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A Solid Alkylation: Highly Recyclable, Flow Chemistry-Ready, Resin-Supported Thioimidazoliums Alkylate Sulfur-Centered Nucleophiles

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KEYWORDS. Merrifield resin; solid-supported ionic liquids; alkylation; flow chemistry.

ABSTRACT: A series of readily regenerable thioimidazolium-based ionic liquids possessing the ability to transfer an alkyl group to a nucleophile are immobilized on cross-linked polystyrene beads. Different alkyl groups can be loaded onto the resin, highlighting the tunability of the material. The efficiency of these materials is demonstrated by their screening against a series of nucleophiles, showing a particular preference for thiols. Finally, these materials were evaluated for use under continuous flow conditions. The flexibility, ease of use, safety, and recyclability of these alkylating resins shows promise for their use in large scale and automated applications.

Alkylation is among the most important reactions in chemistry. Novel synthetic methods and substances that expand our understanding of alkylation chemistry invariably lead to new opportunities in natural product synthesis, pharmaceutical design, polymer innovation, and proteomics. Alkylation continues to find new applications, including as a valuable synthetic process in peptide identification procedures,^[1] peptide modification,^[2] amine chemistry in catalysis,^[3] and of course, for the synthesis of many drug candidates.

Despite these advances in application, the tools themselves remain remarkably unchanged; alkylating reagents are still imagined as soluble substances to be used homogeneously. This is in contrast to other chemistries such as catalysis, ion-exchange, and acid-base neutralization reactions, which often utilize solid-supported materials to simplify product separation or integrate into flow reactors. Alkylation chemistry has yet to make this transition from “molecular alkylators” to “material alkylators”, which would expand the utility of the alkylation reaction beyond the flask and into new settings due to improved safety and convenience. For example, alkyl halides, the workhorses of alkylation, are typically volatile and considered unsafe, thus restricting their use to well ventilated chemical laboratories and used by trained personnel. A “material alkylator” on the other hand would have none of these disadvantages and could be easily incorporated into non-traditional environments such as lab-on-a-chip devices, field analytical tools, microfluidic reactors, and flow-chemistry setups.

Given the importance of alkylation, its safe and easy application would introduce a valuable chemical tool.^[4]

There are only a few examples of general-use solid-supported alkylators in the literature. These include polymer-supported *O*-alkylisoureas for the alkylation of carboxylic acids,^[5] and Evans’ oxazolidinones for asymmetric alkylations.^[6] The synthetic difficulty in preparing or regenerating these reagents is one of the reasons limiting their applications. Ideally, a solid-supported alkylator should be easily synthesized, possess tuneable reactivity, be readily regenerable by the end user (like the commonly used acidic resin DOWEX),^[7] be capable of transferring different alkyl groups, and alkylate a variety of different nucleophiles under mild reaction conditions.

Recently we reported a new class of thioimidazolium-based alkylators that may satisfy these requirements.^[8] These are easy to make, readily tunable, and their reactivity can be modulated by the appropriate choice of cations and anions. Despite this, they have yet to be solid-supported and examined as a “material alkylator”.

Herein, we report the preparation and the application of polystyrene-supported alkylators. We discuss their tunability, and their employment in the synthesis of ethers, thioethers, and amines. Finally, we demonstrate that these can be used in continuous flow for high throughput alkylation with minimal workup, making them the first example of such agents.

RESULTS AND DISCUSSION

Synthesis, reactivity, and properties of solid-supported alkylating ionic liquids

The structure of the solid-(supported) neutral alkylating ionic liquids (**SNAILS**) consists of a thioimidazolium or thiobenzimidazolium cation anchored on a polystyrene-based resin paired by a series of anions (Figure 1). The synthesis is accomplished on a standard Merrifield cross-linked chloromethyl polystyrene resin. Merrifield was chosen due to its broad utility as well as its familiarity to users

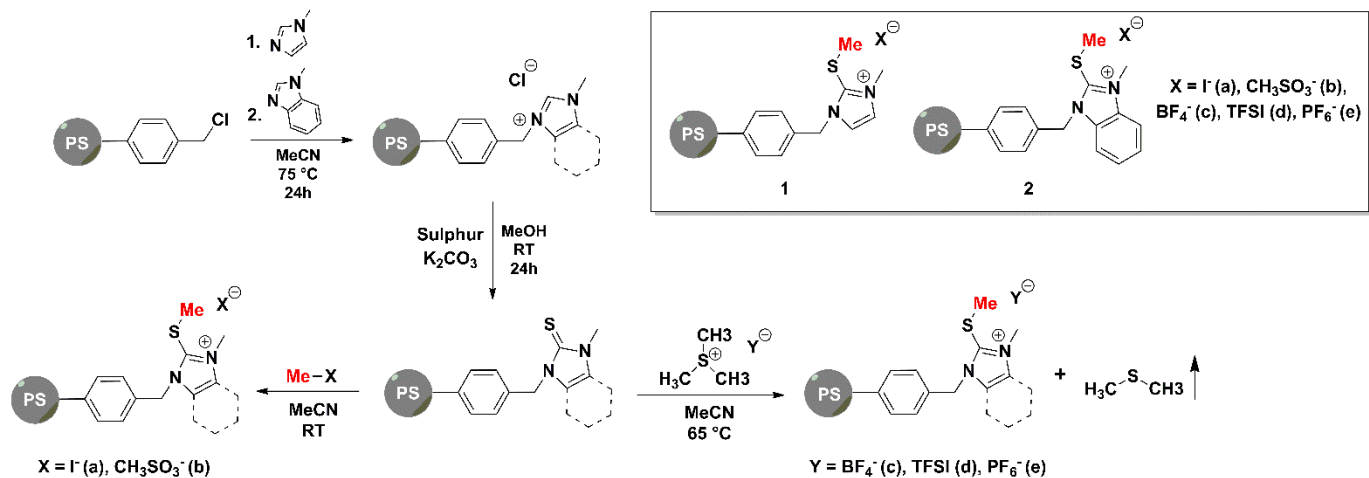


Figure 1. Synthetic procedure for the preparations of materials **1a-e** and **2a-e**.

who employ solid-supports and flow chemistry processes.^[9] It also allows for direct comparison between our materials and the current state of the art. Synthesis of all SNAILs began with the quaternization of either 1-methylimidazole or 1-methylbenzimidazole on Merrifield resin (5.2 mmol chloromethylstyrene per gram) followed by sulfuration in methanol to produce the thione. This can then be activated with the desired alkyl group and associated counterion, in this case through alkylation with methyl iodide (**a**), methyl methanesulfonate (**b**) or more generally, a trimethylsulfonium salt containing the anion of choice, BF_4^- (**c**), TFSI (**d**), PF_6^- (**e**). The use of trimethylsulfonium salts produces dimethylsulfide as the only side product, which evaporates from the reaction mixture. The reaction was monitored by ATR-FTIR spectroscopy for the appearance and disappearance of characteristic vibration signals. Probing **2a** by energy-dispersive X-ray spectroscopy reveals the presence of both sulfur and iodide (Figure S1) providing further evidence for the successful synthesis of solid-supported thioimidazolium salts. The simplicity of this preparation and the use of commercially available reagents makes this approach highly applicable to produce solid-supported alkylators. Other approaches require dry or oxygen free reaction conditions^[10] and the use of metals and catalysts,^[5] which are all avoided in this procedure. We also pursued an approach where we photopolymerized the alkylating agents to resins with very high loading; however, this Merrifield approach is preferable due to its simple incorporation into already existing workflows in standard flow chemistry devices and packed columns, and the avoidance of any additional capital investment or the need to use new chemistry.

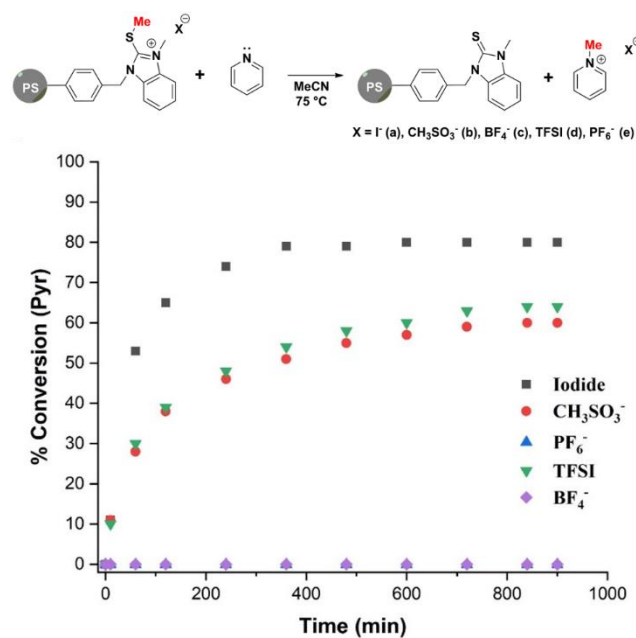


Figure 3. Percentage of pyridine converted by **2a-e** over 15h at 75°C in MeCN-d_3 . The reaction investigated is reported above the graph.

Previously we have shown that more electrophilic cations yield more active alkylating salts.^[8a] To determine whether these same trends were maintained in the solid-supported analogues, resin **1a** and **2a** were compared for the synthesis of 1-methylpyridinium iodide in acetonitrile (Figure 2). Significantly higher activity was observed for the benzimidazolium-containing resin, with ~80% conversion of pyridine to pyridinium after 350 min at 75 °C vs ~20% for imidazolium-containing resin, confirming our previous small-molecule studies. To our knowledge, this is the first example of a solid-supported alkylator with easily tuneable reactivity parameters. Despite using a slight excess of alkylator, a plateau was observed after 300 minutes, which we believe to be due to the volatilization of MeI *via* intramolecular attack of iodide under these reaction conditions.^[8a] Comparison of the kinetics of **2a-e** (Figure 3) demonstrates an anion-induced influence on reactivity, with the iodide anion being the most reactive, followed by TFSI and mesylate. Curiously, no reactivity was observed for the materials bearing either a PF₆⁻ or a BF₄⁻ anion. Such results are consistent with what we have previously shown in our study of the small molecule system. In that study, the role of ion-pairing differences in a series of complexes with various anions in changing the reaction mechanism were highlighted.^[8b] Specifically, we showed that an iodide-based alkylating ionic liquid reacts with nucleophiles *via* a 2-step mechanism, which involves the *in-situ* formation of CH₃I. As this process is temperature controlled, the anchoring of the thioimidazolium cation on a solid support does not hamper the final reactivity of the material. On the other hand, alkylating ionic liquids bearing CH₃SO₃⁻ and TFSI anions react through a 1-step mechanism, in which the anion assists the alkylation of pyridine directly. CH₃SO₃⁻ reacts with a mechanism that is at the border between a 1-step

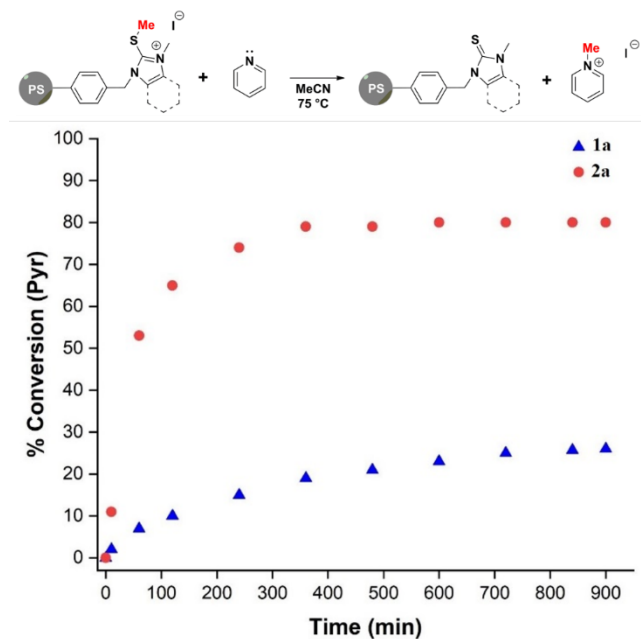


Figure 2. Percentage of pyridine converted by **1a** and **2a** over 15h at 75 °C in MeCN-d₃. The reaction investigated is reported above the graph.

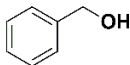
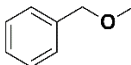
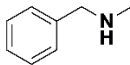
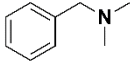
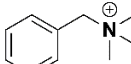
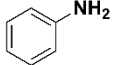
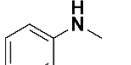
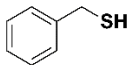
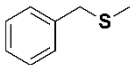
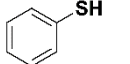
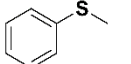
and a 2-step mechanism, while the large size of TFSI inhibits the nucleophilic attack of pyridine. These effects combine to explain why these anions react slower than iodide.

Contrastingly, the poor reactivity of BF₄⁻ and PF₆⁻ can be explained by their lack of nucleophilic character. In fact, such anions cannot form a transient *in-situ* alkylator *via* a 2-step process, nor can they assist the direct attack of pyridine, as observed in the case of PF₆⁻ in a small molecule system, in which its exceptional reactivity was attributed to a combination of attractive interaction between alkylator and nucleophile inside the solvation pocket formed by DMSO and the anion. This phenomenon may be complicated in the case of a solid-supported alkylator, where the presence of the supporting polymer disrupts or impairs the formation of a solvent pocket, thus not allowing for the optimal conditions necessary for reactivity. A similar explanation holds for BF₄⁻.

A crucial property of a solid-supported alkylator is the possibility for its regeneration and re-use. This feature is central to the popularity of ion exchange materials such as Amberlyst resins,^[11] and polymer-supported reagents for flow chemistry applications.^[12] Regeneration of the resin should be possible since the alkylation reaction results in the formation of the thione precursor. Consequently, regeneration studies were performed on **2a**. Fresh resin was used to alkylate an excess amount of 1-methylimidazole and the conversion percentage to the imidazolium salt was measured by ¹H-NMR spectroscopy to determine capacity. The spent resin was then re-alkylated with MeI in different solvents and the reaction with 1-methylimidazole was then repeated. We found that after five such full regeneration cycles, no loss of alkylating efficiency of **2a** is detected and the amount of 1-methylimidazole converted remains constant (Figure S2). These results suggest potential infinite recyclability for this series of solid-supported AILs, as well as great reliability and long-term efficiency. We also found that the resin was regenerable in various solvents for at least 5 cycles with no loss in activity (Table S1). The alkylation capacity of the resin after the first regeneration was different depending on the solvent used in the regeneration cycle; however, the alkylation reactivity then remained consistent across the following 4 cycles. The difference in capacity is likely a result of resin swelling, with ethanol being the most suitable solvent. This behaviour has been previously observed for Merrifield resin when it has been used for other applications.^[13] The ability to regenerate the resin in this simple fashion is particularly convenient in flow systems and is similar to the function of ion-exchange resin, which are routinely repeatedly regenerated once spent.

Previously we have demonstrated that alkylation using thioimidazolium salts is not limited to methylation, but is also compatible with higher alkanes up to C₁₂.^[14] Regeneration of **2a** using other alkyl iodides such as butyl iodide and benzyl bromide is also feasible and broadens the scope of the alkylating resin. Using a single batch of resin starting with

Table 1. Alkylation yields of a series of nucleophiles by **2a**.

Entry	Nucleophile	Product	Yield (%)
1			0
2			10
			6
3			3
4			92
5			99

methyl functionalization, five regeneration cycles using butyl iodide followed by five regeneration cycles with benzyl bromide were conducted through the alkylation of 1-methylimidazole (Figure S3). The ability to easily reuse spent resin and introduce different functionality greatly expands the applicability of the resin in flow systems and saves on cost. To the best of our knowledge this is the only readily regenerated, solid-supported, modular alkylator where different alkyl substituents can be attached and transferred after each cycle. This greatly decreases cost as the same batch of resin can be used as multiple reagents over its lifetime. Extant solid-supported alkylators are far more difficult to recycle.^[10, 15]

SNAILs for organic synthesis

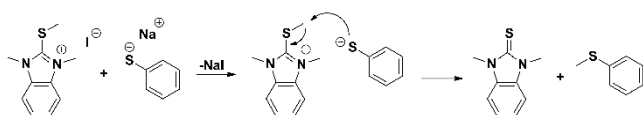


Figure 4. Proposed mechanism for the alkylation of thiophenolate ion by **IL-2a**.

Expanding the scope of nucleophiles beyond pyridine and 1-methylimidazole is critical for SNAILs to prove useful. Consequently we examined the methylation of a variety of representative O-, N-, and S- nucleophiles by **2a** (Table 1, see Figure S4 for a representative reaction with N-methylbenzylamine). In these experiments, resin **2a** and the nucleophile were transferred into a flask in a 10:1 molar

ratio in acetonitrile in the presence of 1 eq. *N,N*-diisopropylethylamine and heated up to 80 °C for 24 hours. The conversion to product was determined by ¹H NMR analysis of the reaction mixture. An excess of solid-supported alkylators was employed to ensure full conversion. Despite a ten-fold excess of alkylator, we observed no reaction towards benzyl alcohol and only very low conversions for a variety of different aliphatic amines. Methylation of *N*-methylbenzylamine results in multiple products, while benzylamine permanently deactivates the resin (See the Supporting Information for additional discussion, spectra, and reaction schemes). Primary amines and alcohols are not suitable substrates for thioimidazolium salt alkylation, while secondary amines are slow and provide low conversions and multiple products. However, near complete conversion of thiols is observed in less than 5 minutes, suggesting selectivity of the alkylator towards certain types of nucleophiles. In the other cases, the mass balance was represented by unreacted starting material. In order to explore this selective behaviour and the factors that influence it, further detailed studies to probe the interaction between the alkylating agent and thiophenol were conducted (Figure 4). Investigative studies were conducted using the small molecule equivalent of **2a**, unbound to the resin, **IL-2a**. The reaction between **IL-2a** and thiophenol was conducted in DMSO-*d*₆ at 80 °C in the presence of 1 eq. of *N,N*-diisopropylethylamine, and the conversion of the nucleophile monitored by tracing the conversion of the methyl resonance from the alkylator ($\delta = 2.44$ ppm) to thioanisole ($\delta = 2.42$ ppm) by ¹H NMR. While these reactions normally require many minutes or hours to occur, here complete conversion of thiophenol to thioanisole was achieved after only 5 minutes. The same reaction, conducted at room temperature, proceeds to 50% conversion after 30 minutes (Figure S5). This demonstrates that the reaction will still proceed with the solid-supported alkylators in environments in which high temperatures are not desirable, such as in studying biochemical processes or protein labelling. In contrast, the pyridine alkylation by a variety of different thioimidazolium salts requires temperatures of at least 50 °C and a few hours to reach higher conversions.^[8a] In order to shed light on the factors that determine such diversity in reactivity, the alkylating potency of **IL-2a** was compared to that of CH₃I in reactions with both pyridine and thiophenol. Pyridine reacted far faster with CH₃I at room temperature in comparison to **IL-2a**, but this stark difference was not observed with thiophenol (Tables S2 and S3). These results suggest a different reaction mechanism for the alkylation of thiolates using thioimidazolium salts than for pyridine.^[8b] A possible explanation for the high observed reactivity is the encapsulation of the two reacting species in a reaction pocket. This is not unprecedented: DMSO and other polar aprotic solvents such as acetonitrile have been shown to surround and encapsulate ion pairs rather than separating them via a solvent separated mode of action for ion pairing species.^[16] We propose that after thiophenol deprotonation by *N,N*-diisopropylethylamine, the solvent drives **IL-2a** and the thiophenolate to interact and

undergo ion exchange, with thiophenolate replacing iodide in **IL-2a**. This close proximity accelerates the reaction *via* an intramolecular nucleophilic substitution to yield thioanisole. The process is shown in Figure 4 and can potentially be equally relevant to **2a**. However, this alternative mechanism would require a more detailed investigation.

On the other hand, the poorer reactivity of **2a** towards amines can be explained by the absence of this process, where the nucleophile must instead encounter the electrophile *via* diffusion rather than through a more favourable electrostatic attraction. A possible explanation involves the amine attacking the C2 position of the resin-supported thioimidazolium moiety. The resulting imine prevents reagent regeneration, *de facto* poisoning it (Figure 5).

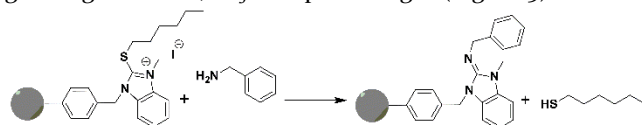


Figure 5. Proposed mechanism for the poisoning of the solid-supported alkylating agent by benzylamine.

To probe this assumption, a hexyl chain was loaded onto resin **2a**, which was then treated with benzylamine under conditions otherwise identical to those used for the methylation. Products were characterized *via* ^1H NMR. Formation of 1-hexanethiol in solution was observed, supporting the supposition that benzylamine attacks the C2 position of the thioimidazolium ring, explaining the irreversibly poisoning of the resin observed for primary amines (Figure S6). The same experiment was conducted with benzyl mercaptan where no such sulfur exchange was observed. Should the same mechanism have been active, we would have observed the formation of hexanethiol, but only the desired thioether was obtained.

To further support our experimental observations of the reactivity trends shown in Table 1, the key transition states corresponding to the alkylation of entries 1-5, through the proposed most possible one step mechanisms were located (Figure 6); however direct attack of the sulfur nucleophiles onto the urea carbon could not be identified. All attempts to obtain that transition state reverted rapidly either to the alkylation reported here or the ground state minima of a complex of alkylating agent and benzylamine, suggesting that it is not a permitted transformation. For each *N*-, *O*-, and *S*-based nucleophilic reagent, the lowest energy transition state corresponded to that leading to the experimentally observed products. Interestingly, the relative reactivity of the various systems aligns exactly with the observed trends; alkylation by **2a** of *S*-centred nucleophiles is significantly favoured over *N*- and *O*-centred systems. For example, the deprotonated thiophenol (thiolate) has the lowest activation barrier of $\Delta G^\ddagger = 17.5$ kcal/mol and is 0.8 kcal/mol more favoured than the analogous transition state arising from using deprotonated benzyl thiol as the nucleophile ($\Delta G^\ddagger = 18.3$ kcal/mol). Both *S*-based alkylating agents form a thermodynamically stable (significantly downhill from

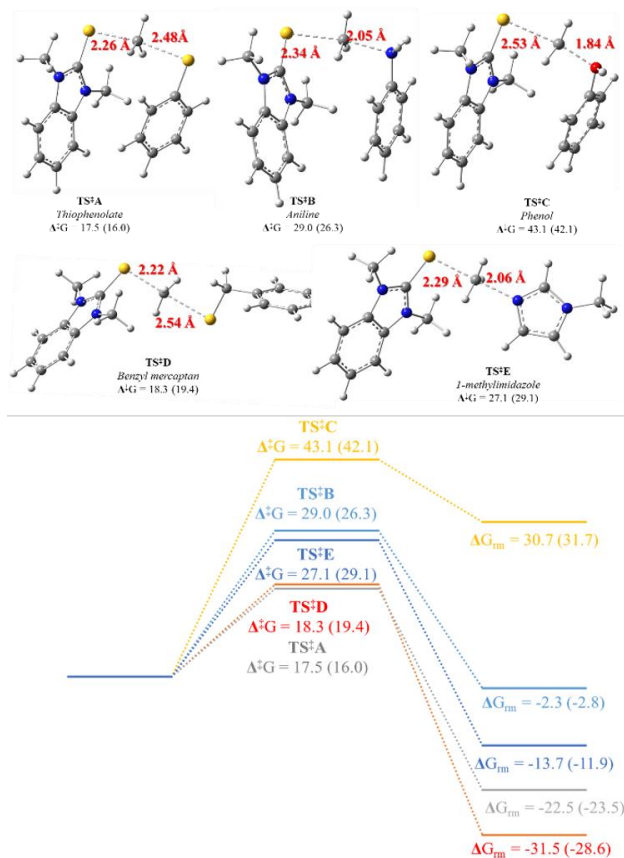


Figure 6. a) The optimized geometry of transition states; b) the calculated kinetics and thermodynamics.

starting materials) alkylated product. The computational data also supports the failure for benzyl alcohol and only the poor conversions noted for a variety of different amines. *O*-alkylation is disfavored both thermodynamically ($\Delta G_{\text{rm}} = 30.7$ Kcal/mol) and kinetically ($\Delta G^\ddagger = 43.1$ Kcal/mol; Figure 6b; see Supporting Information) even for a phenol nucleophile. *N*-alkylation is likewise kinetically challenging, although the reaction is spontaneous ($\Delta G^\ddagger = 29.0$, $\Delta G_{\text{rm}} = -2.3$ Kcal/mol).

Comparing the structural details of the transition states provides additional information, especially for the comparison of the *S*-based TSs, phenylthiolate versus benzylthiolate. The benzylthiolate nucleophile extends away from the **2a** subassembly minimizing interactions, while in the phenylthiolate the reactants align (Figure 6a) inducing a favourable face-to-face stacking interaction involving the aryl-**2a** group and the phenylthiolate's aromatic ring. This stacking interaction is also present as a stabilizing factor in the *O*- and *N*-based TSs; however, the late character of the TS and the weak donor-acceptor interactions exacerbate the existing disfavored energetics in these cases. In addition, TS_{thiolate} and TS_{benzylthiolate} possessed several other notable structural features. They have the early character with long C...S_{Nu}, and short S_{IL}...C bonds compared with the *O*- and *N*-based systems (Figure 7). Each transition state also possesses stabilizing donor-acceptor interactions between

the nucleophilic sulfur and the ring system of **2a**. Of additional interests are the more favoured donor-acceptor interactions (confirmed by Mulliken charges at donor-acceptor sites; S, CH₃, S_{Nu}) (Figure 7). Whereas in the disfavoured N- and O-substituted geometries, these interactions are best defined as a weak electrostatic attraction with smaller Mulliken charges. Taken together, it would appear based upon these DFT calculations that the relative orientation (the flipped alignment) of nucleophile, the early character of the transition state (with shorter S...C(H₃) bond breaking and longer C(H₃)...S_{Nu} bonding forming distances),

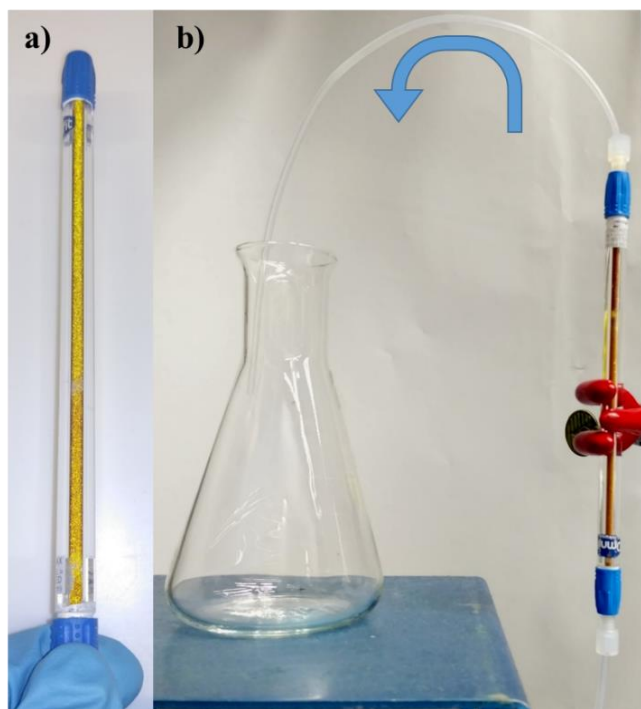


Figure 8. a) Glass tube loaded with **2a**; b) Setup for the collection of the exiting solution.

and presence of a set of stacking and attractive donor-acceptor interactions within TS_{thiolate} and TS_{benzylthiolate} geometries governs the observed reactivity trends of these alkylation reactions. It is important to note that these predictive kinetics and thermodynamics models are highly aligned with the observed experimental formation of the desired product.

Solid-Supported alkylation in flow chemistry

Flow chemistry over a solid support allows for an uninterrupted process and limits the amount of material involved that can cause an incident at any one time. The use of a solid support is highly beneficial in that it simplifies purification; alkylation remains a significant challenge as it is an inherently harsh reaction, but these systems might be very useful for alkylating thiols due to their compatibility with polystyrene. This is not only useful for all the usual benefits of flow chemistry,^[17] but as the resin is readily regenerable, it minimizes handling and simplifies operation, allowing for all the chemistry to take place in a cartridge.

To assess feasibility, a simple setup consisting of a packed column and syringe pump was designed and the alkylation of different substrates examined. In a preliminary reaction setup, a glass tube was loaded with resin **2a** (Figure 8a). The tube was connected on one side to a collection flask (Figure 8b), and on the other side to a syringe, affixed in a mechanical syringe pump, used to introduce an acetonitrile solution containing a test nucleophile, 1-methylimidazole at a fixed flow rate (0.2 mL/min). To control the temperature, the glass tube was surrounded by heating bands held at 80 °C (Figure S7). As expected, room temperature preliminary tests showed only a low conversion. During the reaction, the solution was dispensed by the pump, pushed through the resin-loaded heated glass tube, and collected in the receiving flask. Following reaction, the solution was concentrated and analysed by ¹H NMR spectroscopy to assess the extent of the conversion. In a typical experiment, 0.70 g of **2a** was loaded into the tube (1 mL column volume) and 3 mL of acetonitrile containing 0.10 equivalents of 1-methylimidazole (42 mM) was pumped through the heated column. This leads to a dwell time of approximately 5 minutes, and a total reaction time of 15 minutes. Results (Table 2) show that alkylation proceeds, although admittedly not to completion; a longer dwell—longer than 5 minutes—is likely necessary for complete conversion. When the same flow experiment was conducted using thiophenol, the reaction proceeds extremely smoothly at 80 °C, and moderately at ambient temperature. This same process has been proven to be also suitable for alkylations with higher order electrophiles than methyl.

The presented results not only confirm the efficacy of solid-supported alkylating ionic liquids in organic trans-

TS ^A (thiophenolate)	Δ [‡] G = 17.5 (16.0)	TS ^C (phenol)	Δ [‡] G = 43.1 (42.1)
Bond Length (Å)	Charge (e)	Bond Length (Å)	Charge (e)

Table 2. Conversion percentages for the sequential alkylation of target molecules by material **2a** in a flow process.

Entry	Nucleophile	Product	Temperature (°C)	Yield (%)
1			80	40
2			25	53
3			80	100
4			80	84
5			80	72

formations, but also show their adaptability to different reaction setups. Their incorporation in flow chemistry systems greatly expands their potential and demonstrates the feasibility of their introduction into environments outside a synthetic research lab. Although these novel materials still require further investigations into their applicability to different targets and the extent of their tunability, the results collected so far constitute a proof of principle that SNAILs should find their way into the synthetic chemist's toolbox and studies involving site specific labelling of proteins are underway.

CONCLUSIONS

Solid-supported alkylating agents based on thioimidazolium salts was prepared from Merrifield resin and successfully used in a flow-reactor. Owing to their tuneable reactivity, regenerability of the resin, and their ability to transfer different alkyl groups, and most importantly that these parameters can be tuned independently of one another, these SNAILs are easy to use alkylators. The resin displayed no loss in activity after 11 regeneration cycles using different alkyl substituents, with alkylation capacity ranging from 0.8-4.2 mmol/g depending on the alkyl substituent and choice of regeneration solvent. Packed columns were used in a flow reactor to determine the resin's *O*-, *N*-, and *S*- alkylation potential. We found that this current iteration was suitable for the alkylation of secondary/tertiary amines and thiolates using a variety of different alkyl groups. Unlike amines, thiolate alkylation proceeded at room temperature with very short reaction times, on the order of minutes as opposed to hours. We discovered that this accelerated reaction rate is a result of ion aggregation and/or anion-exchange with the thiolate anion, which does not occur for amines. Computational studies on the alkylator-nucleophile systems have shown a more kinetically and thermodynamically favourable transition state for the reaction with thiols compared to that with alcohols or amines. This is due to the favourable relative orientation of the thiol nucleophiles, and the presence of a set of stacking interactions and other attractive donor-acceptor interactions within the transition states. These findings push the frontier of solid-supported alkylation and provide the first steps towards their use in highly tailored material-based alkylation technologies.

Experimental Section

Materials and Instrumentation

Sulfur (99.98%), pyridine (99.9%, anhydrous) diethyl ether ($\geq 99.9\%$), trimethylsulfonium iodide (98%), thiophenol (97%), potassium hexafluorophosphate ($\geq 99\%$), *N,N*-dimethylformamide (99.8%), *N*-methylbenzylamine, benzyl alcohol (99.8%), aniline (99.5%), benzyl mercaptan (99%), 1-iodohexane (98%), 1-iodobutane (99%), ethanol (97%), Merrifield peptide resin (50-100 mesh, 2.5-4.0 mmol/g Cl⁻ loading) were purchased from Sigma-Aldrich and used as received. Deuterated DMSO was purchased from Sigma-

Aldrich and stored over 4 Å molecular sieves. *N,N*-diisopropylethylamine (99%) was purchased from TCI and used as received. Methyl iodide (99%), 1-methylimidazole (99%), and trimethylsulfonium tetrafluorobromide (98%) were purchased from Alfa Aesar and used as received. Acetonitrile (99.9%) and methanol (99.9%) were purchased from Merck and used as received. Methyl methanesulfonate (99%) 1-methylbenzimidazole (99%) were purchased from Acros and used as received. Lithium bis(trifluoromethane)-sulfonamide (LiTFSI, 99%) was purchased from IOLITEC and used as received. ¹H, 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 12 h. EDX mapping was recorded on a Jeol JSM-7500F scanning electron microscope. FTIR spectra were recorded on a Varian 1000 spectrometer with an attenuated total reflectance setup. Flow chemistry experiments were performed using Omnifit Labware glass columns (L=13,8 cm, D=0,8 cm, V=0,97 mL) connected to a Pump 11 Elite syringe pump apparatus by Harvard Apparatus.

Synthesis of products

***N,N*-dimethylbenzylamine:** *N*-methylbenzylamine (69,8 mL) and resin **2a** (0,4145 g) were transferred into a flask containing acetonitrile (3 mL) in the presence of 1 eq. *N,N*-diisopropylethylamine. The flask was immersed for 24 hours in an oil bath at 80°C, and concentrated by rotary evaporation. ¹H-NMR (400 MHz, CDCl₃): δ = 1.98 (s, 6H), 3.45 (s, 2H), 7.22-7.38 (m, 5H). Spectrum is consistent with commercial material (>99%, 185582, Sigma Aldrich, St. Louis, USA), and the literature.^[18]

***N,N,N*-trimethylbenzylammonium iodide:** *N*-methylbenzylamine (69,8 mL) and resin **2a** (0,4145 g) were transferred into a flask containing acetonitrile (3 mL) in the presence of 1 eq. *N,N*-diisopropylethylamine. The flask was immersed for 24 hours in an oil bath at 80°C, and concentrated by rotary evaporation. ¹H-NMR (400 MHz, CDCl₃): δ = 2.28 (s, 9H), 3.30 (s, 2H), 7.22-7.38 (m, 5H). Spectrum is consistent with commercial material (>95%, J55455, AK Scientific, Union City, CA, USA), and the literature.^[18]

***N*-Methylaniline:** Aniline (55,2 mL) and resin **2a** (0,4077 g) were transferred into a flask containing acetonitrile (3 mL) in the presence of 1 eq. *N,N*-diisopropylethylamine. The flask was immersed for 24 hours in an oil bath at 80°C, and concentrated by rotary evaporation. ¹H-NMR (400 MHz, CDCl₃): δ = 2.73 (s, 3H, N-CH₃), 3.6 (s, 1H), 6.56 (m, 2H), 6.69 (m, 1H), 7.17 (m, 2H). Spectrum is consistent with commercial material (>98%, M29304, Sigma Aldrich, St. Louis, USA), and the literature.^[18]

Thioanisole: Thiophenol (66,6 mL) and resin **2a** (0,5033 g) were transferred into a flask containing acetonitrile (3 mL) in the presence of 1 eq. *N,N*-diisopropylethylamine.

The flask was immersed for 24 hours in an oil bath at 80°C, and concentrated by rotary evaporation. ¹H-NMR (400 MHz, DMSO-d₆): δ = 2.42 (s, 3H, S-CH₃), 7.09-7.24 (m, 5H). Spectrum is consistent with commercial material (>99%, T28002, Sigma Aldrich, St. Louis, USA), and the literature.^[18]

Benzyl methyl sulfide: Benzyl mercaptane (76,6 mL) and resin **2a** (0,5032 g) were transferred into a flask containing acetonitrile (3 mL) in the presence of 1 eq. *N,N*-diisopropylethylamine. The flask was immersed for 24 hours in an oil bath at 80°C, and concentrated by rotary evaporation. ¹H-NMR (400 MHz, CDCl₃): δ = 2.05 (s, 3H, S-CH₃), 3.58 (s, 2H), 7.26-7.38 (m, 5H). Spectrum is consistent with commercial material (>98%, AR003OTE, Aaron Chemicals, Nanjing, China), and the literature.^[18]

1,3-dimethylimidazolium iodide: 1-methylimidazole (10 mL) was transferred into a flask containing acetonitrile (2 mL). The solution was then pumped through a glass column packed with resin **2a** (0,7034 g) and heated at the temperature of 80°C, at a flow rate of 0.2 ml/min. The solution was collected from the other side of the column and concentrated by rotary evaporation. ¹H-NMR (400 MHz, DMSO-d₆): δ = 3.89 (s, 6H), 7.73 (m, 2H), 9.12 (s, 1H). Spectrum is consistent with commercial material (>95%, D23670, Synthonyx, Wake Forest NC, USA), and the literature (different solvent).^[19]

Hexyl phenyl sulfide: Thiophenol (16,87 mL) was transferred into a flask containing acetonitrile (2 mL). The solution was then pumped through a glass column packed with resin **2a** (0,1272 g) loaded with a hexyl chain and heated at the temperature of 80°C, at a flow rate of 0.2 ml/min. The solution was collected from the other side of the column and concentrated by rotary evaporation. ¹H-NMR (400 MHz, CDCl₃): δ = 0.90 (m, 3H), 1.22-1.56 (m, 6H), 1.66 (m, 2H), 2.93 (m, 2H), 7.05-7.15 (m, 1H), 7.19-7.38 (m, 4H). Spectrum is consistent with the literature.^[20]

Benzyl phenyl sulfide: Thiophenol (16,87 mL) was transferred into a flask containing acetonitrile (2 mL). The solution was then pumped through a glass column packed with resin **2a** (0,1281 g) loaded with a benzyl moiety and heated at the temperature of 80°C, at a flow rate of 0.2 ml/min. The solution was collected from the other side of the column and concentrated by rotary evaporation. ¹H-NMR (400 MHz, CDCl₃): δ = 4.15 (s, 2H), 7.20-7.39 (m, 6H). Spectrum is consistent with commercial material (>95%, J52677, AK Scientific, Union City, CA, USA), and the literature.^[18]

Computational studies

The DFT calculations using Mo62X and Pople's 6-311++G(d,p) basis set and SCRF=SMD (applying the default solvent parameters for DMSO) solvation model have been carried out using the Gaussian 09 suite of programs. All geometries presented here were optimized and subjected to

frequency calculations at the same level of theory. Structures with all real vibrational frequencies were further characterized as local minima on the potential energy surface while first order transition states possessed one imaginary frequency. The IRC was used to obtain the minima of products and the starting materials on either side of each the optimized transition state. Structure analysis, such as visualization of imaginary transition state frequencies, was performed using GaussView 2.9 and Maestro 11. The donor-acceptor interactions were quantified using Mulliken charge analysis to trace the electronic structures of transition state geometries. All calculations were performed using the Gaussian 09 suite of programs on Compute Canada.

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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KEYWORDS

Alkylation; solid-support; protein methylation; thiol; mechanism

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A mild alkylating agent can be immobilized and used to alkylate thiols and nitrogenous heterocycles, with low to poor ability to alkylate amines, and no reactivity against water or alcohols. Once depleted, the alkylating agent can be regenerated by treatment with alkyl iodide. The immobilized agent can be incorporated into a small flow reactor, allowing for increased ease of use.

