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Thioimidazolium Ionic Liquids as Tunable Alkylating Agents

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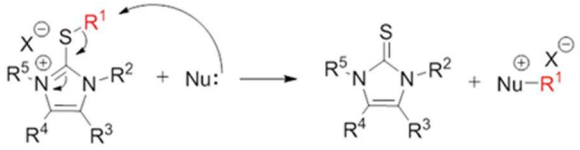


ABSTRACT

Alkylating ionic liquids based on the thioimidazolium structure combine the conventional properties of ionic liquids, including low melting point and non-volatility, with the alkylating function. Alkyl transfer occurs exclusively from the *S*-alkyl position, thus allowing for easy derivatization of the structure without compromising specificity. We apply this feature to tune the electrophilicty of the cation to profoundly affect the reactivity of these alkylating ionic liquids, with a caffeine-derived compound possessing the highest reactivity. Anion choice was found to affect reaction rates, with iodide anions assisting in the alkylation reaction through a "shuttling" process. The ability to tune the properties of the alkylating agent using the toolbox of

ionic liquid chemistry highlights the modular nature of these compounds as a platform for alkylating agent design and integration in to future systems.

INTRODUCTION

Ionic liquids (ILs) serve as a platform to design countless chemical structures with a broad range of chemical, physical, and functional properties. The designer nature of ILs is key to their implementation for specific functions or applications, including extractions,[1] solvents,[2–5] polymers,[6] electrolytes,[7] therapeutics,[8] among many more.[9] Despite these examples, one function that has not been introduced is the ability to alkylate, where the IL can selectively transfer one of its alkyl groups under mild conditions. Such alkylating ionic liquids would combine the highly useful designer nature of ILs, such as tunable thermal properties,[10,11] ionic conductivity,[12,13] and small-molecule affinity,[14,15] with the function of alkylation simultaneously. This approach could help to interface ILs with alkylation chemistry to address the growing need for new strategies aimed at producing synthetically challenging, high-valued organic compounds,[16] including aminomethylation, esterification, among others.[17–21] For example, the synthesis of secondary amines from primary still represents a challenge that could benefit from alkylators that possess defined, yet tunable reactivity.[22,23] It would also introduce a new platform for molecular design and scope to conjugate these molecules to complex systems like biomolecules, polymers, materials, surfaces, and particles in a simple fashion, a feature not possible with conventional alkylators yet are common to ionic liquids.[24–26] Their non-volatility also reduces exposure during handling, allows for their integration in to lab-on-chip devices, and improve overall safety, which is a consistent problem with many alkylating agents such as MeI, dimethylsulfate, and methyltriflate.

To date, some ILs/salts have been used for alkylation reactions.[27] In each case however, their inherent limitations prevent their use as a more general platform for alkylating ionic liquid design. Common imidazolium salts are too stable and low yielding for such applications and require microwave irradiation and/or heating above 300 °C,[28] or in some cases the addition of a strong acid.[29] Meerwein's reagent ($[Et_3O][BF_4]$) is highly effective for O- and N-alkylations, but suffers from moisture sensitivity and poses a significant hazard. Other reactive alkylators such as oxonium ($[OR^1R^2R^3]^+$), sulfonium ($[SR^1R^2R^3]^+$)[30], and tetraalkylammonium[31] species suffer from mixed product formation upon alkyl transfer unless all substituents are identical, thus lacking synthetic and structural versatility. To overcome these limitations, the cation must weakly bind an alkyl group from one specific position while leaving all others free for derivatization; a property not yet realized.

In this context, we introduce the 1,3-dialkyl-2-alkylthioimidazolium structure as a platform for designing a new class of alkylators (Figure 1). Despite their previous discovery and simple synthesis,[32,33] very little is known about their chemical or physical properties. We found that the key to their utility is the exclusive transfer of the S-alkyl moiety to a variety of different nucleophiles, leaving all other positions (R^2-R^5) untouched. This high level of specificity allows for derivatization at the nitrogen and alkenyl positions independently of its alkylation abilities, thus acting as a platform for further design. By fine-tuning the electrophilicty of the thioimidazolium cation reactivity can be controlled, with alkylating ionic liquids derived from simple caffeine capable of alkylating at mild temperature. Surprisingly, the choice of anion had profound effects on the alkylation process, with iodide anions acting as a methyl "shuttle", thus increasing reaction rate. This combination of structural diversity, ease of synthesis, alkyl transfer

specificity, and tunable reactivity underscores these compounds as a platform for alkylating agent design.

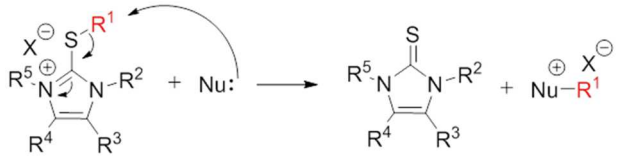


Figure 1. 1,3-dialky-2-thioalkylimidazolium salt as an alkylating agent.

RESULTS AND DISCUSSION

Synthesis of the thioimidazolium salts is described in Scheme S1, which begins with quaternization of 1-alkylimidazole and subsequent sulfurization to create the 1,3-diakylimidazole-2-thione. Alkylation of the thione with methyliodide proceeds at room temperature and reintroduces the cationic charge (See SI for procedure). This simplistic and stepwise synthesis provides a high degree of user control to define the architecture of these compounds, thus allowing for a chemical library to be easily synthesized. Structures examined include thioimidazolium cations bearing *N*-methyl, benzyl, phenyl, or 2-chlorophenyl groups, derived from benzimidazole or caffeine, as well as their iodide and bis(trifluoromethane)sulfonimide (TFSI) salts (Figure 2).[34] The labile nature of the thioalkyl bond was previously described for thiouronium compounds,[35] where at elevated temperatures underwent dealkylation by the nucleophilic attack of the anion. Thermogravimetric analysis (TGA) of our compounds revealed a similar trend, with mass loss at ~120 °C for iodide salts vs. ~300 °C for TFSI. Complete mass loss was observed at ~300 °C for all iodide salts (Figure S1), suggesting that the compounds are undergoing dealkylation, followed by volatilization. This

feature is important as it shows these salts do not evaporate under normal handling condition, thus limiting exposure and improving safety.

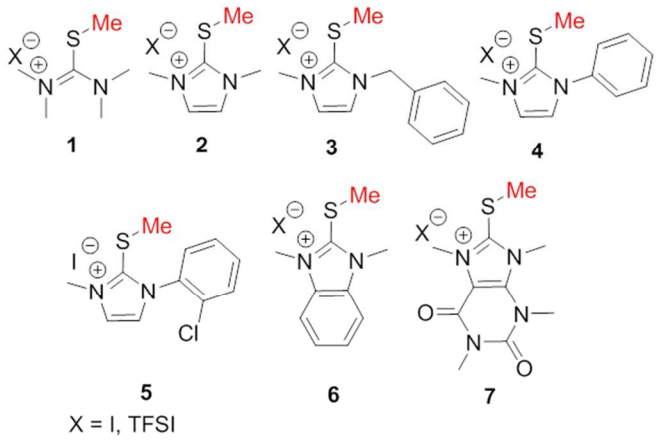
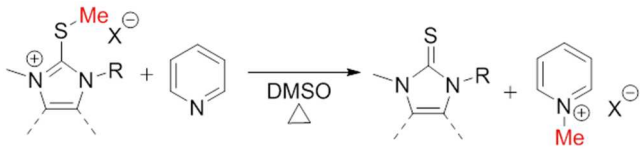


Figure 2. Chemical structures of thioimidazolium salts examined for their alkylation abilities. The red methyl group is transferred to the nucleophile.

The susceptibility of these salts to nucleophilic attack by a relatively benign halide suggests that they may also alkylate other nucleophiles. To assess the role different substitutions and anion has on the reactivity of these compounds, we examined the reaction kinetics for the methylation of pyridine; a moderate nucleophile suitable for this study. Upon treatment of **2-I** with pyridine (DMSO at 90 °C, 13 h) and analysis by ^{1}H-NMR spectroscopy, we observed the formation of 1-methylpyridinium iodide and the appearance of 1,3-dimethylimidazole-2-thione with no byproducts and high conversion (86 %; Scheme 1, Figure S2).

Scheme 1. Model for examining alkylating reactivity.



To confirm that methylation proceeds from the *S*-alkyl position exclusively, the thione precursor was methylated with CD_3I and then reacted with pyridine (Figure S3). While resonances consistent with the formation of 1-methylpyridinium iodide was detected for the aryl hydrogens, the singlet (N-CH_3) at 4.41 ppm was not observed, indicating that only CD_3 was transferred from the sulfur position. This finding is significant as it allows for manipulation of the thioimidazolium structure without compromising its precise alkylation properties. One possible approach to adjust their alkylating abilities is to control the electrophilicty of the thioimidazolium cation. It is well known that good electrophiles are also good alkylators, and that increasing electrophilicity can improves their reactivity. For example, methyltriflate (MeOTf) violently hydrolyzes in water unlike the more stable methylmesylate (MeOMs), resulting from the heightened electrophilicity introduced by the trifluoromethyl. To assess this property for these alkylating agents, the iodide and TFSI salts of compounds **1**-**7** were reacted with one equivalent of pyridine in DMSO and the %converstion to 1-methylpyridinium monitored by ^{1}H-NMR spectroscopy for up to 13 h. Second-order rate constants were obtained by plotting $1/[Pyr]_t$ as a function of time and measuring the slope (Table 1, Figure S4 and S5).

Table 1. Rate constants for reaction of 1-7 with pyridine.

Compound*	Temperature (°C)	X = Iodide Rate Constant (k, $M^{-1}min^{-1}$); ($k_{x\text{-}I}$ /$k_{2\text{-}I}$)**	X = TFSI Rate Constant (k, $M^{-1}min^{-1}$)
1	90	4.7×10^{-3};**0.26**	No rxn
2	90	1.8×10^{-2};**1.0**	2.7×10^{-4}
	50	7.0×10^{-4};**0.04**	-
3	90	4.0×10^{-2};**2.2**	5.0×10^{-4}
4	90	6.9×10^{-2}; **3.8**	5.9×10^{-4}
	50	9.8×10^{-4};**0.05**	-
5	50	2.3×10^{-3};**0.13**	-
6	50	9.2×10^{-2};**5.1**	1.6×10^{-4}
7	50	3.0×10^{-1};**17**	4.9×10^{-4}

*A 1:1 molar ratio of compound (0.1851 mmol) and pyridine were combined in DMSO-d6 (0.400 mL). Rate constants obtained from pyridine conversions. **$k_{2\text{-}I}$ value used for ratio obtained at 90 °C.

With respect to reactivity, we found that both substitution and anion choice had a significant effect on the alkylating abilities of these salts. Unexpectedly, the bis(trifuoromethane)sulfonimide (TFSI) salts possessed significantly lower rate constants (a factor of ~100 for a given cation structure). This finding indicates that there may be participation of the anion in the alkylation process. In the presence of KI we found an increase in reaction rate for **3-TFSI**, with greater amounts of iodide further increasing the reaction rate (Figure 3A). The

reaction rate of **3-TFSI** with 1 equivalent of KI was identical to that of **3-I**, supporting the participation of iodide in the alkylation process. Given the high nucleophilicity of iodide, we believe that at reaction temperature, an equilibrium is established between the thioimidazolium salt and its thione + MeI (Scheme 2). While this equilibrium was previously described in a related system,[36] this is the first case where it can be used for an alkylation process. Upon formation of this equilibrium, pyridine irreversibly reacts with MeI, which is then replenished to continue the reaction. Since iodide is never consumed in the process, it continuously facilitates the alkylation by "shuttling" the methyl group, leading to faster kinetics. Both TGA-MS and ^{1}H NMR spectroscopy experiments confirm that MeI is released upon heating, both neat and in solution (Figure S6 and S7). The TFSI anion is not sufficiently nucleophilic to dealkylate the cation and establish such an equilibrium, thus pyridine must attack the thioimidazolium cation directly, resulting in slower kinetics.

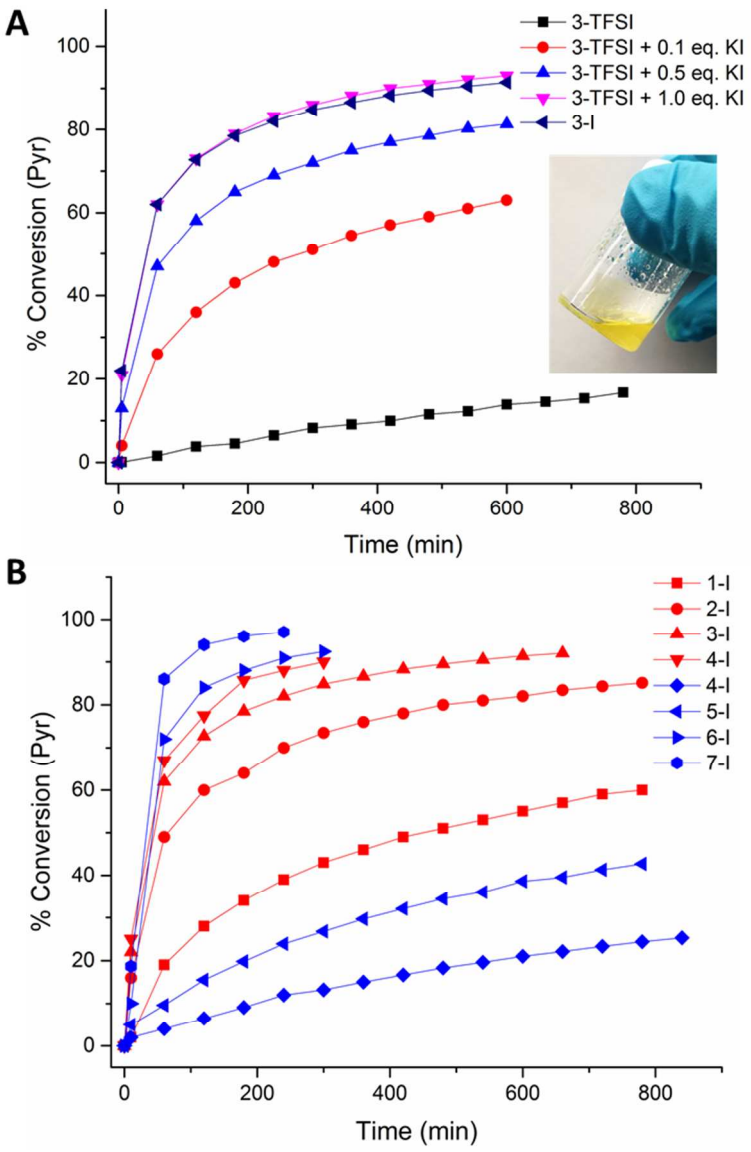
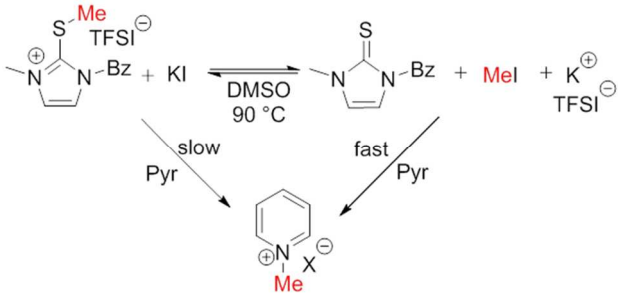


Figure 3. Conversion plots for the alkylation of pyridine to 1-methylpyridinium under various conditions. A) The influence of iodide concentration on the methylation of pyridine by **3-TFSI** (inset shows pristine **3-TFSI**). B) Comparing the alkylating power of **1-7** iodide salts at either 90 °C (red) or 50 °C (blue). A 1:1 ratio of alkylator and pyridine was used.

Scheme 2. Iodide-assisted alkylation with 3-TFSI



The reactivity trend with respect to thioimidazolium substitution follows a more predictable trend, although with even greater differences in reactivity (Table 1 and Figure 3B). Comparing **1-I** and **2-I**, we found that cyclic structures work best for the alkylation process and that aromatic systems are favourable. Surprisingly, the steric influence of the benzyl and phenyl varieties appear to be negligible compared to their electron withdrawing properties, with compound **4-I** possessing a rate constant 4x that of **2-I** and 20 % higher conversion after 240 min. The presence of chlorine at the 2-phenyl position in **5-I** further increases reactivity and confirms that electron withdrawing groups increases reactivity. In the case for **6-I** and **7-I**, extending conjugation at the alkenyl positions dramatically increased reactivity, allowing for 90 %+ conversion in only a few hours at 50 °C. In comparison, **1-3** iodide salts required upwards of 660+ minutes at 90 °C for similar or slightly less conversions. At 50 °C, the rate constant for **7-I** is ~425x larger than **2-I**, illustrating the profound effect chemical structure has on reactivity for these compounds. The highly electron-withdrawing property of the caffeine structure provided the greatest reactivity and demonstrates a unique application for this alkaloid as an alkylating ionic liquid precursor. We assessed the ability of **2-I** to alkylate a variety of other substrates to broaden the scope of these compounds (Table S1). We found that primary, secondary, tertiary amines, and triphenylphosphine underwent alkylation at low temperatures, while sodium acetate required elevated temperatures. Diphenylsulfide, acetic acid, water, and alcohols were non-reactive under tested reaction conditions, however alkaline solutions in either methanol or water quickly

degraded the cations. The ability to discriminate between functional groups is important and relies on the reactivity of the alkylator, which we believe will be of interest for future studies. Further investigations revealed that **2-I** is remarkably resistant to hydrolysis, with only ~1-2 % decomposition after 24 h in D_2O (95 °C) while all other salts could be converted to the TFSI form in water without decomposition. This demonstrates that the presence of water should not significantly interfere or hinder the use of these compounds as alkylating agents, or compete with a nucleophile. We also examined the shelf stability of these compounds and found that after 6 months there were no signs for decomposition. It is possible that dealkylation can only proceed in solution or at elevated temperatures.

CONCLUSIONS

In summary, we demonstrate the synthesis and application of alkylating ionic liquids using the thioimidazolium structure. The synthesis process is simple and uses common reagents, such as imidazole or naturally occurring caffeine. Alkylation proceeds exclusively from sulfur, providing the opportunity to manipulate the other positions of the thioimidazolium cation without risk of mixed product formation. Because of this high degree of specificity, we were able to accelerate its alkylating kinetics by a factor of ~400 in steps. Introducing electron withdrawing groups at one nitrogen position increases reactivity by up to 10x, while extending conjugation at the alkenyl positions increases reactivity by over 400x. Compounds possessing highly conjugated structures, such as those derived from caffeine and benzimidazole possessed the greatest reactivity. We also discovered that iodide serves as an activator for the alkylation process by "shuttling" the methyl group from the thione to the nucleophile, boosting the reaction kinetics by up to 100x. The reaction can be further tuned depending on the amount of iodide added to the

system. Finally, we show that this process is general, applies to other nucleophiles, and represents a convenient platform for alkylating agent design. One challenge that remains is the use of these alkylating ionic liquids for practical alkylation reactions, which includes purification of the product from the thione. This can be addressed either by solid-supporting the structures on a resin or intelligently designing the thione for easy removal. Given the vast utility of both ILs and alkylating agents, we believe their amalgamation will allow for their integrations in to many other systems, including, polymers, materials, new synthesis, and therapeutics.

EXPERIMENTAL

Reagents Caffeine (99 %, anhydrous), 1-phenylimidazole (99 %), 1-(2-chlorophenyl)imidazole (99 %), benzyl chloride (99 %), pyridine (99 %, anhydrous), sulfur (99.98%), diethylether (≥99 %), methyl-d3 iodide (99 %), tetramethylthioura (99 %), benzylamine (99 %), diethylamine (≥99.5 %), triethylamine (≥99 %), benzylalcohol (99.8 %), methyl acetylacetonate (99 %), 4-aminophenol (≥98 %), diphenylsulfide (≥99%) and potassium iodide (≥99 %) were purchased from Sigma-Aldrich and used as received. Deuterated DMSO was purchased from Sigma-Aldrich and stored over 4 Å molecular sieves. Methyl iodide (99 %), 1-methylimidzole (99 %), 1-methylbenzimidazole (99 %), 1,1,3,3-tetramethylguinidine (99 %), and triphenylphosphine (99 %) were purchased from Alfa Aesar and used as received. Potassium carbonate (>99.92 %, anhydrous) was purchased from Fisher-Scientific and used as received. Methanol (99.9 %), 2-pyrrolidione (99 %), and acetonitrile (99.9 %) were purchased from Merck and used as received. Lithium bis(trifluoromethane)sulfonylimide (Li TFSI, 99%) was purchased from IOLITEC and used as received. Ethanolamine (99 %) was purchased from Acros and used as received. L-alanine (99 %) was purchased from Senn chemicals and used as received. ^{1}H, $^{13}C\{^{1}H\}$, and $^{19}F\{^{1}H\}$ NMR spectra were collected on a Bruker DPX-400 spectrometer for the

characterization of all compounds, while the alkylation kinetic experiments were conducted on a Varian 600 MR with a OneNMR probe. Spectra were acquired every hour for up to 13 h. Elemental analysis (EA) was conducted on a VarioMICRO instrument. Thermogravimetric analysis (TGA) experiments were conducted using a Netzsch TG209-F1 apparatus with a heating rate of 10 K min^{-1} under nitrogen flow. TGA-MS measurement was performed using a thermo microbalance TG 209 F1 Libra (Netzsch, Selb, Germany) coupled with a Thermostar Mass spectrometer (Pfeiffer Vacuum; Asslar/Germany) with a ionization energy of 75eV. An aluminium crucible was used for the measurement of ~10 mg of sample under a flow of nitrogen (10ml/min) and a purge flow of 10 ml min^{-1}. The samples were heated at a heat rate of 2.5 K min^{-1} to 600 °C in a first measurement with bargraph cyles from m/z 1 to 200 to first observe all fragments. In a second measurement the found masses were measured in an MID mode with a heating rate of 0.5 K min^{-1}. Because an exothermal process was detected in the first run and the TGA thermostate is overcooling the reaction was decelerated. Data was recorded and analyzed by the Proteus (6.0.0) and Quadstar (7.03, MID modus) software package. Reported decomposition temperatures were taken at 1% mass loss. Differential scanning calorimetry (DSC) experiments were performed on a Perkin-Elmer DSC-1 instrument at a heating/cooling rate of 10 K min^{-1} under nitrogen flow and cycled five times. Melting points and glass transitions were acquired from the final heating cycle. If a melting point could not be observed, it was determined by visual observation using a Thermo Scientific 9300 melting point apparatus. Compounds **1-I** and **1-TFSI** were synthesized according to a literature procedure.[21] Mass spectrometry was conducted on either a HPLC Series 1100 with an ESI-Single Quadropol from Agilent, or a UPLC Acquity H-class with ESI-QTOF G2-Xevo-Xs from Water. All solvent was LC-MS grade from sigma Aldrich.

Nucleophile screening procedure

Compound **2-I** (20 mg, 0.074 mmol) was combined with 1 eq. of substrate (see Table S1) and DMSO-d6 (0.5 mL) in an NMR tube. After 24 h the reaction mixture was analyzed by ^{1}H-NMR spectroscopy to determine whether methylation proceeded. Conversion values were determined by comparing the integration values of the N-CH_3 functionality on **2-I** (δ = 3.901) to N-CH_3 on the 1,3-dimethylimidazolethione byproduct (δ = 3.448) after alkylation. Reactions were then heated to 50 °C and then 80 °C at 24 hour intervals, and analyzed by ^{1}H-NMR spectroscopy prior to increasing temperature. We found that **2-I** is stable at these temperatures in DMSO, so that any decomposition that occurs must be a result of nucleophilic substitution. Substrates examined include: methanol, acetic acid sodium salt, acetic acid, aniline, triphenylphosphine, diphenylsulfide, 1,1,3,3-tetramethylguanidine, 4-aminophenol, methylacetoacetate, L-alanin, diethylamine, ethanolamine, triethylamine, 2-pyrrolidone, benzylamine, benzylalcohol.

Kinetics experiment procedure

A 1:1 molar ratio of alkylating agent (compounds **1**-**7**, both their iodide and TFSI salts) and pyridine (0.1851 mmol) were dissolved in DMSO-*d6* (0.4 mL) and added to a standard NMR tube. The sample was then heated to reaction temperature (50 or 90 °C) and analyzed *in-situ* every hour by ^{1}H-NMR spectroscopy for up to 13 h. Pyridine conversion was determined by comparing the integration values of pyridine (δ = 7.99 or 7.35) to 1-methylpyridinium product (δ = 8.13), while alkylating agent conversion was determined by comparing the integration values of the thioimidazolium salt to the thione product. Second-order rate constants were obtained by plotting $1/[Pyr]_t$ as a function of time and measuring the slope. In all cases, we found

the rate of consumption for the alkylator to be equal to the rate of production of 1-methylpyridinium (Figure S8).

Synthesis

1,3-dimethyl-2-(methylthio)-imidazolium iodide (**2-I**): 1,3-dimethylimidazole-2-thione[19] (1.00 g, 7.80 mmol) was dissolved in acetonitrile (10.0 mL) and methyl iodide (1.661 g, 11.70 mmol) was added dropwise and stirred for 24 h under room temperature. The solution as then precipitated in diethylether (2x50 mL) and volatiles removed *in-vacuo* leaving a white powder, identified as compound **2-I** (1.26 g, 60%) ^{1}H-NMR (400 MHz, DMSO-d6): δ = 2.52 (s, 3H), 3.90 (s, 6H), 7.91 (s, 2H). ^{13}C{^{1}H}-NMR (100 MHz, DMSO-d6): δ = 17.01 (s), 36.10 (s), 124.66 (s), 140.73 (s). T_{dec} = 157.3 °C; T_g = not obs; T_m = 161.0 – 163.8 °C. EA calcd. for $C_6H_{11}IN_2S$: C, 26.68; H, 4.10; N, 10.37. Found: C, 26.73; H, 4.07; N, 10.37.

1,3-dimethyl-2-(methylthio)-imidazolium bis(trifluoromethylsulfonyl)imide (**2-TFSI**): Compound **2-I** (1.00 g, 3.70 mmol) was dissolved in dichloromethane (5.0 mL), followed by the addition of lithium bis(trifluoromethylsulfonyl)imide (1.277 g, 4.444 mmol) and stirred for 72 h. The solution was then diluted with dichloromethane (20 mL) and transferred to an extraction funnel, washed with ultrapure water (3x7.5 mL). The dichloromethane layer was then dried with a small amount of magnesium sulphate, filtered, and the solvent removed *in-vacuo* at 60 °C, leaving a clear, slightly yellow liquid identified as compound **2-TFSI**, (0.939 g, 60 %) ^{1}H-NMR (400 MHz, DMSO-d6): δ = 2.51 (s, 3H), 3.90 (s, 6H), 7.88 (s, 2H). ^{13}C{^{1}H}-NMR (100 MHz, DMSO-d6): δ = 16.82 (s), 36.01 (s), 119.42 (q, ^{1}J = 319.5 Hz), 124.71 (s), 140.75 (s). T_{dec} = 282.2 °C; T_g = not obs; T_m = 26.6-26.7 C. EA calcd. for $C_8H_{11}F_6N_3O_4S_3$: C, 22.70; H, 2.62; N, 9.93. Found: C, 22.84; H, 2.73; N, 9.96.

1-benzyl-3-methyl-2-(methylthio)-imidazolium iodide (**3-I**): 3-methyl-1-benzyl-1,3-dihydroimidazole-2-thione[37] (2.00 g, 9.79 mmol) was dissolved in acetonitrile (10.0 mL) followed by the addition of methyl iodide (2.084 g, 14.69 mmol) dropwise. The mixture was stirring for 24 h and then precipitated in diethylether (2x50 mL) and volatiles removed *in-vacuo* leaving a white powder, identified as compound **3-I** (2.20 g, 65 %). ^{1}H-NMR (400 MHz, DMSO-d6): δ = 2.38 (s, 3H), 3.93 (s, 3H), 5.54 (s, 2H), 7.41 (m, 5H), 7.97-8.02 (m, 2H). ^{13}C{^{1}H}-NMR (100 MHz, DMSO-d6): δ = 17.36 (s), 36.20 (s), 52.06 (s), 124.02 (s), 125.55 (s), 127.70 (s), 128.46 (s), 128.90 (s), 134.76 (s), 140.70 (s). T_{dec} = 120.9 °C; T_g = not obs.; T_m = 123.1-124.5 °C. EA calcd. for $C_{12}H_{15}IN_2S$: C, 41.63; H, 4.37; N, 8.09. Found: C, 41.32; H, 4.31; N, 8.00.

1-benzyl-3-methyl-2-(methylthio)-imidazolium bis(trifluoromethylsulfonyl)imide (**3-TFSI**): Compound **3-I** (1.00 g, 2.89 mmol) was dissolved in dichloromethane (5.0 mL), followed by the addition of lithium bis(trifluoromethylsulfonyl)imide (0.995 g, 3.47 mmol) and stirred for 72 h. The solution was then diluted with dichloromethane (20 mL) and transferred to an extraction funnel, washed with ultrapure water (3x7.5 mL). The dichloromethane layer was then dried with a small amount of magnesium sulphate, filtered, and the solvent removed *in-vacuo* at 60 °C, leaving a clear, slightly yellow liquid identified as compound **3-TFSI**, (0.937 g, 65 %) ^{1}H-NMR (400 MHz, DMSO-d6): δ = 2.38 (s, 3H), 3.94 (s, 3H), 5.55 (s, 2H), 7.41 (m, 5H), 7.96-8.01 (m, 2H). ^{13}C{^{1}H}-NMR (100 M, DMSO-d6): δ = 17.22 (s), 36.11 (s), 52.11 (s), 119.44 (q, ^{1}J = 319.8 Hz), 124.04 (s), 125.57 (s), 127.69 (s), 128.46 (s), 128.88 (s), 134.72 (s), 140.71 (s). T_{dec} = 282.4 °C; T_g = -50.5 °C; T_m = not obs. EA calcd. for $C_{14}H_{15}F_6N_3O_4S_3$: C, 33.67; H, 3.03; N, 8.41. Found: C, 33.71; H, 2.98; N, 8.38.

1-phenyl-3-methyl-2-(methylthio)-imidazolium iodide (**4-I**): 1-methyl-3-phenylimidazole-2-thione[19] (0.439 g, 2.27 mmol) was dissolved in acetonitrile (5 mL) followed by the addition of

methyliodide (0.484 g, 3.41 mmol). The solution was stirred for 24 h and then precipitated in diethylether (50 mL). The solution was decanted and volatiles removed *in-vacuo* leaving a white powder identified as **4-I** (0.609 g, 80%). ^{1}H-NMR (400 MHz, DMSO-d6): δ = 2.34 (s, 3H, S-C*H*$_3$), 4.00 (s, 3H), 7.67 (m, 5H), 8.12-8.18 (m, 2H). ^{13}C-NMR (100 MHz, DMSO-d6): δ = 17.2 (s), 36.3 (s), 125.0 (s), 125.1 (s), 126.3 (s), 129.7 (s), 130.5 (s), 135.3 (s), 141.8 (s). T_{dec} = 138.1 °C; T_g = 87.3 °C; T_m =not obs. EA calcd. for $C_{11}H_{13}IN_2S$: C, 39.77; H. 3.94; N, 8.43. Found: C, 39.89; H. 3.63; N, 8.49.

1-phenyl-3-methyl-2-(methylthio)-imidazolium bis(trifluoromethylsulfonyl)imide (**4-TFSI**): Compound **4-I** (0.347 g, 1.04 mmol) was dissolved in deionized water (5 mL) followed by the addition of LiTFSI (0.315 g, 1.10 mmol) in deionized water (3 mL). The mixture was stirred for 24 h and then decanted. The residue was then rinsed with fresh deionized water (3x5 mL) and volatiles removed *in-vacuo* resulting in a clear viscous oil identified as **4-TFSI**. ^{1}H-NMR (400 MHz, DMSO-d6): δ = 2.33 (s, 3H, S-C*H*$_3$), 4.00 (s, 3H), 7.67 (m, 5H), 8.12-8.18 (m, 2H). ^{13}C-NMR (100 MHz, DMSO-d6): δ = 17.2 (s), 36.3 (s), 125.0 (s), 125.1 (s), 126.3 (s), 129.7 (s), 130.5 (s), 135.3 (s), 141.8 (s). ^{13}C-NMR (100 MHz, DMSO-d6): δ = 17.1 (s), 36.3 (s), 119.4 (q, $^{1}J_{C-F}$ = 320 Hz), 125.1 (s), 125.2 (s), 126.3 (s), 129.7 (s), 130.6 (s), 135.3 (s), 141.8 (s). T_{dec} = 290.7 °C; T_g = not obs; T_m = 112.0 °C. MS (ESI+) m/z: $[M]^+$ Calcd for $[C_{11}H_{13}N_2S]^+$ 205.08; Found 205.10 ($[cation]^+$, 100).

1-(2-chlorophenyl)-3-methylimidazolium iodide (**R1-5**): 1-(2-chlorophenyl)imidazole (1.00 g, 5.60 mmol) was dissolved in acetonitrile (10 mL) and methyl iodide (1.59 g, 11.20 mmol) added dropwise. The solution was stirred for 24 h and volatiles removed *in-vacuo* leaving a slightly yellow powder identified as 1-(2-chlorophenyl)-3-methylimidazolium iodide (1.79 g, 99%). ^{1}H-NMR (400 MHz, DMSO-d6): δ = 3.98 (s, 3H), 7.67 (m, 2H), 7.76-7.84 (m, 4H), 7.98

(s, 1H), 8.12 (s, 1H), 9.58 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d6): δ = 36.2 (s), 123.8 (s), 123.9 (s), 128.6 (s), 128.7 (s), 128.8 (s), 130.6 (s), 132.3 (s), 132.4 (s), 138.0 (s). T_{dec} = 220 °C; T_g = not obs.; T_m = 124.4-130.0 °C. EA calcd. for $C_{10}H_{10}ClN_2I$: C, 37.47; H. 3.14; N, 8.74. Found: C, 37.57; H. 3.26; N, 8.76.

1-(2-chlorophenyl)-3-methylimidazole-2-thione (**R2-5**) :1-(2-chlorophenyl)-3-methylimidazolium iodide (2.59 g, 8.08 mmol) was dissolved in methanol (50 mL) followed by the addition of sulfur (0.412 g, 12.12 mmol) and stirred for 10 minutes. Potassium carbonate (1.45 g, 10.5 mmol) was then added and the mixture stirred for 24 h. Methanol was then fully evaporated *in-vacuo* and the residue rinsed with water (3x50 mL), recrystallized from isopropanol, and dried *in-vacuo* to leaving yellow crystals identified as 1-(2-chlorophenyl)-3-methylimidazole-2-thione (0.724 g, 40%). ^{1}H-NMR (400 MHz, DMSO-d6): δ = 3.54 (s, 3H), 7.24-7.33 (m, 2H), 7.49 (m, 3H), 7.66-7.68 (m, 1H). ^{13}C-NMR (100 MHz, DMSO-d6): δ = 34.6 (s), 118.2 (s), 119.3 (s), 127.9 (s), 130.0 (s), 130.6 (s), 130.62 (s), 131.2 (s), 135.7 (s), 163.2 (s). T_m = 111-112 °C. HRMS (ESI+/TOF) m/z: $[M]^+$ Calcd for $C_{10}H_9ClN_2S$ 224.01750; Found 224.0143.

1-(2-chlorophenyl)-3-methyl-2-(methylthio)-imidazolium iodide (**5-I**): 1-(2-chlorophenyl)-3-methylimidazole-2-thione (0.512 g, 2.28 mmol) was dissolved in acetonitrile (30 mL) and methyl iodide (0.647 g, 4.56 mmol) added dropwise. The solution was stirred for 24 h and volatiles removed *in-vacuo* leaving a slightly yellow powder identified as **5-I** (0.836 g, 99%). ^{1}H-NMR (400 MHz, DMSO-d6): δ = 2.40 (s, 3H, S-CH_3), 4.00 (s, 3H), 7.67-7.87 (m, 4H), 8.21-8.23 (m, 2H). ^{13}C-NMR (100 MHz, DMSO-d6): δ = 17.2 (s), 36.6 (s), 125.4 (s), 125.8 (s), 128.7 (s), 129.8 (s), 130.1 (s), 130.4 (s), 132.6 (s), 132.9 (s), 142.5 (s). T_{dec} = 112.1 °C; T_g =

not obs; T_m = 112 °C. EA calcd. for $C_{11}H_{12}ClN_2S$: C, 36.04; H. 3.30; N, 7.64. Found: C, 35.55; H. 3.10; N, 7.46.

1,3-dimethyl-2-(methylthio)-benzoimidazolium iodide (**6-I**): 1,3-dimethylbenzimidazole-2-thione[38] (1.15 g, 6.39 mmol) was added to acetonitrile (30 mL) and stirred for 10 minutes before adding methyl iodide (1.36 g 9.59 mmol). The solution was stirred for 24 h, concentrated by rotary evaporation, and precipitated in diethylether (100 mL). The solution was then decanted and volatiles removed *in-vacuo*, leaving a white powder identified as **6-I** (0.83 g, 41 %). ^{1}H-NMR (400 MHz, DMSO-d6): δ = 2.72 (s, 3H, S-CH_3), 4.13 (s, 6H), 7.72 (m, 2H), 8.06 (m, 2H). ^{13}C-NMR (100 MHz, DMSO-d6): δ = 17.1 (s), 33.2 (s), 113.2 (s), 126.7 (s), 132.1 (s), 149.9 (s). T_{dec} = 114.8 °C; T_g = 88.5 °C; T_m = 108.0-108.2 °C. EA calcd. for $C_{10}H_{13}IN_2S$: C, 37.51; H. 4.09; N, 8.75. Found: C, 38.11; H. 3.83; N, 8.84.

1,3-dimethyl-2-(methylthio)-benzoimidazolium bis(trifluoromethylsulfonyl)imide (**6-TFSI**): Compound **6-I** (0.950 g, 2.967 mmol) was dissolved in deionized water (10 mL) followed by the dropwise addition of LiTFSI (0.894 g, 3.115 mmol) in deionized water (5 mL). The solution was stirred for 24 h and the precipitate rinsed with deionized water (3x5 mL) and dried *in-vacuo* to isolate a white powder identified as **6-TFSI** (0.883 g, 65%). ^{1}H-NMR (400 MHz, DMSO-d6): δ = 2.71 (s, 3H, S-CH_3), 4.13 (s, 6H), 7.72 (m, 2H), 8.07 (m, 2H). ^{19}F-NMR (376 MHz, DMSO-d6): δ = -78.8 (s) ^{13}C-NMR (100 MHz, DMSO-d6): δ = 17.0 (s), 33.1 (s), 113.2 (s), 119.4 (q, $^1J_{C-F}$ = 320 Hz), 126.8 (s), 132.1 (s), 149.9 (s). T_{dec} = 265.9 °C; T_g = 13.9 °C; T_m = 120 °C. EA calcd. for $C_{12}H_{13}F_6N_3O_4S_3$: C, 30.44; H. 2.77; N, 8.88. Found: C, 30.72; H. 2.72; N, 8.90.

1,3,7,9-tetramethyl-8-thioxo-3,7,8,9-tetrahydropurine-2,6-dione (**RS7**): Compound **RS7** was prepared according to a modified literature procedure.[39] Compound **R7** (3.86 g, 11.5 mmol)

was dissolved in methanol (175 mL), followed by the addition of sulfur (0.44 g, 13.8 mmol), and potassium carbonate (3.18 g, 23.0 mmol). The mixture was stirred for 48 h and volatiles removed by rotary evaporation. The residue was rinsed with deionized water (3x50 mL) and recrystallized from isopropanol, and volatiles removed *in-vacuo* leaving a white crystals identified as **RS7** (1.11 g, 40 %). ^{1}H-NMR (400 MHz, DMSO-d6): δ = 3.23 (s, 3H), 3.71 (s, 3H), 3.79 (s, 3H), 3.79 (s, 3H), 3.96 (s, 3H). T_m = 267.4-269.3 °C.

1,3,7,9-tetramethyl-8-(methylthio)-2,6-dioxo-2,3,6,9-tetrahydropurinium iodide (**7-I**): Compound **RS7** (1.03 g, 4.16 mmol) was combined with methyl iodide (6.20 g, 41.6 mmol) in acetonitrile (20 mL) and stirred for 7 days at room temperature. Volatiles were then removed *in-vacuo* leaving a yellow powder identified as compound **7-I** (1.64 g, 99%). ^{1}H-NMR (400 MHz, DMSO-d6): δ = 2.59 (s, 3H, S-C*H*$_3$), 3.29 (s, 3H), 3.79 (s, 3H), 4.19 (s, 3H), 4.23 (s, 3H). ^{13}C-NMR (100 MHz, DMSO-d6): δ = 17.6 (s), 28.5 (s), 32.1 (s), 35.7 (s), 36.3 (s), 108.6 (s), 140.0 (s), 145.8 (s), 150.00 (s), 152.90 (s). T_{dec} = 126.8 °C; T_g = not obs; T_m =not obs. EA calcd. for $C_{10}H_{15}IN_4O_2S$: C, 31.42; H. 3.96; N, 14.66. Found: C, 31.80; H. 3.72; N, 14.69.

1,3,7,9-tetramethyl-8-(methylthio)-2,6-dioxo-2,3,6,9-tetrahydropurinium bis(trifluoromethylsulfonyl)imide (**7-TFSI**): Compound **7-I** (1.55 g, 4.07 mmol) was dissolved in deionized water (50 mL) and combined with an aqueous solution (10 mL) of LiTFSI (1.23 g, 4.27 mmol), resulting in the formation of a precipitate. After stirring for 24 h, the precipitate was rinsed with water (3x10 mL) and volatiles removed *in-vacuo*, leaving a white powder identified as **7-TFSI** (1.31 g, 60%). ^{1}H-NMR (400 MHz, DMSO-d6): δ = 2.59 (s, 3H, S-C*H*$_3$), 3.29 (s, 3H), 3.79 (s, 3H), 4.19 (s, 3H), 4.23 (s, 3H). ^{13}C-NMR (100 MHz, DMSO-d6): δ = 17.5 (s), 28.5 (s), 32.1 (s), 35.6 (s), 36.3 (s), 108.6 (s), 119.4 (q, $^{1}J_{C-F}$ = 320 Hz) 140.0 (s), 145.8 (s), 150.0 (s),

152.9 (s). T_{dec} = 269.1 °C; T_g = 75 °C; T_m = 143 °C. EA calcd. for $C_{12}H_{15}F_6N_5O_6S_3$: C, 26.92; H. 2.82; N, 13.08. Found: C, 27.13; H. 2.72; N, 13.03.

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Author Contributions

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Supporting information. The synthetic scheme, TGA thermographs, NMR experiments, and kinetic data.

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