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Aminoxylation of Thioalkynes through Radical-Polar Crossover

Giovanni Di Mauro
Martina Drescher
Sara Tkaczyk
Nuno Maulide*

Institute of Organic Chemistry, University of Vienna, Währinger Strasse 38, 1090 Vienna, Austria
nuno.maulide@univie.ac.at

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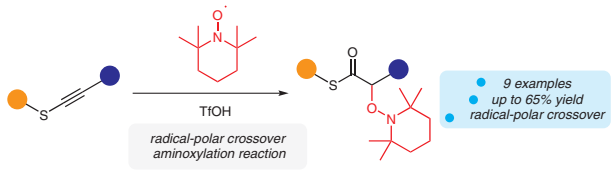

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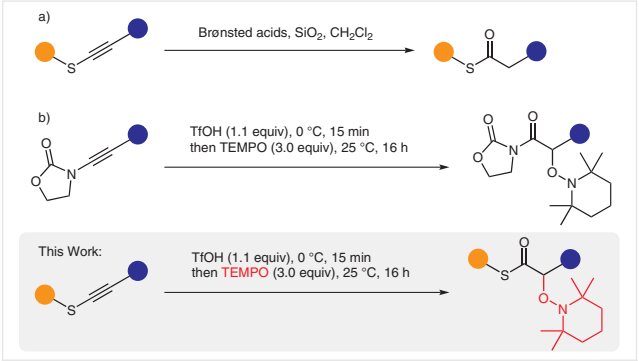
Abstract A one-pot procedure for the aminoxylation of thioalkynes for the direct formation of α-functionalized thioesters under mild reaction conditions is reported. A ketenethionium ion is the key intermediate, which is generated in situ by Brønsted acid mediated protonation and undergoes a radical-polar crossover.

Key words thioalkynes, aminoxylation, radical-polar crossover, thioester

Alkynes are privileged, versatile functional groups in organic synthesis.[1,2] Juxtaposing an alkyne and a sulfur atom leads to thioalkynes or alkynylsulfides, an interesting class of electron-rich acetylenes.[3] Thioalkynes serve as interesting precursors to thioesters,[4–6] offering an alternative to the classical synthetic approach of combining a thiol and an acyl chloride. Indeed, the direct acidic hydrolysis of alkynylsulfides delivers thioesters in a mild manner (Scheme 1, a).

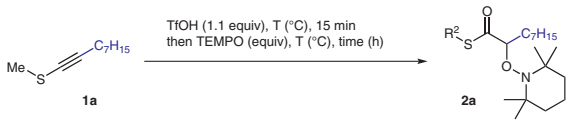


Scheme 1 Generic pathways for conversion of (a) thioalkynes to thioesters, (b) aminoxylation of ynamides, and (c) aminoxylation of thioesters

Reactivity pathways that allow the direct formation of α-functionalized thioesters from thioalkynes are of even greater interest. In this context, our group and others have engaged thioalkynes in acid-catalyzed arylative rearrangements employing arylsulfoxides,[7,8] while Zhao and Sun have exploited scandium catalysis to access substituted α,β-unsaturated thioesters.[9] Following our recent report on the acid-promoted reaction of TEMPO with activated ynamides (Scheme 1, b),[10] we were eager to extend those investigations to thioalkynes. Herein, we report the development of an aminoxylation of thioalkynes as well as several intriguing mechanistic features of the process.

We started our investigations using nonyne-derived alkynylsulfide **1a** and employing conditions akin to those previously employed for ynamides. In the event (Table 1), dichloromethane proved to be the best solvent. Thus, preactivation of the thioalkyne using TfOH for 15 minutes at 0 °C followed by addition of 3 equivalents of TEMPO, warm-

Table 1 Optimization of the Reaction Conditions



Solvent [M]	Temp (°C)	TEMPO (equiv)	Time (h)	Isolated yield (%)
CH_2Cl_2[0.1]	0 to 25	2.2	12	39
CH_2Cl_2[0.1]	0 to 25	3	4	58
CH_2Cl_2[0.1]	0 to 25	3	16	70
CH_2Cl_2[0.1]	–78 to 25	3	16	36
$C_2H_4Cl_2$[0.1]	0 to 25	3	16	48
CH_3CN [0.1]	0 to 25	3	16	0

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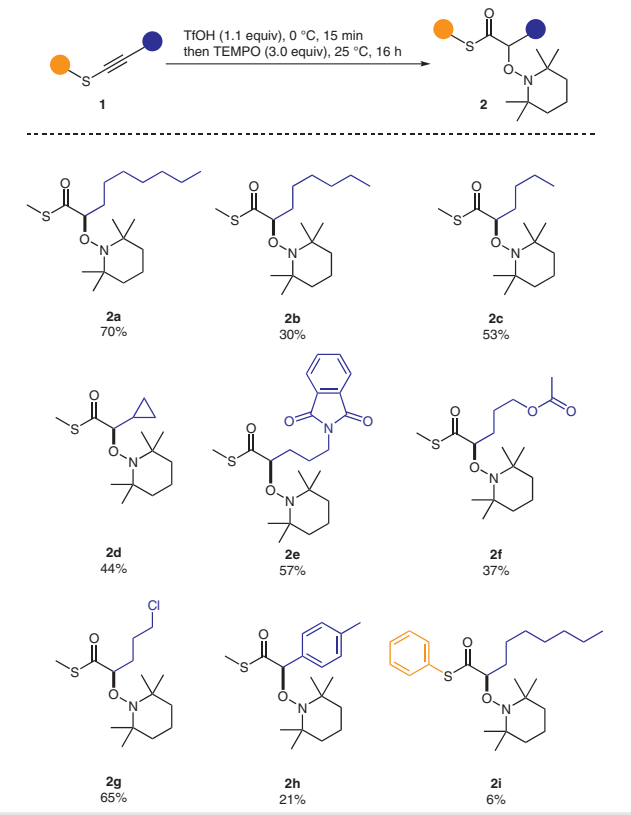
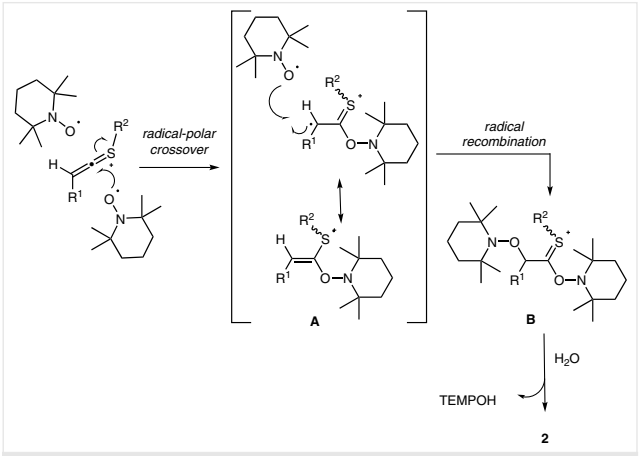
ing up to room temperature, afforded the product **2a** in reproducible 70% yields. Lower temperatures during the activation event proved not to be beneficial.

Having identified suitable conditions for the transformation, the scope of the reaction was investigated (Scheme 2). Alkyl substitution on the thioalkyne partner was tolerated (**2a–c**),[11,12] affording the aminoxylation products in moderate yields due to the formation of relatively complex mixtures of unidentifiable byproducts, from which chromatographic isolation of the desired adducts was troublesome. Cyclopropyl substitution was also accommodated without any ring-opening products being detected (**2d**). Protected nitrogen moieties (cf. phthalimide **2e**) did not interfere with the transformation. An ester (cf. **2f**) and a primary halide (cf. **2g**) could also be tolerated.



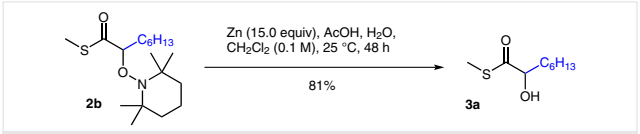
Scheme 2 Substrate scope for the aminoxylation of thioalkynes

Aromatic residues either attached to the thioalkyne (**2h**) or directly bound to sulfur (–SPh, cf. **2i**) led to significantly lower yields. Mechanistically and in analogy to our prior work,[10] we surmise that after protonation of the thioalkyne a radical-mediated C–O bond formation takes place. This leads to a sulfur-centered radical cation **A** for which two mesomeric forms can be depicted (Scheme 3). The requirement for an excess of TEMPO is, as before, most likely connected to a mechanistic scenario whereby 2 equivalents of the persistent aminoxyl radical are incorporated in the final product.



Scheme 3 Proposed mechanism

The presence of an aryl moiety directly attached to the thioalkyne (R^1 = Ar), such as in **2h**, is likely to stabilize intermediate **A**. A similar stabilizing effect can be anticipated for S-aryl thioalkynes (R^2 = Ar), such as in **2i**. The reason for the experimentally observed lower yields and more complex mixtures in the case of those substrates can thus be ascribed to either a higher barrier to radical recombination or a propensity of the more stabilized **A** to undergo deleterious side reactions (see Supporting Information for unsuccessful attempts on related substrates). Product **2b** was amenable to reductive N–O cleavage affording product **3a** in 81% yield (Scheme 4).



Scheme 4 Reductive N–O bond cleavage

In summary, we have developed an aminoxylation of thioalkynes that proceeds by a radical-polar crossover mechanism. The process involves addition of a radical species to a ketenethionium intermediate that ultimately evolves to an α-aminoxylated thioester.

Funding Information

Generous funding by the European Research Council (Grant No. CoG VINCAT 682002) and the Austrian Science Fund (FWF, Grant No. P32206) is acknowledged.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1689925.

References and Notes

(1) Trost, B. M.; Weiss, A. H. *Angew. Chem. Int. Ed.* **2007**, *46*, 7664.
(2) Trost, B. M.; Tracy, J. S. *Isr. J. Chem.* **2018**, *58*, 18.
(3) Frei, R.; Wodrich, M. D.; Hari, D. P.; Borin, P.-A.; Chauvier, C.; Waser, J. *J. Am. Chem. Soc.* **2014**, *136*, 16563.
(4) Braga, A. L.; Martins, T. L. C.; Silveira, C. C.; Rodrigues, O. E. D. *Tetrahedron* **2001**, *57*, 3297.
(5) Hoshi, M.; Masuda, Y.; Arase, A. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 447.
(6) Racine, S.; Hegedüs, B.; Scopelliti, R.; Waser, J. *Chem. Eur. J.* **2016**, *22*, 11997.
(7) Hu, L.; Gui, Q.; Chen, X.; Tan, Z.; Zhu, G. *J. Org. Chem.* **2016**, *81*, 4861.
(8) Kaldre, D.; Maryasin, B.; Kaiser, D.; Gajsek, O.; González, L.; Maulide, N. *Angew. Chem. Int. Ed.* **2017**, *56*, 2212.
(9) Liu, B.; Wang, Y.; Chen, Y.; Wu, Q.; Zhao, J.; Sun, J. *Org. Lett.* **2018**, *20*, 3465.
(10) Pinto, A.; Kaiser, D.; Maryasin, B.; Di Mauro, G.; Gonzàles, L.; Maulide, N. *Chem. Eur. J.* **2018**, *24*, 2515.
(11) **General Procedure for the Synthesis of 2**
To a solution of the thioalkyne (1.00 equiv) in CH_2Cl_2 (0.1 M) in a flame-dried Schlenk tube, trifluoromethanesulfonic acid (1.10 equiv) was added, and the mixture was stirred for 15 min at 0°C. TEMPO (3.00 equiv) was added in one portion, and the resulting solution was allowed to warm up to 25 °C and stirred over 16 h. The reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$. The product was extracted with CH_2Cl_2, and the resulting organic phase was dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure. The product was purified by flash chromatography on silica gel using heptane methyl-*tert*-butyl ether as eluent.
(12) **Analytical Data for Compound 2c**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.75 (d, *J* = 8.8 Hz, 1 H), 2.28 (s, 3 H), 1.65–1.40 (br, 6 H), 1.30 (br, 3 H), 1.18 (br, 6 H), 1.12–1.06 (m, 1 H), 1.03 (br, 3 H) 0.75–0.45 (m, 4 H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 201.4, 94.5, 40.3 (2 C), 34.4, 33.5, 20.4, 20.1, 17.1, 15.1, 10.9, 7.5, 2.05 (quaternary carbons in the TEMPO moiety not visible in ^{13}C NMR). HRMS (ESI+): *m/z* calcd for ($C_{15}H_{28}N_2OS^+$) [M + H]$^+$: 286.1835; found: 286.1830. IR (neat): ν_{max} = 3005, 2972, 2929, 2359, 1684, 1465, 1376, 900 cm^{-1}.