ChemComm

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2021, **57**, 1943

Received 8th December 2020,
Accepted 18th January 2021

DOI: 10.1039/d0cc07988j

rsc.li/chemcomm

3-Thiolated pyrroles/pyrrolines: controllable synthesis and usage for the construction of thiolated fluorophores†

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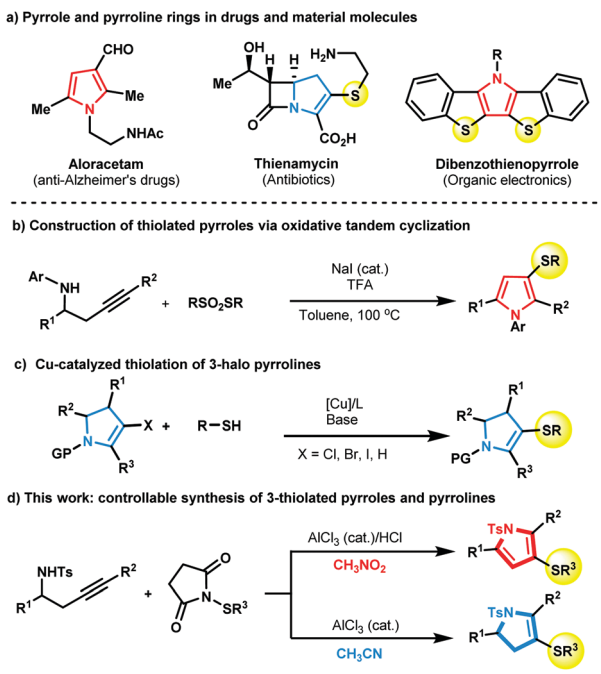
Thiolation/cyclization of homopropargylic tosylamides allowed the selective synthesis of 3-thiolated pyrroles and pyrrolines controlled by solvents. Moreover, the desired 3-thiolated pyrroles were readily transformed to organic fluorophores benzothienopyrrole and bisthiolated boron dipyrromethene (S-BODIPY).

As two important N-heterocycles, pyrrole and pyrroline rings are privileged structural subunits present in many drugs, natural products and organo-functional materials.[1] In particular, when the heterocycles incorporated a thio group, excellent physical, chemical, and biological properties were usually exhibited (Scheme 1a).[2] Although the functionalization and modification of pyrroles and pyrrolines have been well studied,[3] the construction of thiolated pyrroles and pyrrolines is of great interest but less explored. The electrophilic thiolation of pyrroles is a straightforward way to obtain 3-thiolated pyrroles, while the controlled incorporation of a monothio group is still a problem due to the high reactivity of the pyrrole ring.[4] A worthwhile endeavour was thus turned to the thiolation/cyclization of alkyne derivatives triggered by thio-radicals or thio-electrophiles,[5] which led to the construction of thiolated pyrroles with high regioselectivity and efficiency. For example, Yan and co-workers disclosed a tandem thiolation/cyclization of homopropargylic amines with thiosulfonates to access 3-thiolated pyrroles, and thiosulfonates were employed as both oxidants and electrophiles (Scheme 1b).[5b] As for the synthesis of 3-thiolated pyrrolines, methods are mainly focused on the copper-catalysed C–S cross coupling of 3-halo pyrrolines with thiols (Scheme 1c).[6] Considering the importance and structural similarity of these two N-heterocycles, the development of synthetic methods from common precursors is convenient and thus valuable.

The mutual conversion of pyrroles with pyrrolines could be achieved through oxidation or hydrogentation,[7] while the sulfur-incorporation usually affected this conversion due to oxidation tendency and catalyst poisoning of sulfur.[8] Encouraged by the thiolation/cyclization of alkynes induced by *N*-thiosuccinimides,[9] we speculated that the cyclization of homopropargylic tosylamides would make the construction of thiolated N-heterocycles possible, and the control of reaction



Scheme 1 Significance and synthetic strategies of 3-thiolated pyrroles and pyrrolines.

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† Electronic supplementary information (ESI) available. CCDC 2036448–2036449. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0cc07988j

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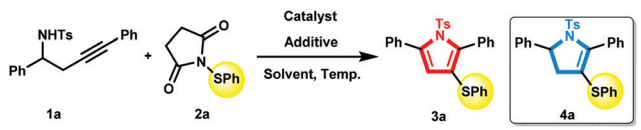
solvents would discriminate the oxidation state of thiolated products, which led to the synthesis of 3-thiosubstituted pyrroles or pyrrolines selectively (Scheme 1d). Recently, nitromethane (CH_3NO_2), a common solvent, has emerged as a useful carbon donor or nitrogen source to access useful molecules,[10] and the generated HCHO, HNO and other *N*-containing species through the Nef process played an important role in these transformations.[11] These oxidative species would enable CH_3NO_2 as a potential oxidant for the dehydrogenative aromatization of pyrrolines. Herein, with our continuous interest in thioelectrophiles,[12] we wish to report a switchable strategy for the synthesis of 3-thiosubstituted pyrroles or pyrrolines through $AlCl_3$-subcatalysed electrophilic thiolation/cyclization of homopropargylic tosylamides, and the selectivity of products was controlled by the use of CH_3NO_2 or MeCN as the solvent.

To get the optimal reaction conditions, homopropargylic tosylamide **1a** and *N*-phenylthio succinimide **2a** were employed as model substrates for the thiolation/cyclization, and both **1a** and **2a** could be readily prepared from commercially available compounds. At first, several catalysts that can activate *N*-thiosuccinimides were screened with CH_3NO_2 as the solvent at 60 °C (Table 1, entries 1–4), and it was found that 3-thiolated pyrrole **3a** was obtained when using $AlCl_3$ as the catalyst (entry 4). Increasing the amount of $AlCl_3$ could improve the yield of **3a** (entries 4–6), and further test indicated that 0.4 equiv. of $AlCl_3$ was a better choice (entry 5).[13] The attempt with higher temperature did not give a better result (entry 7). It is known that acidic conditions benefited the production of oxidative species through the Nef process in CH_3NO_2,[11] and we investigated several acids as additives for this reaction (entries 8–13). Notably, the use of 1.0 equiv. of HCl as the additive could improve the yield of **3a** to 75%. Other solvents were also examined for this transformation, while none of them could give a better yield of **3a** than CH_3NO_2 (entries 14–17). To our delight, when CH_3CN was employed as the solvent in the presence of 0.3 equiv. of $AlCl_3$, the 3-thiolated pyrrole **3a** was not detected at all, and 3-thiolated pyrroline **4a** was afforded in 80% yield (entry 17). Thus, by switching reaction solvents, 3-thiolated pyrrole **3a** and 3-thiolated pyrroline **4a** could be selectively produced.

Table 1 Optimization of reaction conditions[a]



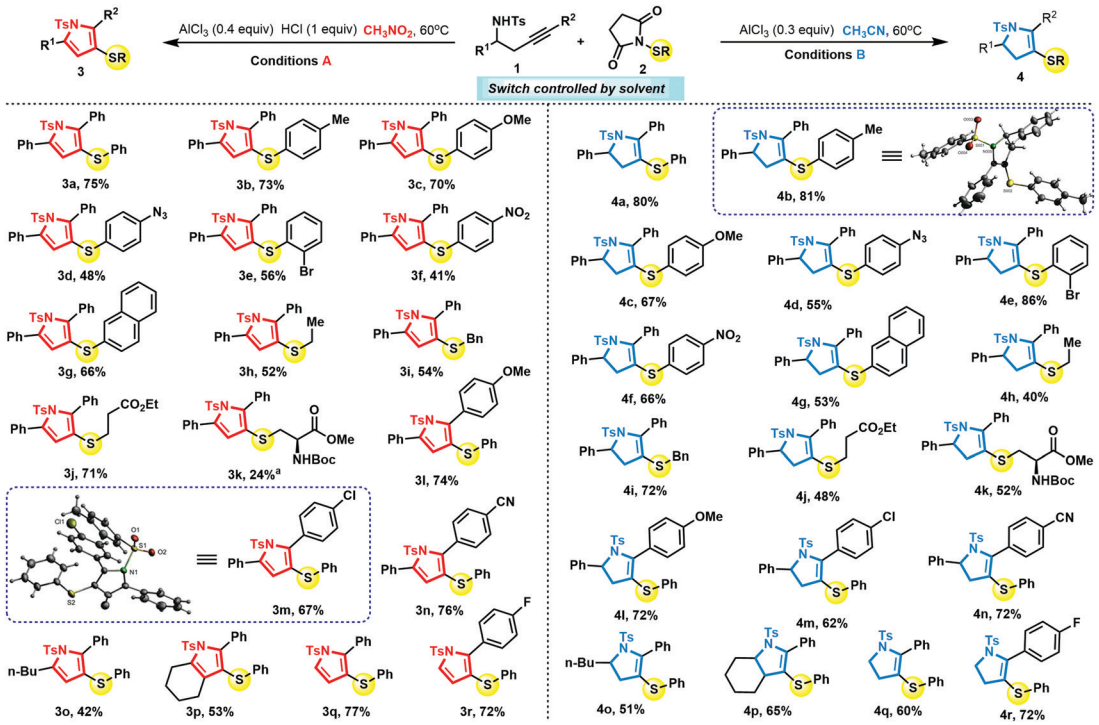
Entry	Solvent	Cat. (equiv)	Add. (equiv)	Yield[b] (%)
1	CH_3NO_2	CuCl (0.2)	—	0
2	CH_3NO_2	$Cu(OAc)_2$ (0.2)	—	0
3	CH_3NO_2	$BF_3{\cdot}Et_2O$ (0.2)	—	0
4	CH_3NO_2	$AlCl_3$ (0.2)	—	47
5	CH_3NO_2	$AlCl_3$ (0.4)	—	67
6	CH_3NO_2	$AlCl_3$ (0.6)	—	67
7[c]	CH_3NO_2	$AlCl_3$ (0.4)	—	61
8	CH_3NO_2	$AlCl_3$ (0.4)	TfOH (0.4)	21
9	CH_3NO_2	$AlCl_3$ (0.4)	TFA (0.4)	64
10	CH_3NO_2	$AlCl_3$ (0.4)	HCl (0.4)	70
11	CH_3NO_2	$AlCl_3$ (0.4)	HCl (1.0)	75
12	CH_3NO_2	$AlCl_3$ (0.4)	*p*TsOH (1.0)	61
13	CH_3NO_2	$AlCl_3$ (0.4)	TMSCl (1.0)	67
14	DMF	$AlCl_3$ (0.4)	HCl (1.0)	0
15[d]	THF	$AlCl_3$ (0.4)	HCl (1.0)	Trace
16[e]	CH_3CN	$AlCl_3$ (0.4)	HCl (1.0)	14
17[f]	CH_3CN	$AlCl_3$ (0.3)	—	0

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), catalyst (0.02 mmol), in CH_3NO_2 (1.5 mL) at 60 °C for 1–6 h. [b] Isolated yield. [c] The reaction was carried out at 80 °C. [d] **4a** was isolated in 47% yield. [e] **4a** was isolated in 74% yield. [f] **4a** was isolated in 80% yield.

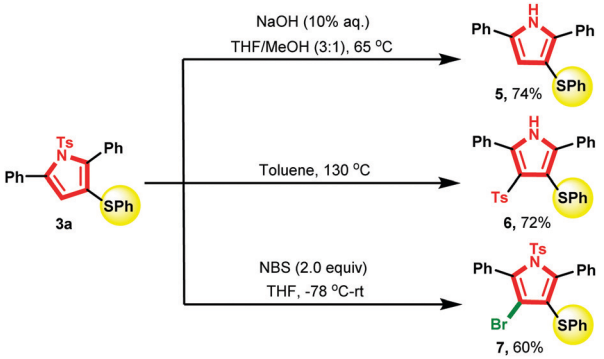
With the optimized conditions in hand, a series of *N*-thiosuccinimides and homopropargylic tosylamides were investigated (Scheme 2). *N*-Arylthio succinimides with various substituents, such as methyl, methoxy, azide, bromide, and nitro groups, could be well tolerated in this reaction, and gave the corresponding products in moderate to good yields (**3a–f**, **4a–f**). The electrophile with 2-thionaphthalene could also promote this reaction, and the desired products were obtained in moderate yields (**3g** and **4g**). Furthermore, several *N*-alkylthio succinimides including ethylthio, benzylthio and 3-(ethoxy-3-oxopropyl)thio groups were also evaluated, and both the 3-thiolated pyrrole and pyrroline products could be produced smoothly (**3h–j**, **4h–j**). Notably, the cyclization promoted by the electrophile derived from L-cysteine also proceeded (**3k** and **4k**), providing an elaborate access to late-stage modification of amino acids. The variation of substituents on the 2-aryl ring was tested as well, and both the electron-donating (–OMe) and -withdrawing groups (–Cl, and –CN) were suitable for the cyclization, and the desired 3-thiolated products were produced in good yields (**3l–n**, **4l–n**). The functional groups at the α-position of tosylamides were not limited to the aromatic systems, and products bearing an *n*-butyl or a cyclohexyl group could also be afforded in moderate yields (**3o**, **3p**, **4o**, and **4p**). Additionally, this cyclization also proceeded to afford 3-thiolated-4,5-unsubstituted products (**3q**, **3r**, **4q**, and **4r**), which left flexible positions for further derivation.

Having successfully achieved the selective synthesis of 3-thiolated pyrroles, further synthetic derivation of 3-thiolated pyrrole **3a** was also explored (Scheme 3). For example, the tosyl group could be readily removed by hydrolysis to access **5** or migrated to the 4-position to afford full substituted pyrrole **6**. Furthermore, in the presence of NBS, the bromination of **3a** was also successfully achieved to give **7**, which would facilitate the linkage of arenes with pyrroles through the cross coupling reaction.

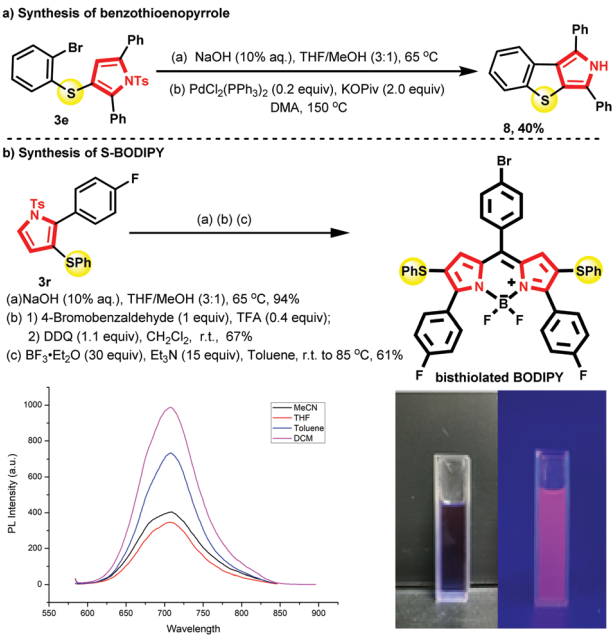
Benzothienopyrroles, that contain both sulfur and nitrogen, are important objectives in polymeric materials possessing good electronic properties.[14] With the use of obtained 3-thiolated pyrrole **3e**, the highly conjugated benzothienopyrrole **8** could be prepared in 40% yield after detosylation and intramolecular C–C bond formation (Scheme 4a). Moreover, the pyrrole ring is also a key unit in fluorescent boron-dipyrromethenes (BODIPY) that have been used as versatile photosensitizers for imaging, sensing, polymerization, and photodynamic therapy applications.[15] The optoelectronic properties of BODIPY could be tuned by incorporating appropriate substituents onto the BODIPY framework.[16] Detosylation of 3-thiolated pyrrole **3r**



Scheme 2 Scope of the selective synthesis of 3-thiolated pyrroles and pyrrolines. Conditions A: **1** (0.1 mmol), **2** (0.15 mmol), $AlCl_3$ (0.04 mmol), in CH_3NO_2 (1.5 mL) at 60 °C for 1–6 h; conditions B: **1** (0.1 mmol), **2** (0.15 mmol), $AlCl_3$ (0.03 mmol), in CH_3CN (1.5 mL) at 60 °C for 2–6 h. [a] The reaction was run without HCl.



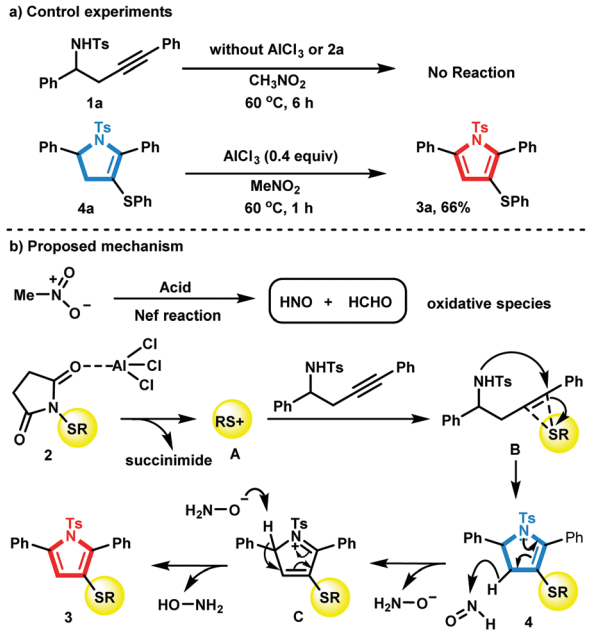
Scheme 3 Further derivation of 3-thiolated pyrrole **3a**.



Scheme 4 Synthesis of bisthiolated organic fluorescent molecules.

followed by condensation with 4-bromobenzaldehyde and dehydrogenation gave the bis-thiolated dipyrromethane, which was complexed with boron trifluoride etherate to afford the bisthiolated BODIPY in 61% yield (Scheme 4b). This new kind of BODIPY dye with diphenylthio groups exhibited an intense bathochromic fluorescence with λ_{max} at around 710 nm, and a Stokes shift in the range of 132–151 nm.[13]

To understand the mechanism, several control experiments were conducted (Scheme 5a). In the absence of thioelectrophiles or $AlCl_3$, the cyclization of **1a** did not occur. These results indicated that the reaction was initiated from the activation of *N*-thiosuccinimides with $AlCl_3$. In addition, 3-thiolated pyrroline **4a** could be transformed to 3-thiolated pyrrole **3a** in the CH_3NO_2 solvent *via* dehydrogenative aromatization, which demonstrated that some oxidative species were generated in nitromethane catalysed by $AlCl_3$. On the basis of these results and literature reports,[9–11] a possible mechanism is proposed in Scheme 5b. The oxidative species such as hyponitrous acid



Scheme 5 Control experiments and proposed mechanism.

(HNO) and formaldehyde (HCHO) could be generated *via* the Nef process in CH_3NO_2 under acidic conditions. On the other hand, *N*-thiosuccinimides were firstly activated by $AlCl_3$ to generate sulfenium cation **A**,[17] which could induce the intramolecular cyclization of homopropargylic tosylamide **1** to form pyrroline **4**. In the MeCN solvent, 3-thiolated pyrroline **4** was stable enough and could be isolated as it was; however, in the CH_3NO_2 solvent, the pyrroline framework would be aromatized to the pyrrole ring by the oxidation of HNO.

In summary, we have developed $AlCl_3$-subcatalysed electrophilic thiolation/cyclization of homopropargylic tosylamides for the synthesis of 3-thiolated pyrroles and pyrrolines, which were selectively produced by the use of nitromethane or acetonitrile as the solvent. This protocol featured simple and mild reaction conditions, a broad substrate scope, good regioselectivity and controllable products. More importantly, 3-thiolated pyrroles were applied to the synthesis of organo-optoelectronic benzothienopyrroles and bisthiolated BODIPY, providing new avenues for the preparation of S-containing material molecules. Efforts to exploit this strategy for other applications are underway.

This work was supported by the National Natural Science Foundation of China (No. 21901179), the Key R&D Program of Shanxi Province (International cooperation) (No. 201803D421093), the Natural Science Foundation of Shanxi Province (No. 201901D211052), the Scientific Activities of Selected Returned Overseas Professionals of Shanxi Province (No. 20200002) and the Research Project of Shanxi Scholarship Council (No. HGKY2019029 and 2020-053).

Conflicts of interest

There are no conflicts to declare.

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