be the *least* nucleophilic of the three, an outcome borne out in the apparent inertness of the hydrazide cations toward CO<sub>2</sub>. Notably, in both ions the -NH<sub>2</sub> groups are separated from the formal cation "core" by four bonds, yet the different natures of these linkages appear to have a profound effect on the relative electron density at the -NH<sub>2</sub> groups. Even so, the linker is clearly not alone in influencing the electron density at that site, as can be seen from the differences in the electrostatic potentials between the neutral and cationic hydrazides. For example, in the neutral species, the site of highest potential is the amide N-H (+49 kcal mol<sup>-1</sup>). In contrast, that site in the Girard cation is neither the quaternary ammonium center (+133 kcal mol<sup>-1</sup>) or the amide N-H (+126 kcal mol<sup>-1</sup>) but rather the carbonyl carbon atom (+137 kcal mol<sup>-1</sup>). Overall, it appears that the chemistry of the -NH<sub>2</sub> group is influenced by both the presence of a cationic charge within the gross structure, as well as the nature (and, we speculate, the distance) of the linker between the group and the cationic center.

In summary, the reactivities of hydrazide-functionalized TSILs toward synthetically important, frequently used electrophile classes parallel those of established resins with amine functionalities. Further, the negligible need for swelling before use and their ease of preparation are attributes of considerable practical value that stand in contrast to those of functionally comparable resins. Consequently, these TSILs appear to be well-poised to become a useful new tool for solution-phase nucleophilic scavenging.

**Acknowledgment.** J.H.D. thanks Chevron for support of this work, Rhodia for a gift of HTf<sub>2</sub>N, and acknowledges Merck KGaA as the licensee of the TSILs described herein. R.E.S. would like to thank the Department of Energy and Oak Ridge National Laboratory for the loan of an X-ray diffractometer.

**Supporting Information Available.** Experimental procedures, representative NMR spectra, X-ray crystallographic details, additional X-ray structures, and a summary of MS results. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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