A general design platform for ionic liquid ions based on bridged multi-heterocycles with flexible symmetry and charge†

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A conceptual design platform for new ionic liquids with variable heterocycles, bridges, symmetry, and charge was developed using simple alkylation, click, and ionic liquid chemistries and demonstrated with 1-(2-(5-tetrazolidyl)ethyl)-3-(5-1*H*-tetrazolyl)-methylimidazolium and its conversion into room-temperature ionic liquids as cation or as anion.

Ionic liquids (ILs, salts that exhibit melting points at or below 100 °C[1]) have been identified as attractive candidates for new and improved propellants[2,3] and explosives[4,5] due to several features ideal for energetic materials (EMs) such as low vapor pressures, broad liquid ranges, low melting points, reduced sensitivities to impact, and frequently high heats of formation and temperatures of decomposition. Perhaps more importantly, the unique dual-functional nature of ILs permits the independent modification of structure of either ion, allowing both targeting of optimal performance and reduction of materials hazards in the final product with minimal or no covalent modifications.[6]

While others have been pursuing new examples of ILs that are energetic,[4,5,7] where the primary driver for the synthesis of these materials has been to include energetic ions with targeted physical properties, it has been our interest to understand the underlying science behind how proper combinations of performance and physicochemical characteristics might be incorporated into energetic ILs.[8–11] We have not tried to make energetic materials *per se*, but to understand the influence of added energetic components on IL behavior. We have investigated structural modifications that afford predictable changes in both the properties and reactivity of the final materials,[12] while at the same time exploring new ion platforms and improved synthetic routes to them.[13]

The relationships between materials properties and structure of ILs have been extensively researched and reviewed,[14,15] and for nitrogen heterocycles include changes in the length of alkyl substituents on azolium ions to result in predictable viscosity, melting point, hydrophilicity–hydrophobicity, and density;[16,17] variations in the size and shape of the ions; total ion charge; and charge distribution.[18,19] Several "rules-of-thumb" have been imported from more general IL research, resulting in the push to include ions with low, delocalized charge and asymmetry.

Nonetheless, the research to date in introducing *multi-heterocyclic ions* has primarily focused on the synthesis of 'bolo'-type ILs that featured symmetric heterocycles bridged by either alkyl or ether linkages and with a formal charge on each head group.[20–22] Shreeve and coworkers, however, have reported both non-bridged[23] and bridged tetrazole-functionalized bi-heterocycles from *in situ* generation and reaction of cyanogen azide,[24] and Armstrong *et al.* have also reported the synthesis of some asymmetric alkyl-bridged ammonium-heterocyclic dications.[25] In most cases, the introduction of an additional heterocycle resulted in an increase in the overall charge and increased melting points and viscosity.

We were interested in developing a generalized synthetic platform that would allow us to construct *singly-charged* multi-heterocycle cations and anions with design flexibility in (i) the identity and/or number of incorporated heterocycles, (ii) their charges (+1 or −1), (iii) bridging units (*e.g.*, alkylene, alkylene ethers, *etc.*), and (iv) type and length of substituents appended to each heterocyclic core. Such a degree of synthetic flexibility would provide a systematic approach to control symmetry, charge, and structure in the final product, while at the same time increasing the number of energetic azole cores per cation or anion. This strategy might be considered as intermediate between the well-studied single-azole ion ILs[5] and solid-state energetic polymers that utilize azole building blocks,[26] thus allowing multi-heterocycle design while retaining the properties of a liquid.

To address this challenge, we propose a systematic and versatile multi-heterocyclic synthetic platform combining (a) classic alkylation reactions, (b) click chemistry, and (c) IL strategies (Fig. 1) to obtain highly variable anions, cations, and zwitterions for potential application as novel energetic ILs. Such a generalized approach allows (i) simple formation of functionalized azoles capable of further cyclization, (ii) facile cyclization of functionalized azoles to form bridged multi-heterocyclic compounds, and (iii) utilization of IL-based strategies to access zwitterions, neutral molecules, anions, and cations from common multi-heterocyclic precursors. Here we illustrate the utility of this approach with the synthesis and characterization of bicyclic and tricyclic precursors and their use in the formation of ILs.

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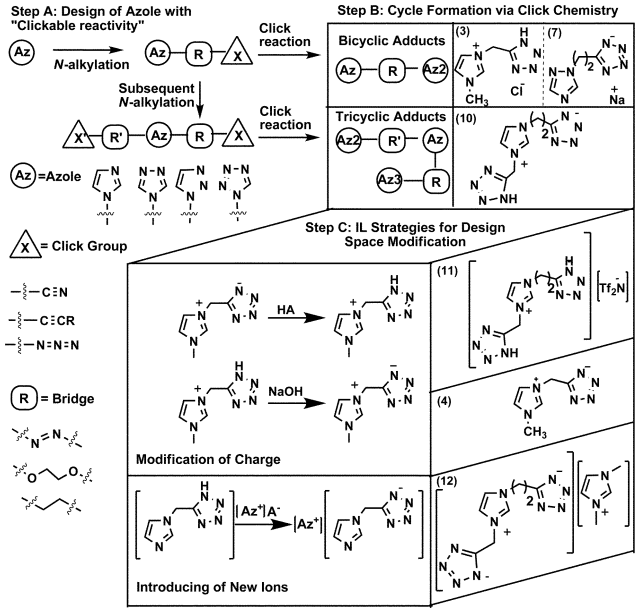
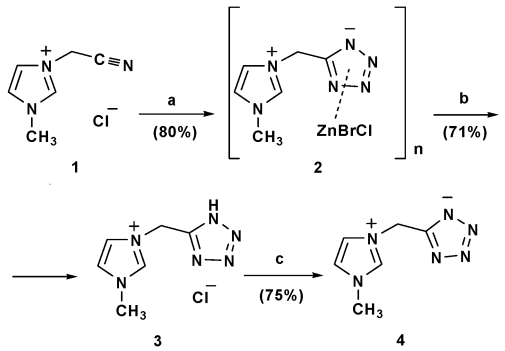


Fig. 1 A flexible platform for the synthesis of multi-heterocyclic targets and their utilization within IL-based design strategies. Numbered compounds have been prepared in this study.

The overall design strategy begins (Step A, Fig. 1) with selection of a starting azole core (Az) which is alkylated one or more times with one or more alkylating agents containing a "clickable" unit (RX and/or R′X, where X = cyano, azo, *etc.*). (Although the core heterocycle could itself be formed *via* click chemistry, a general class of 3+2 dipolar cycloaddition reactions that occur with fast reaction times, mild conditions, and good to excellent yields,[27] we have chosen to start the discussion of our platform approach from the point where most IL researchers entered the field, by alkylation of an azole core.) The number of alkylations corresponds to the number of desired heterocycles to be appended to the core; the alkyl group (R) in the alkylating agent determines the length and nature of the bridges between the heterocycles, and the clickable reagent (X) determines the identity of the appended heterocycles after 'clicking' (Step B Fig. 1).

Step C implements IL-based strategies to obtain the final products. For example, the overall *charge* may be altered through simple protonation/deprotonation, alkylation, *etc.*, resulting in anionic, cationic, zwitterionic, or even neutral products. Additional modification (*e.g.*, alkylation/acylation) of the new heterocyclic cores can introduce new functionalities to tune the final properties of the product or introduce new reactive sites for additional synthetic (*e.g.*, click) operations.

We began our investigations with the simplest example of the design approach, a bicyclic system prepared as in Scheme 1. 1-Methylimidazole was alkylated neat with a slight excess of chloroacetonitrile using a literature protocol to prepare 1-cyanomethyl-3-methylimidazolium chloride (**1**).[28] Reaction of **1** with sodium azide and zinc bromide provided the desired bicyclic core in the form of the Zn-coordinated 1-(5-tetrazolidyl)methyl-3-methylimidazolium·(ZnBrCl) (**2**).[27] Fast formation of **2** (greater than 85% conversion within 2.5 h, estimated by ^{1}H NMR data, see ESI†) was achieved under mild aqueous conditions at room temperature, suggesting



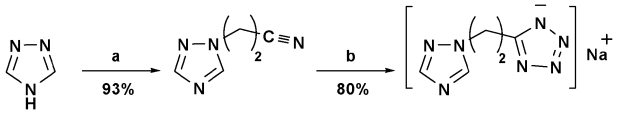
Scheme 1 Synthesis of imidazole–tetrazole bicyclic targets: (a) NaN_3 (1.1 eq.), $ZnBr_2$, water (24 h, RT); (b) BioRad AG 1-X8 (Cl^- form) in 9 N HCl; (c) BioRad AG 1-X8 (OH^- form). **1** was prepared by a solvent-free, RT modification of a literature procedure.[30]

preferable conditions for scale-up, as the solid product **2** readily precipitates from the reaction mixture and was characterized by single-crystal X-ray diffraction (see ESI†).

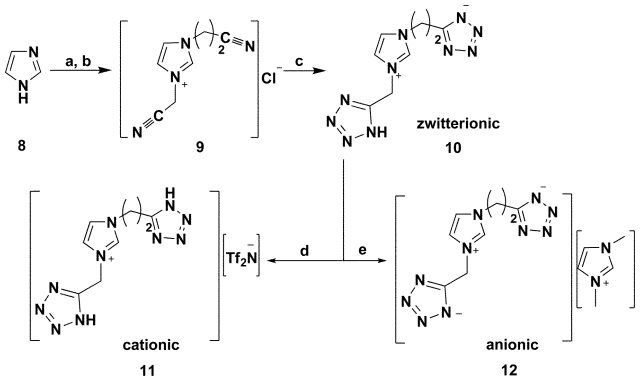
Removal of Zn metal was achieved by a preparatory-scale adaptation of a literature procedure[29] utilizing a strongly basic anion exchange resin (Bio-Rad AG1-X8 in Cl^- form) under high chloride concentration (9 N HCl) to afford the protonated chloride salt **3** (crystallographically confirmed, see ESI†) in 71% yield. Final treatment of **3** with the OH^- form of the same exchange resin resulted in the free zwitterion **4** that was isolated in 75% yield upon filtration of the resin and removal of water.

To demonstrate the anionic case proposed in Fig. 1, we started with 1,2,4-triazole (**5**) and prepared 1-(2-cyanoethyl)-1,2,4-triazole (**6**) by reaction with acrylonitrile with heating in toluene at 70 °C. Treatment of **6** with NaN_3 in the presence of AcOH afforded colorless crystals of sodium 5-(2-(1,2,4-triazol-1-yl)ethyl)tetrazolate dihydrate (**7**·2H_2O) in a single step. The structure of **7**·2H_2O was confirmed crystallographically (see ESI†) (Scheme 2).

In order to more fully demonstrate the scope and versatility of the proposed platform, we designed and prepared the tri-heterocyclic system (Scheme 3) to demonstrate possible incorporation of (i) asymmetric alkyl units bridging each heterocycle and (ii) tunability of charge from cationic, zwitterionic, to anionic in the same molecule. The cationic 1-(2-cyanoethyl)-3-(1-cyanomethyl)imidazolium chloride (**9**) was prepared by a sequence of alkylation reactions including reaction of imidazole (**8**) with acrylonitrile under base-catalyzed conditions to result in the *in situ* formation of 1-(2-cyanoethyl)-imidazole and further alkylation with chloroacetonitrile to form **9**. Next, reaction of **9** with 2.2 eq. of NaN_3 under weakly acidic conditions (AcOH) afforded the tricyclic zwitterionic



Scheme 2 Synthesis of sodium 5-(2-(1,2,4-triazol-1-yl)ethyl)tetrazolate, **7**, from 1,2,4-triazole, **5**: (a) acrylonitrile (1 eq.), Et_3N (cat.), toluene, reflux, 30 h; (b) NaN_3 (1.1 eq.), AcOH, 60–70 °C, 24 h.



Scheme 3 Top: synthesis of zwitterionic **10** from **8**: (a) acrylonitrile (1 eq.), Et_3N (cat.), toluene, reflux, 30 h; (b) chloroacetonitrile, ethyl acetate, RT, 48 h; (c) NaN_3 (2.2 eq.), AcOH, 70 °C, 48 h. Bottom: synthesis of **11** and **12** from zwitterionic **10**. (d) Hydrogen bis(trifluoromethanesulfonyl)amide ($HNTf_2$), MeOH/water 1/1, RT, 72 h; (e) 1,3-dimethylimidazolium-2-carboxylate, MeOH/water 1/1, DMSO (cat.), RT, 72 h.

1-(2-(5-tetrazolidyl)ethyl)-3-(5-1*H*-tetrazolyl)methylimidazolium (**10**), in a single step.

The ready isolation of zwitterion **10** in good yield and purity *via* crystallization allowed us to easily prepare two ILs from this precursor with synthetic operations we normally use to prepare ILs. The protonation of **10** with hydrogen bis(trifluoromethane sulfonyl)amide resulted in quantitative formation of 1-(2-(5-1*H*-tetrazolyl)ethyl)-3-(5-1*H*-tetrazolyl)methylimidazolium bis(trifluoromethane sulfonyl)amide (**11**). Deprotonation of **10** was realized by reaction with l,3-dimethylimidazolium-2-carboxylate (as described in procedures published by our group[13]) leading to 1,3-dimethylimidazolium 1-(2-(5-tetrazolidyl)ethyl)-3-(5-tetrazolidyl)methylimidazolium (**12**) in quantitative yield in a single step. Each of the salts derived from the parent zwitterion were liquid at room temperature (T_m = 10.5 °C and −25.4 °C for **11** and **12**, respectively), thereby demonstrating how one may selectively obtain either cationic or anionic components for ILs from this single zwitterionic precursor utilizing known IL-based strategies.

The design strategy for a systematic and versatile multi-heterocyclic synthetic platform allows for formation of highly variable anions, cations, and zwitterions for potential application as novel IL components or precursors. We believe that the ability to extend the number, identity, and bridging of heterocycles, especially to *asymmetric*, *singly-charged molecular ions* will be a more useful strategy to make ILs than any of the known oligomeric approaches to multi-heterocyclic IL ions. We have demonstrated this here with low-valent, bridged bi- and tricyclic compounds, including the synthesis of the crystalline zwitterion 1-(2-(5-tetrazolidyl)ethyl)-3-(5-1*H*-tetrazolyl)methylimidazolium and its conversion into room temperature ionic liquids as either the cation or the anion. Given the richness of this design space—from available multi-heterocyclic precursors to the diversity enabled by IL-based modifications—we foresee this platform as a powerful tool that may be utilized towards new multi-heterocyclic IL targets of yet unlimited scope or even as an alternative to some of the polymer synthesis approaches to energetic oligomers.

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