



Technology Offer

Thioimidazolium ionic liquids as non-volatile and derivatizable alkylating reagents

File no.: MI0401-5411

Summary

The offered thioimidazolium ionic liquids are a class of easily synthesized and harnessed alkylating agents that are completely non-volatile. The active alkylating species is produced in-situ, thus eliminating exposure and the need for specialized equipment. These features can also be used in the solid-state by their attachment to a poly(styrene) support, which allows for easy purification of the product and regeneration of the thioimidazolium alkylator and could be of special interest for flow chemistry applications.

Background

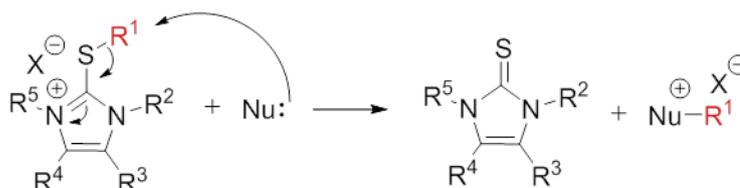
Alkylating agents are among the most widely utilized reagents in synthetic chemistry, biochemistry and cancer therapies. Unfortunately many useful alkylators such as MeI, MeOTf, and methyl-sulfates are limited to use in specialized facilities because of their high volatility, reactivity, pronounced toxicity, and carcinogenic nature. They also possess low degrees of chemical functionality and are unsuitable for attachment on to solid-supports commonly used in integrated chemistry systems. Thus the use of completely non-volatile, yet sufficiently reactive and derivatizable alkylators would simplify user handling by reducing exposure to vapours, and allow for their integration on to materials/polymers. This approach can result in the use of alkylating agents in previously ill-suited territory where exposure to these volatile reagents is prohibited, or where solid-supported systems are desired.

Technology

Thioimidazolium ionic liquids are bench-stable salts that alkylate nucleophiles from the *S*-alkyl position exclusively (Figure 1). They are synthesized from 1,3-dialkyl-imidazole-2-thione precursors which are derived from commercially available 1,3-dialkyl-imidazolium salts. The mildly nucleophilic C=S group can be alkylated using MeI or other alkyl iodides to create a non-volatile salt, however these structures are only meta-stable and react under specific reaction conditions.

Figure 1.

1,3-dialkyl-2-thioalkylimidazolium salt as an alkylating agent



For example, alkylators **1**, **2**, and **3**, with iodide anions can cleanly alkylate nucleophiles such as pyridine (1:1 eq.) in DMSO under mild temperatures, with more electrophilic cations possessing greater alkylating power (Figure 2). The thione by-product can be removed by precipitation in water to isolate the pyridinium salt.

Electrophilic thioimidazolium alkylators derived from benzimidazole (**2**) or caffeine (**3**) easily methylate pyridine to near completion (93-97 %) in 2 hr, in comparison to the more stable cation (**1**). In solution with mild heating, the iodide anion attacks the methyl group to produce small amounts of MeI *in situ*, which then reacts with the pyridine nucleophile. The latent reactivity of these reagents ensures that MeI is *only produced in the reactor vessel where it is immediately consumed*, making the overall chemistry significantly

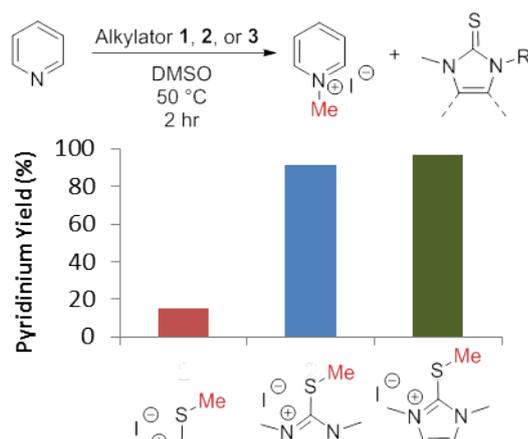


Figure 2. Alkylation of pyridine using different thioimidazolium ionic liquids (1:1 ratio).



safer. The electrophilicity of the cation dictates the activation temperature at which this occurs and is a tunable parameter for a given alkylation reaction. In the solid-state however, these reagents are stable to ~ 150 °C, upon which methyl iodide is released (Figure 3A). Replacement of iodide with a non-nucleophilic anion such as bis(trifluoromethane)sulfonamide (TFSI) improves the thermal stability to ~ 300 °C. Methylation

using a TFSI-based salt is much slower than the iodide-based salts, with only 11 % conversion for 1-TFSI (90 °C, 13 hr; Figure 3B). Reactivity can be restored upon addition of 1.0 eq. KI to the reaction (90 %, 6 hr) and was found to be applicable to all tested thioimidazolium salts. These results demonstrate that thioimidazolium methylators are non-volatile under normal handling/transport conditions and are much safer alternatives to methyl iodide. As well, the TFSI-based salts display very high thermal and chemical stability until activated by both iodide and mild heating, thus substantially increasing the safety of these alkylators without compromising reactivity.

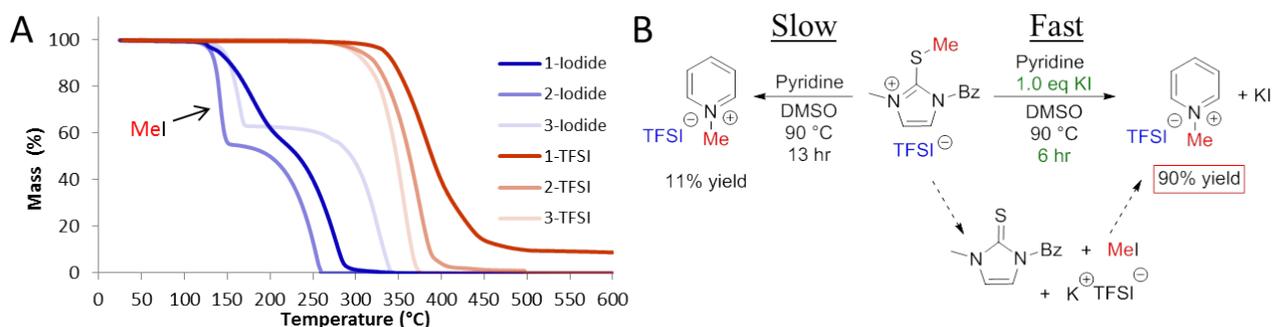


Figure 3. A) TGA thermographs of the iodide and TFSI salts. For the iodide salts, MeI is released at ~ 150 °C. B) 2-TFSI reacts slowly with pyridine unless KI is added, which helps to transiently form MeI and accelerate the reaction.

The derivatizable nature of these reagents provides easy access for their attachment on to solid-supported systems, such as their synthesis on commonly used crosslinked poly(styrene) (Merrifield Resin; Figure 4). The supported systems have alkylating capacities of 1.0-2.0 mmol/g with similar reactivity to their unsupported congeners. This approach allows for easy purification of the alkylated product by filtration, while the resin can be regenerated by treatment with MeI. Similar to the unsupported systems, the alkylating strength of the resin is dependent on the electrophilicity of the thioimidazolium salt. Hexyl and dodecyl substituents were also appended to the resin structures and transferred in a similar fashion. We envision the use of these regenerable resins as invaluable tools in flow chemistry applications. While the alkylating power of these salts do depend strongly on the cation structure, we found that these alkylators were capable of alkylating other compounds such as primary, secondary, and tertiary amines, and tertiary phosphines at 50 °C, and sodium acetate at 80 °C in DMSO.

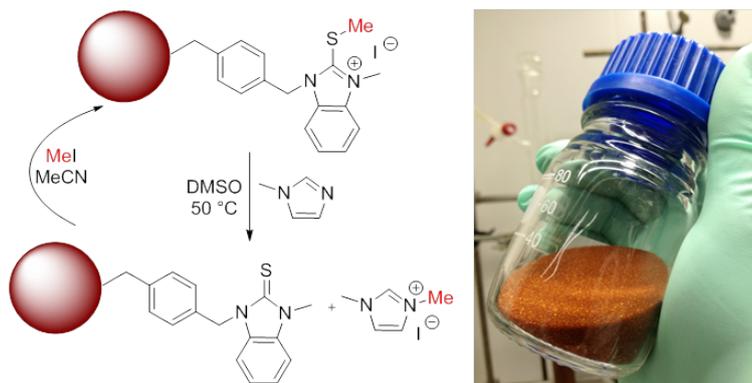


Figure 4. Merrifield Resin functionalized with a thioimidazolium alkylator. These resins are recoverable, regenerable, and amenable to flow and batch reactors.

In summary, these thioimidazolium ionic liquids are a class of easily synthesized and harnessed alkylating agents, yet are completely non-volatile. The active alkylating species is produced *in-situ*, thus eliminating exposure and the need for specialized laboratory equipment. These features can also be harnessed in the solid-state by their attachment to a poly(styrene) support, which allows for easy purification of the product and regeneration of the thioimidazolium alkylator.



Literature

R. Guterman*, H. Miao, M. Antonietti: "Thioimidazolium Ionic liquids as Tunable Alkylating Agents", *J. Org. Chem.*, **2018**, 83(2), 684-689.

Patent Information

EP priority patent application filed September 2017

PCT patent application filed in September 2018

Contact

Dr. Lars Cuypers

Phone: +49 (89) 29 09 19 - 21

cuyper@max-planck-innovation.de