Synthesis of new hybrid 1,4-thiazinyl-1,2,3-dithiazolylium cations via Smiles rearrangement†

Petra Vasko, Juha Hurmalainen, Akseli Mansikkamäki, Anssi Peuronen, Aaron Mailman* and Heikki M. Tuononen

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-dithiazolylium 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-dithiazolylium moieties.

Regardless of the wealth of data on cation radicals of phenothiazine, little is known about neutral phenothiazinyls even though these radicals were reported in the early 1960s. The majority of data on phenothiazinyl radicals are limited to spectroscopic studies and, to the best of our knowledge, there are no reports of X-ray crystallographic investigations. This is surprising considering that the related heterocyclic 1,2-thiazinyl radicals have been thoroughly characterized despite their persistent nature. Consequently, 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-dithiazolylium 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 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, which have been characterized by both EPR spectroscopy and X-ray crystallography. In recent years, the materials-oriented research has shifted the synthetic focus towards linked and fused oligomers of phenothiazine as well as phenothiazine-based polymers because of their applicability as switchable molecules, photosensitizers, cathode-active materials, and organic open-shell polymers to name a few.

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] 70%, 5b[OTf] 43%, 5d[OTf] 48%, 5e[OTf] 78%, 5b' 81%, and 5e' 70%.

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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,13} 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{11b} Thus, the pursuit of new molecular thiazyl 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-aminobenzethiols (1a,b) and 3-aminopyrazinethiols (1c,d,e) with 2-amino-6-fluoro-N-methylpyridinium triflate (2\textsuperscript{+}[OTf])\textsuperscript{12} in the presence of excess anhydrous Na\textsubscript{2}CO\textsubscript{3} in acetonitrile (MeCN) afforded N-methylpyridinium thioether salts 3a-c\textsuperscript{+}[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 (1H, 13C\{1H\}) 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 (80%) 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{+}[OTf] (Fig. 1b). The 1H-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 1H-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 Int1.\textsuperscript{3} This step has a very high activation barrier, TS\textsubscript{1}, 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{−}, which renders the overall reaction exergonic by 43 kJ mol\textsuperscript{−1}. In this respect, it is surprising that no SR reaction was realized 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
reaction becomes less-favoured for each chlorine substituent added, making 4c` the most favourable product of the different derivatives a-e considered. Consequently, 4c` is the only species generated under the experimental reaction conditions.

Having confirmed the identity of 4c`[OTf], its cyclocondensation with excess S₂Cl₂ 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 5e`[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 crystallized from the reaction mixture using MeCN, affording a small amount of purple blocks. Unsurprisingly, with the low yield of 5e`[OTf], we attempted the direct reaction of S₂Cl₂ with thiocarbonitrile (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 S₂Cl₂ 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 S₂Cl₂ 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 S₂Cl₂ 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-Bu₄NPF₆ as the supporting electrolyte) displayed a reversible +1/0 redox couple with E₁/₂ = 0.031 V and 0.220 V (vs. SCE) for 5b`[OTf] and 5e`[OTf], respectively. The cathodic shift in E₁/₂ 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 E₁/₂ values for 5b`[OTf] and 5d`[OTf] clearly demonstrate that octamethylferrocene (Me₈Fc) 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_{cell} of 5e`[OTf] is 0.720 V, which is smaller than those of related bisdithiazolyl radicals (E_{cell} = 0.851 V) but comparable to analogous bisthiaseelenazolyls (E_{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 Me₈Fc. 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 centrosymmetric monoclinic space group P2₁/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 α-spin density of 5b` on the 1,4-thiazinyl and 1,2,3-dithiazolyl moieties, respectively; the spin distribution of 5e` is slightly more localized 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 CH₂Cl₂ (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_n = 0.383 mT) and thiazyl

Fig. 3 ORTEP plot of the asymmetric unit of 5b` (thermal ellipsoids at 50% probability).
In this context, delocalization of the spin density on the 1,4-cations, the stability of the radicals is of particular importance. Thus, we chose the quinoxaline derivative $4f^+\text{[OTf]}$ as our primary target (Chart 1). The synthesis of $3f^+\text{[OTf]}$ from 3-aminoquinoxalinethiol and 2-amino-6-flouro-N-methylpyridinium trifluoromethanesulfonate was performed as described in Scheme 1 (step i). To our delight, $3f^+\text{[OTf]}$ undergoes the SR reaction (step ii) extremely easily as some $4f^+\text{[OTf]}$ was formed even during recrystallization of $3f^+\text{[OTf]}$. Complete conversion required refluxing $3f^+\text{[OTf]}$ in MeCN for 6 h, giving $4f^+\text{[OTf]}$ in high isolated yield (80%). The identity of $3f^+\text{[OTf]}$ and $4f^+\text{[OTf]}$ 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 $4f^+\text{[OTf]}$, 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 $5^+\text{[OTf]}$, 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


