Synthesis of new hybrid 1,4-thiazinyl-1,2,3-dithiazolyl radicals via Smiles rearrangement†

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The condensation reaction of 2-aminobenzenethiols and 3-aminopyrazinethiols with 2-amino-6-fluoro-N-methylpyridinium triflate afforded thioether derivatives that were found to undergo Smiles rearrangement and cyclocondensation with sulphur monochloride to yield new hybrid 1,4-thiazine-1,2,3-dithiazolylum cations. The synthesized cations were readily reduced to the corresponding stable neutral radicals with spin densities delocalized over both 1,4-thiazinyl and 1,2,3-dithiazolyl moieties.

The heterocyclic benzo-1,4-thiazine, or simply phenothiazine, was first synthesized more than a century ago.¹ Over the years, phenothiazine and its numerous derivatives have been broadly examined, largely due to their biological activity and use as antipsychotic drugs.² The widespread interest in the medicinal chemistry of phenothiazine has also spurred the development of a variety of synthetic protocols for the preparation of new compounds. Of topical interest is the Smiles rearrangement,³ an intramolecular nucleophilic ipso-substitution reaction, which has found extensive use in the preparation of a number of phenothiazine-based heterocycles.⁴

The application potential of phenothiazines extends beyond pharmaceuticals and they can also be used as building blocks for functional materials. This stems from the ability of phenothiazine and its derivatives to undergo facile one-electron oxidation to persistent radical cations,⁵ which have been characterized by both EPR spectroscopy and X-ray crystallography.⁶ Consequentiy, in an effort to extend the chemistry of neutral phenothiazinyl derivatives, we report the use of the Smiles rearrangement reaction to prepare new stable radicals ⁵ that fuse the 1,4-thiazinyl and 1,2,3-dithiazolyl moieties into a single framework (Scheme 1).

The molecular scaffold in radicals ⁵ was chosen because of the wide range of physical and chemical properties of thiazyl-based radicals that make them useful building blocks for

Scheme 1 Synthesis of neutral radicals ⁵. Reagents and general conditions: (i) Na₂CO₃, MeCN, 5 h; (ii) MeCN, sealed vessel, 110 °C; (iii) excess S₂Cl₂, MeCN, reflux, 16 h; (iv) excess S₂Cl₂, MeCN, reflux, 16 h; (v) excess Me₈Fc, MeCN. Highest yields obtained: 4c' [OTf] 79%, 5a' [OTf] 2%, 5b' [OTf] 43%, 5d' [OTf] 48%, 5e' [OTf] 78%, 5b' 81%, and 5e' 70%.
molecular materials, both as free species and as coordinating ligands.\textsuperscript{11} While the first examples of closely related hybrid 1,2,3-dithiazolo-1,2,4-thiadiazinyl radicals have only been reported in the last few years,\textsuperscript{12} N-alkylpyridinium bridged bis-1,2,3-dithiazolyls and their selenium variants, with mirror plane symmetry, have been extensively explored.\textsuperscript{11b,11c} Many of these radicals were initially pursued as possible single component molecular conductors. However, their diverse magnetic properties, including ferromagnetic ordering, are notable compared to related classes of light atom molecular radicals such as nitroxides, triazinyls, and verdazyls.\textsuperscript{11} Thus, the pursuit of new molecular thiaryl radicals continues to attract considerable attention, which has now lead us to explore new extended aromatic systems based on the synthetically useful N-alkylpyridinium template.

The condensation reaction of 2-aminobenzenethiols (1a,b) and 3-aminopyrazinethiols (1c,d,e) with 2-amino-6-fluoro-N\texttextsuperscript{-}methylpyridinium triflate (2\textsuperscript{+}[OTf])\textsuperscript{12} in the presence of excess anhydrous Na\texttextsuperscript{2}CO\texttextsuperscript{3} in acetonitrile (MeCN) afforded N-methylpyridinium thiocarbamates 3a–c[OTf] (Scheme 1, step i).

Recrystallization of 3\textsuperscript{+}[OTf] from appropriate solvents gave analytically pure crystalline solids, which were characterized by IR and NMR (\textit{1}H, 13C\texttextsuperscript{1}H) spectroscopy as well as by single crystal X-ray diffraction analysis (for 3c\textsuperscript{+}[OTf], Fig. 1a).

It was anticipated that the salts 3\textsuperscript{+}[OTf] would undergo S → N Smiles rearrangement (SR) reaction by intramolecular nucleophilic ipso-substitution at the thioether bond of the N-methylpyridinium, affording N-substituted derivatives 4\textsuperscript{+}[OTf] (Scheme 1, step ii). After screening different reaction conditions on NMR scale, an essentially quantitative reaction was realised for 3c\textsuperscript{+}[OTf] but only after heating for 8 days at 80 °C. The purported SR reaction was performed on preparative scale in a sealed pressure vessel at 110 °C in MeCN, which gave an isolated product in high yield (90%) only after 40 h.

Single crystal X-ray diffraction analysis confirmed the heavy atom (non-hydrogen) connectivity of 4c\textsuperscript{+}[OTf], but instead of the expected thiol, the product was found to be the tautomeric pyrazinethione derivative 4c\textsuperscript{M}[OTf] (Fig. 1b). The \textit{1}H-NMR spectrum of the product (in anhydrous CD\textsubscript{3}CN) revealed that the signals for the pyridinium –NH\textsubscript{2} and pyrazine C–H protons are distinctively downfield shifted compared to 3c\textsuperscript{+}[OTf] and the appearance of a broad singlet at δ 9.60 ppm is tentatively assigned to the pyrazino –NH proton (N3 in Fig. 1b). It is notable that the \textit{1}H-NMR spectrum of 4c\textsuperscript{+}[OTf] does not show an observable signal for the bridging –NH group (N5 in Fig. 1b).

The lack of similar reactivity for the other thioether salts 3\textsuperscript{+}[OTf] even under more forceful conditions led us to perform a density functional study of the reaction mechanism at the PBE1PBE-IEFPCM/def2-TZVP level of theory. The results of computational investigations are summarized in Fig. 2 for two representative systems, 3a\textsuperscript{+} and 3c\textsuperscript{+}.

It is evident from the computed data (Fig. 2) that the initial reaction pathway is similar for both 3a\textsuperscript{+} and 3c\textsuperscript{+}. It was assumed that the SR reaction begins with an intramolecular nucleophilic attack of the benzo/pyrazine –NH\textsubscript{2} group to form a cationic Meisenheimer complex \textit{Int1}.\textsuperscript{3} This step has a very high activation barrier, TS1, in agreement with experimental observations. Furthermore, the formation of 4a\textsuperscript{+} and 4c\textsuperscript{+} is in both cases an essentially energy neutral process. However, what drives the SR reaction forward in the case of 3c\textsuperscript{+} is the possibility for 4c\textsuperscript{+} to tautomerize to the experimentally characterized form 4c\textsuperscript{M}, which renders the overall reaction exergonic by 43 kJ mol\textsuperscript{-1}. In this respect, it is surprising that no SR reaction was realised for 3d\textsuperscript{+} and 3e\textsuperscript{+} even though these derivatives are also able to tautomerize to the corresponding pyrazinethiones. A computational analysis of their reaction pathways showed that the formation of both 4d\textsuperscript{+} and 4e\textsuperscript{+} is exergonic, though only by 20 and 11 kJ mol\textsuperscript{-1}, respectively. Hence, the SR

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**Fig. 1** ORTEP plots (left, thermal ellipsoids at 50% probability) and line drawings (right) of the cations in (a) 3c\textsuperscript{+}[OTf] MeCN and (b) 4c\textsuperscript{+}[OTf].

**Fig. 2** Reaction coordinate diagram (PBE1PBE-IEFPCM/def2-TZVP) for the Smiles rearrangement reaction of 3a\textsuperscript{+} (red) and 3c\textsuperscript{+} (blue). For clarity, the structures of intermediates and transition states are only shown for the pathway from 3c\textsuperscript{+} to 4c\textsuperscript{+}. 

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reaction becomes less-favoured for each chlorine substituent added, making $4c^+$ the most favourable product of the different derivatives $a$–$e$ considered. Consequently, $4e^+$ is the only species generated under the experimental reaction conditions.

Having confirmed the identity of $4c^+$[OTf], its cyclocondensation with excess S$_2$Cl$_2$ was performed by refluxing the reactants in MeCN for 16 h (Scheme 1, step iii). Low-resolution positive ion electrospray ionization mass spectrometry (+ESI-MS) showed that the main products from the reaction were the salt $5e^+$[OTf] and the doubly chlorinated analogue $5c^+$[OTf]. Repeated syntheses confirmed that the $5c^+$[OTf]: $5e^+$[OTf] ratio is variable and does not depend on the reaction conditions in any obvious manner. However, the chlorinated product $5e^+$[OTf] could be crystallised from the reaction mixture using MeCN, affording a small amount of purple blocks. Unsuccessful with the low yield of $5e^+$[OTf], we attempted the direct reaction of S$_2$Cl$_2$ with triothiole $3e^+$[OTf] that already contains an appropriate substitution of chlorine on the pyrazine ring to potentially afford another route to $5e^+$[OTf] (Scheme 1, step iv). To our delight, $5e^+$[OTf] was obtained in good isolated yield (78%) as confirmed by IR spectroscopy and +ESI-MS.

To explore the scope of this alternative pathway to $5^+$[OTf], the reactivity of $3a^+$[OTf], $3b^+$[OTf], and $3d^+$[OTf] with S$_2$Cl$_2$ was also investigated. In the case of $3a^+$[OTf], +ESI-MS suggested that the product is a mixture of the non-chlorinated salt $5a^+$[OTf] with its chlorinated analogues containing one or more chlorine atoms. Hence, $5a^+$[OTf] was obtained in very low isolated yield (2%). Condensation reactions of S$_2$Cl$_2$ with aromatic amines containing an unsubstituted para-position (or those containing a good leaving group) are well-known to undergo simultaneous chlorination. Consequently, the reaction of S$_2$Cl$_2$ with the chlorinated species $3b^+$[OTf] and $3d^+$[OTf] was found to offer a practical route to derivatives $5b^+$[OTf] and $5d^+$[OTf] without further chlorination, albeit in moderate yield (43 and 48%, respectively). This further demonstrates that SR and cyclocondensation can take place concomitantly rather than sequentially, providing another route to different derivatives of $5^+$[OTf].

Cyclic voltammetry performed on solutions of $5^+$[OTf] in MeCN (with 0.1 M n-Bu$_4$NPF$_6$ as the supporting electrolyte) displayed a reversible $+1/0$ redox couple with $E_{1/2} = 0.031$ V and 0.220 V (vs. SCE) for $5b^+$[OTf] and $5c^+$[OTf], respectively. The cathodic shift in $E_{1/2}$ indicates that the heterocyclic aromatic substituent affects the electrochemical behaviour of the cations by altering the energy of their lowest unoccupied molecular orbital. This provides opportunities to fine-tune the electronic properties of the cations $5^+$ through careful choice of substituents. Furthermore, the $E_{1/2}$ values for $5b^+$[OTf] and $5d^+$[OTf] clearly demonstrate that octamethylferrocene (Me$_8$Fc) is a suitable reducing agent for both cations. The cyclic voltammetry measurements also revealed that the 0/−1 redox couple is irreversible for $5e^+$[OTf], while $5b^+$[OTf] appears to undergo significant decomposition under the same conditions. The estimated $E_{\text{cell}}$ of $5e^+$[OTf] is 0.720 V, which is smaller than those of related bisdithiazolyl radicals ($E_{\text{cell}} = 0.851$ V) but comparable to analogous bisthiasedenazoxylys ($E_{\text{cell}} = 0.745$ V).

Reduction of $5b^+$[OTf] and $5e^+$[OTf] was performed by slow diffusion of a degassed MeCN solution of the salt through a medium porosity sintered glass frit into a similar degassed MeCN solution of excess of Me$_8$Fc. This afforded the radicals $5b^−$ and $5e^−$ as analytically pure crystalline solids (Scheme 1, step v). In the case of $5b^−$, crystals suitable for single crystal X-ray diffraction were obtained as small lustrous bronze blocks. The crystal structure of $5b^−$ belongs to the monoclinic space group $P2_1/c$. The asymmetric unit consists of two essentially coplanar radicals in trans-cofacial arrangement (Fig. 3) with the shortest intermolecular C⋯C interactions very close to the sum of van der Waals radii. This suggests that the radicals are not strongly interacting in the solid state. The radicals in the asymmetric unit of $5b^−$ and those related to them by an inversion centre form π-stacked motifs that are arranged in a herringbone pattern similar to those typically observed for related bisdithiazolyl radicals.

The electronic structures of $5b^−$ and $5e^−$ were investigated by a combination of computational (PBE1PBE/def2-TZVP) methods and EPR spectroscopy. The calculations showed that the singly occupied molecular orbital and the spin density of $5^+$ are delocalized over the molecular backbone (Fig. 4). Specifically, natural population analysis assigned 40 and 55% of the $\alpha$-spin density of $5b^−$ on the 1,4-thiazinyl and 1,2,3-dithiazolyl moieties, respectively; the spin distribution of $5e^−$ is slightly more localised on the 1,2,3-dithiazolyl moiety. Consequently, the radicals $5$ can be considered hybrids of 1,4-thiazinyls and 1,2,3-dithiazolyls, which underlines the fact that the line drawing in Scheme 1 is an oversimplified picture of their electronic structure. In this respect, population analyses of $5b^−$ and $5d^−$ showed that the sulphur atom on the 1,4-thiazine ring is the single most positively charged nucleus in the structures. However, the shortest anion⋯cation contacts in crystal structures of $5b^−$[OTf] and $5d^−$[OTf] involve the two sulphur atoms on the 1,2,3-dithiazolyl moiety.

The room-temperature EPR spectrum of $5b^−$ in CH$_2$Cl$_2$ (Fig. 5a) consists of an eight line pattern with $g = 2.0071$ and no fine-structure. A good simulation of the spectrum was obtained by using hyperfine couplings (hfcs) to the nitrogen nuclei in the dithiazolyl ($a_{\text{N1}} = 0.383$ mT) and thiazyl

![Fig. 3 ORTEP plot of the asymmetric unit of 5b− (thermal ellipsoids at 50% probability).](image-url)
In this context, delocalization of the spin density on the 1,4-thiazinyl moiety is desired. Thus, we chose the quinoxaline derivative 4f[OTf] as our primary target (Chart 1). The synthesis of 3f[OTf] from 3-aminoquinoxalinethiol and 2-amino-6-fluoro-N-methylpyridinium trifluoromethanesulfonate was performed as described in Scheme 1 (step i). To our delight, 3f[OTf] undergoes the SR reaction (step ii) extremely easily as some 4f[OTf] was formed even during recrystallization of 3f[OTf]. Complete conversion required refluxing 3f[OTf] in MeCN for 6 h, giving 4f[OTf] in high isolated yield (80%). The identity of 3f[OTf] and 4f[OTf] was confirmed by both NMR spectroscopy and single-crystal X-ray crystallography. This demonstrates that, when using appropriate 3-aminoquinoxalinethiols, the SR reaction is an extremely viable pathway for the synthesis of salts 4f[OTf], which yield the corresponding stable neutral radicals 5` after ring closure and reduction.

### Conclusions

In this communication, we have shown that the Smiles rearrangement reaction, either followed by cyclocondensation or performed concurrently with it, offers a viable and modifiable route to a new class of hybrid 1,4-thiazine-1,2,3-dithiazolyl salts 5`[OTf], which can be readily reduced to yield the corresponding neutral radicals 5` with spin densities delocalized over both 1,4-thiazinyl and 1,2,3-dithiazolyl moieties. Future work will focus on the characterisation of transport properties of 5` and related radicals, along with the exploration of their coordination chemistry. This will provide opportunities for the design of molecular materials that may exhibit novel physical properties.

### Conflicts of interest

There are no conflicts to declare.

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Notes and references


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