Strain-Promoted 1,3-Dithiolium-4-olates/Alkyne Cycloaddition

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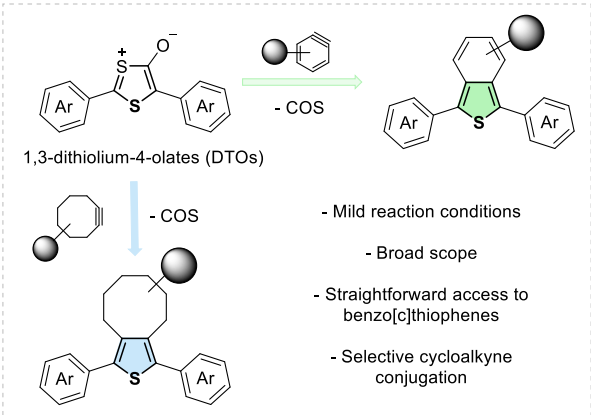
Strain-Promoted 1,3-Dithiolium-4-olate–Alkyne Cycloaddition

Ramar Arun Kumar,[a] Manas R. Pattanayak,[a] Expédite Yen-Pon,[a] Jijy Elyian,[a] Karine Porte,[a] Sabrina Bernard,[a] Margaux Riomet,[a] Pierre Thuéry,[b] Davide Audisio[a],* and Frédéric Taran[a],*

Abstract: We report the reactivity of mesoionic 1,3-dithiolium-4-olates towards strained alkynes. In the process, we discovered the potential of these dipoles towards orthogonal ligation with azides and a versatile platform to access benzo[c]thiophenes in an unprecedented divergent fashion, which provides a new entry to unconventional poly-aromatic thiophenes

Mesoionics are an exotic class of dipoles holding much promise in cycloaddition reactions. Although their synthesis and reactivity have been reported since the 60s, their potential is far from been fully explored.[1] Mesoionic compounds represent a large family of five-membered heterocycles that cannot be represented by Lewis structures not involving charge separation. Over the last decade, the popularity of this exotic family of heterocycles has suddenly increased and caught much attention.[2] In particular, nitrogen-containing mesoionics such as münchnones and sydnones were reported to be competent dipole partners for strain-promoted cycloaddition reactions. Their reactivity with arynes, described by Larock and Shi,[3] Garg and Houk,[4] and others,[5] offered novel synthetic opportunities to access to substituted pyrazoles and pyrroles, not trivial to assemble by traditional synthetic methodologies. Moreover, the use of the aryne-sydnone cycloaddition was recently described for the unconventional, direct assembly of helicene scaffolds.[6] In recent years, sydnones and imino-sydnones were identified as promising dipoles for copper-free, strain-promoted ligation with cyclooctynes.[7,8] These transformations hold much promise for click and biorthogonal chemistry and a variety of applications were reported in cell[9] and living organisms.[10]

While the community has accepted nitrogen-containing mesoionics as versatile platform in synthetic organic chemistry, sulfur-based derivatives remain a mere textbook curiosity and their reactivity is only partially explored. First reported in 1964,[11] 1,3-dithiolium-4-olates (DTOs) are essentially known to undergo thermal 1,3-dipolar cycloaddition in presence of activated alkynes followed by a retro-Diels Alder to deliver substituted thiophenes.[12] This thermal process has received limited attention, probably due to the poor regioselectivity, the limited scope and the drastic conditions required to assemble the thiophene unit. Their reactivity with activated alkenes such as fulvenes,[13] azirines,[14] maleimides[15] and acenaphthylene[16] has also been sporadically reported. Surprisingly, less than twenty articles describe cycloaddition reactions with these dipoles. Given the fundamental importance of thiophenes in organic chemistry, in particular medicinal and material science, we decided to investigate in detail the reactivity of DTOs. In this report, we describe the cycloaddition between DTOs and strained alkynes, focusing on cyclooctynes and arynes. In the event, we unveil a novel ligation strategy, which is orthogonal to the well-established azide-cycloalkyne click reaction, as well as a complementary pathway to access a variety of substituted benzo[c]thiophenes with possible implications in material science (Scheme 1).



Scheme 1. Reactivity of 1,3-dithiolium-4-olates (DTOs) with strained alkynes.

At the outset, we prepared a library of DTOs, according to previous synthetic protocols developed by Potts[17] and Gotthardt[18] in a three-step procedure. Grignard reagents were reacted in presence of carbon disulphide at room temperature. The corresponding dithioic acids underwent nucleophilic substitution in presence of *α*-bromophenyl acetic acids under aqueous conditions. Without further purification, the phenyl acetic acid derivatives were cyclized in presence of acetic anhydride and triethylamine, to deliver the desired DTOs **1**-**12** as dark blue solids in moderate to good yields (Scheme 2). Products are bench-stable and display strong absorbance properties. With this series of DTOs, we next started the investigation of their reactivity with cyclooctynes. When 2,5-diphenyl DTO **1** was mixed with bicyclo[6.1.0]non-4-yne-9,9-diyldimethanol (**BCNDM**)[19] a smooth conversion was observed at room temperature in chloroform, and the thiophene cycloadduct **13** was isolated in quantitative yield. It should be noted that the retro-Diels Alder step generates the desired thiophene with equimolar amounts of carbonyl sulfide (COS), whose relevance has been recently described for the therapeutic delivery of H_2S.[20] The evolution of the reaction could be easily visualized by the discoloration of the dark mesoionic solution: while DTO **1** has characteristic dark color but display no fluorescence, thiophene **13** is a colorless fluorescent molecule.

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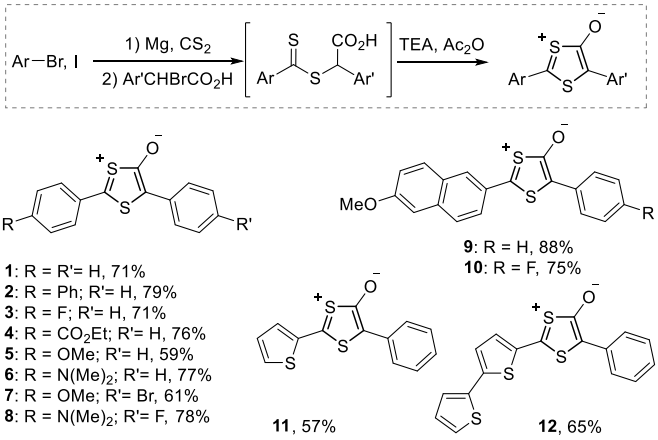
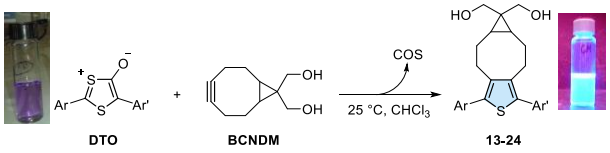


Scheme 2. Synthesis of 1,3-dithiolium-4-olates.

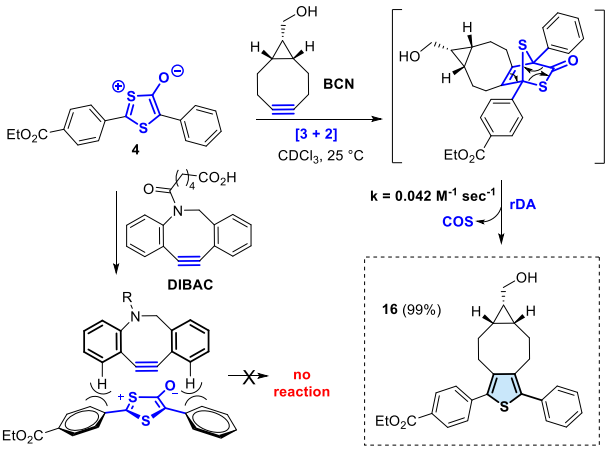
Turn-on probes based on bioorthogonal ligation and click reactions are remarkable chemical tools to label, visualize and study drugs and biomolecules. These transformations have been extensively studied and several fluorogenic azide,[21] tetrazine[22] and sydnone probes[23] have been developed. In light of their promising optical properties, DTOs **1**-**12** were reacted with **BCNDM** to afford quantitatively the corresponding thiophene products (see Table 1). The photo-physical properties of both DTOs and thiophenes were measured and the second-order kinetics determined. Comparative kinetics (Table 1) highlighted the importance of both substituents on positions 2 and 5 of the mesoionic core. Kinetic values of the Strain-Promoted 1,3-Dithiolium-4-olates/Alkyne Cycloaddition (SPDAC) reaction, ranging from 0.016 to 0.18 M^{-1} sec^{-1}, are comparable to the well-known strain-promoted azide-alkyne cycloaddition (SPAAC) click reaction. While for azides and sydnones the use of highly strained cyclooctynes increases the reaction rates, in striking contrast, no reaction occurred between **4** and **DIBAC** at room temperature, even after prolonged stirring. This unexpected lack of reactivity might be rationalized by the steric hindrance resulting from the 2,5-diaryl substituents of the mesoionic and the aromatic rings adjacent to the alkyne (Scheme 3). Given this peculiar orthogonal behaviour, we designed the dual probe **26**,[24] bearing an alkyl azide connected to the DTO, which was synthetized in 67% yield from **25**. In a proof-of-concept experiment, **26** reacted exclusively at the azide moiety in presence of **DIBAC**, the sequential addition of **BCN** allowing the clean formation of **27** in a quantitative fashion.[24] Similar results were obtained with functionalized cyclooctynes: complete orthogonal ligations after sequential addition of a DIBAC-biotine conjugate and a BCN bearing the cyclic RGD peptide affording selectively **28**. This experiment shows the potential of DTO as competent dipoles for orthogonal ligations with azides (Scheme 4).

Table 1. Photophysical data of compounds **DTOs** and **cycloadducts** and kinetic studies on cycloaddition reactions.[a]

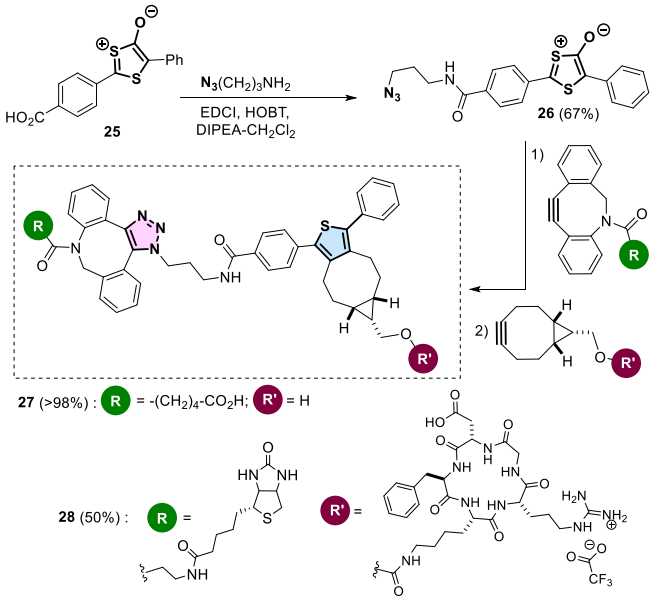


Ar	Ar'	**DTO:** λ_{max} (ε)[b]	**Adduct:** yield $\lambda_{ex}/\lambda_{em}$[c]	k[d]
		1: 543 (10200)	**13**: 97% 296/381	0.071 ± 0.005
Ph		**2**: 559 (20200)	**14**/99% 312/397	0.099 ± 0.002
F		**3**: 548 (8400)	**15**/96% 293/379	0.128 ± 0.004
EtO_2C		**4**: 560 (11800)	**16**/98% 324/424	0.042 ± 0.003
MeO		**5**: 557 (12600)	**17**/90% 299/390	0.082 ± 0.002
N		**6**: 595 (22700)	**18**/99% 316/401	0.016 ± 0.001
MeO	Br	**7**: 563 (11900)	**19**/96% 303/396	0.054 ± 0.001
N	F	**8**: 595 (17900)	**20**/97% 316/392	nd
MeO		**9**: 566 (17300)	**21**/96% 310/392	0.071 ± 0.001
MeO	F	**10**: 568 (16300)	**22**/99% 310/387	0.101 ± 0.001
S		**11**: 576 (10800)	**23**/97% 311/411	0.184 ± 0.003
S		**12**: 625 (12300)	**24**/98% 361/460	nd

[a] Kinetics were conducted with 150 µM of **DTO** and **BCNDM** in $CHCl_3$. [b] λ_{max}: nm ε :$M^{-1}.cm^{-1}$. [c] λ_{ex} and λ_{em} of thiophene cycloadduct (nm). [d] $M^{-1}.sec^{-1}$

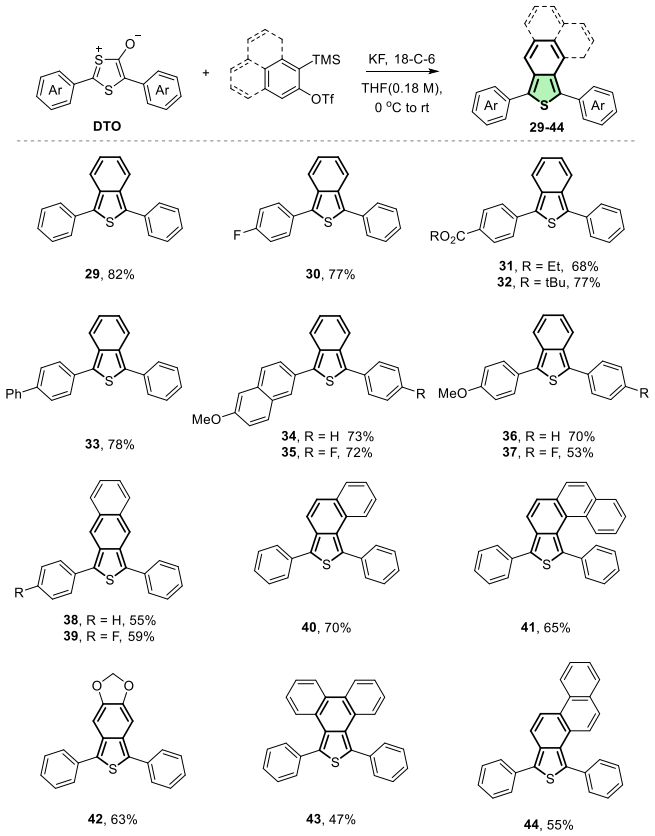


Scheme 3. Reactivity of DTO **4** with cyclic alkynes.

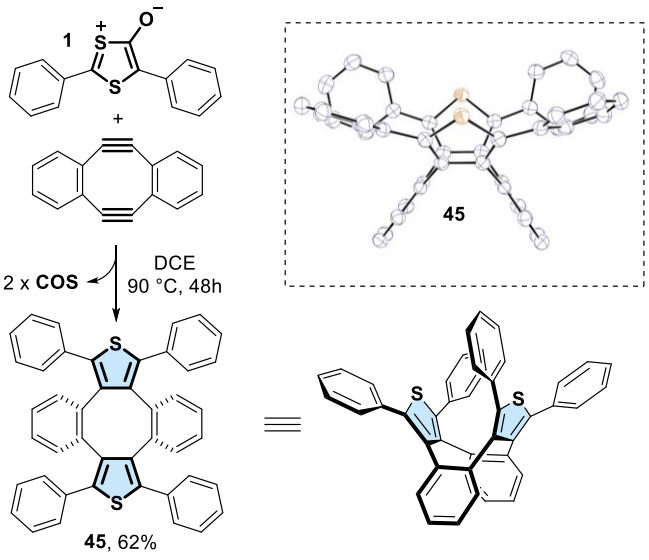


Scheme 4. Orthogonality between dithiolium-SPDAC and azide-SPAAC cycloaddition reactions (only one regioisomer of triazole product is represented).

After showcasing the SPDAC as potential tool for orthogonal cycloadditions with cyclooctynes, we next explored the reactivity of these sulphur-based mesoionics with arynes.[25] The importance of benzo[c]thiophenes in material science, in particular for their non-linear optical (NLO) properties,[26] low bandgap conjugated polymers[27] and their use as near-infrared fluorophore subunits is well-established.[28] Nonetheless, synthetic access to benzo[c]thiophenes and derived S-heteroacenes still remains challenging and requires time-consuming, multi-step convergent approaches. It is somehow surprising that the most common strategy still relies on the venerable Paal-Knorr cyclization, from the corresponding 1,4-diketone precursors in presence of excess of a source of sulphur.[29] In this context, the SPDAC with arynes would provide a divergent entry to benzo[c]thiophenes and streamline the access to unconventional derivatives. After careful optimization,[24] **29** could be isolated in 82% yield from **1** and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate, in presence of KF (4 equiv.) and 18-crown-6 ether (4.5 equiv.) in THF. With this optimized set of conditions, benzo[c]thiophenes **29**-**37** were isolated in moderate to good yields from the corresponding DTOs. To investigate the versatility of the transformation, we next reacted the mesoionics with previously reported polyaromatic arynes.[30] In presence of 2,3-naphthyne precursor, the desired S-heteroacenes **38** and **39** were isolated in 55% and 59% yield. Interestingly, acenothiophenes **29** and **38** were recently reported by the group of Chi, by means of a Paal-Knorr sequence in 65% and 50% yield ?, respectively, from the corresponding diketones.[31] These results show the divergence of SPDAC over current available methods. The reaction with *ortho*-fused 1,2-naphthyne and 3,4-phenanthryne precursors delivered the helical derivatives **40** and **41** in good yield. Finally, thiophene **42**-**44** were isolated in 47 to 63% yield. The use of 9,10-phenanthryne is particularly interesting because it generates phenanthro[9,10-c]thiophenes such as **43**, whose synthesis has so far only been poorly explored.[32]



Scheme 5. Exploring the SPDAC for the synthesis of benzo[c]thiophenes.



Scheme 6. Synthesis of **43** from DTO **1** and the Sonheimer diyne.

Finally, we investigated double SPDAC reaction of DTO **1** with the Sondheimer-Wong diyne (Scheme 6).[33] As expected, the

reaction was slower than with **BCNDM**, however a clean formation of dithiophene-diphenylene **45** was observed, upon heating at 90 °C during 48 hours. As highlighted by X-ray analysis, **45** adopts a unique saddle-shaped structure with the two thiophene moieties on the same side of the molecule. This new skeleton might therefore represent a promising candidate for the development of chiral functional molecules.[34]

In conclusion, we have studied the virtually unexplored reactivity of DTO towards strained alkynes. These mesoionics can be successfully used for orthogonal double click reactions and provide a versatile platform to access benzo[c]thiophenes and dithiophene-diphenylene structures in an unprecedented divergent fashion, which will provide a new entry to unconventional poly-aromatic thiophenes. Further work on these molecules is currently ongoing.

Acknowledgements

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Keywords: Mesoionics • Click chemistry • Screening • Cycloaddition • Thiophene

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[24] See Supporting Information for experimental details.

[25] To the best of our knowledge, we are aware of one single example of cycloaddition between DTO **1** and benzyne. The product was obtained in 36% yield and the aryne generated from 1-aminobenzotriazole with $Pb(OAc)_4$. See: H. Kato, S. Nakazawa, T. Kiyosawa, K. Hirakawa, *J. Chem. Soc., Perk. Trans. 1* **1976**, 672-675.

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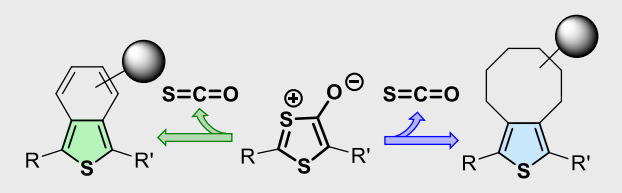

Strain-Promoted 1,3-Dithiolium-4-olates/Alkyne Cycloaddition: 1,3-dithiolium-4-olates reacted with strained alkynes in very clean processes affording poly-aromatic thiophene structures in high yields. Their use for ligation applications has also been investigated with cyclooctynes offering a new orthogonal reaction to the strain-promoted azide/alkyne reaction.

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