4-Cyano-3-oxotetrahydrothiophene (c-THT): An Ideal Acrylonitrile Anion Equivalent

François Richard^a
 Carlos Mateos^b
 Stelios Arseniyadis^a

^a Queen Mary University of London,
 School of Biological and Chemical Sciences, London, E1 4NS, UK
 s.arseniyadis@qmul.ac.uk

^b Centro de Investigación Lilly S.A., Avda. de la Industria 30,
 Alcobendas-Madrid 28108, Spain

Dedicated to Professor K. C. Nicolaou on the occasion of his 74th birthday

Received: 06.01.2021

Accepted after revision: 20.01.2021

Published online: 01.02.2021

DOI: 10.1055/s-0040-1706019; Art ID: so-2021-d0002-r

License terms:

© 2021. The Author(s). This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Abstract 4-Cyano-3-oxotetrahydrothiophene (c-THT) has much more to offer than just a platform to various heterocyclic scaffolds. This solid, bench-stable and commercially available reagent can be readily transformed into thioglycolic acid and acrylonitrile upon simple addition of a hydroxide anion. This interesting feature enables its use as a particularly versatile acrylonitrile anion surrogate.

Key words acrylonitrile, surrogate, heterocycle, alkylation, Michael addition, palladium, retro-Dieckmann

4-Cyano-3-oxotetrahydrothiophene **1** (c-THT) is a commercially available reagent commonly used for the preparation of a variety of heterocycles including thiophenes,¹ furans² and pyrazoles (Scheme 1A).³ However, another facet of this reagent has remained underexploited. The presence of the α -cyanoketone moiety within the tetrahydrothiophene ring weakens the C₃–C₄ bond, which can undergo a retro-Dieckmann fragmentation upon addition of a hydroxide anion, to release thioglycolate **3** ($pK_a = 3.83$) and acrylonitrile **4**. Ultimately, this interesting feature enables the use of c-THT as a synthetic equivalent of an acrylonitrile anion (Scheme 1B). As a result, this solid, bench-stable and relatively safe to use reagent provides an interesting access to nitrile-containing compounds without using hazardous cyanide anion equivalents.

Baraldi and co-workers were the first to demonstrate the applicability of this acrylonitrile surrogate for synthetic applications.⁴ Indeed, after alkylation with various alkyl ha-

Scheme 1 Retro-Dieckmann fragmentation of c-THT

lides using potassium carbonate as a mild base and running the reaction in acetone, the crude intermediate **5** was subsequently fragmented at room temperature using 5% aqueous sodium hydroxide in a biphasic water/Et₂O system (Scheme 2). This two-step sequence afforded a particularly straightforward access to a variety of α -substituted acrylonitriles **6** in moderate to good yields.

More recently, Leiros, Bayer and co-workers took advantage of Baraldi's methodology to prepare new metallo- β -lactamase inhibitors (Scheme 3).⁵ Their strategy relied on

the use of c-THT to incorporate an acrylonitrile moiety, which could then be used as a true launching pad for further modifications. Hence, after alkylation following Baraldi's protocol, the key intermediate **7** was converted into the corresponding vinyl tetrazole **8** upon heating in dioxane at 150 °C under MW irradiation in the presence of TMSN₃ and a catalytic amount of *n*-Bu₂SnO (78% yield). The

latter proved to be an excellent Michael acceptor and allowed the introduction of various thiol moieties in high yields.

Biographical Sketches

François Richard first earned a Technical Degree in Chemistry from the Institut Universitaire de Technologie de Orsay and then joined the Ecole Nationale Supérieure de Chimie de Montpellier (ENSCM). His educational

background allowed him to get industrial placements at Bayer CropScience (Lyon) and Syngenta (Stein). In March 2017, he joined the Arseniyadis group at Queen Mary University of London for his masters thesis and

started his PhD in collaboration with Lilly. His research focuses on the construction of complex architectures via metal-catalysed asymmetric allylic alkylation and C–H activation processes.

Carlos Mateos obtained his degree in Organic Chemistry in 1998, in the University of Oviedo (Spain). Then, he moved to Leverkusen (Germany) to enjoy an industrial internship in Bayer AG. In 1999, he moved back to

Spain to pursue a PhD under the supervision of Prof. José Barluenga. In 2004, Carlos joined the CRO Galchimia (Santiago de Compostela, Spain) as a project manager. In 2006, he joined Lilly (Alcobendas, Spain) where he

is currently working in the Med-Chem group. His main research interests include drug discovery, flow chemistry, process development and external R&D collaborations.

Stellios Arseniyadis received his PhD from the University of Strasbourg under the guidance of Dr. C. Mioskowski. After various postdoctoral stints in industry (Rhodia Chirex, Boston, USA, in collaboration with Prof. S. L. Buchwald, MIT) and in academia

(Prof. A. C. Spivey – Imperial College London and Prof. K. C. Nicolaou – The Scripps Research Institute), he started his academic career in France first as a permanent CNRS researcher and later as a CNRS Director earning the CNRS Bronze Medal

in 2015. The same year, he moved to Queen Mary University of London where his group is interested in developing new methods for more efficient and sustainable organic syntheses.

Our group has also been interested in evaluating the synthetic potential of c-THT as an acrylonitrile anion equivalent, deeply convinced that it could be used in a broader range of reactions. Encouraged by the results we obtained over the years in the field of palladium-catalysed allylic alkylation,⁶ we logically became interested in applying this strategy to c-THT with the idea of generating 1,4-dienes (Scheme 4). Interestingly, subjecting c-THT to a sequential palladium-catalysed allylic alkylation/retro-Dieckmann fragmentation afforded a highly straightforward and scalable route to the desired 1,4-dienes **11** bearing an acrylonitrile moiety.⁷ The latter were eventually converted into various useful building blocks using biocatalytic transformations.

Encouraged by these results, which provided clear evidence of c-THT's compatibility with metal-catalysed transformations, and with the idea of developing an enantioselective method to incorporate an acrylonitrile moiety onto a pro-chiral substrate, we set out to evaluate the feasibility of an asymmetric one-pot Michael addition/retro-Dieckmann fragmentation (MARDi). To our satisfaction, this one-pot, two-step sequence featuring a highly enantioselective scandium-catalysed Michael addition was successfully applied to α,β -unsaturated-2-acylimidazoles **14**,⁸ affording the corresponding acrylonitrile-containing derivatives in both high yields and excellent enantioselectivities (up to 96% ee) (Scheme 5).⁹ Interestingly, tetrabutylammonium hydroxide (TBAH, 1 M in methanol) was used instead of aqueous sodium hydroxide to prevent a potential erosion of the enantiomeric excess.

Most importantly, to demonstrate the synthetic utility of the resulting enantioenriched α -substituted acrylonitriles, several post-functionalisations were performed, affording some particularly interesting building blocks for natural product synthesis.

In summary, c-THT has become a go-to reagent when wanting to introduce an acrylonitrile moiety within a molecule. Considering the importance of the acrylonitrile motif in medicinal, agrochemical and polymer chemistry, there is no doubt that this acrylonitrile anion equivalent will become an essential tool in the synthetic chemist's toolbox.

Funding Information

Eli Lilly and Queen Mary University of London are gratefully acknowledged for financial support.

References

- (a) Hergué, N.; Mallet, C.; Savitha, G.; Allain, M.; Frère, P.; Roncali, J. *Org. Lett.* **2011**, *13*, 1762. (b) Moussallem, C.; Olivier, S.; Grolleau, J.; Allain, M.; Mallet, C.; Savitha, G.; Gohier, F.; Frère, P. *Chem. Eur. J.* **2016**, 6510.
- Redman, A. M.; Dumas, J.; Scott, W. J. *Org. Lett.* **2000**, *2*, 2061.
- Kovács, D.; Molnár-Tóth, J.; Blaskó, G.; Fejes, I.; Nyerges, M. *Synth. Commun.* **2015**, *45*, 1675.
- Baraldi, P. G.; Pollini, G. P.; Zanirato, V.; Barco, A.; Benetti, S. *Synthesis* **1985**, 969.
- Skagseth, S.; Akhter, S.; Paulsen, M. H.; Muhammad, Z.; Lauksund, S.; Samuelsen, Ø.; Leiros, H. K. S.; Bayer, A. *Eur. J. Med. Chem.* **2017**, *135*, 159.
- (a) De Oliveira, M. N.; Arseniyadis, S.; Cossy, J. *Chem. Eur. J.* **2018**, *24*, 4810. (b) Song, T.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2019**, *21*, 603. (c) Aubert, S.; Katsina, T.; Arseniyadis, S. *Org. Lett.* **2019**, *21*, 2231. (d) De Oliveira, M. N.; Fournier, J.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2017**, *19*, 14. (e) Fournier, J.; Arseniyadis, S.; Cossy, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 7562. (f) Fournier, J.; Lozano, O.; Menozzi, C.; Arseniyadis, S.; Cossy, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 1257. (g) Arseniyadis, S.; Fournier, J.; Thangavelu, S.; Lozano, O.; Prevost, S.; Archambeau, A.; Menozzi, C.; Cossy, J. *Synlett* **2013**, 2350. (h) Elhachemia, H.; Cattoen, M.; Cordier, M.; Cossy, J.; Arseniyadis, S.; Iltki, H.; El Kaïm, L. *Chem. Commun.* **2016**, *52*, 14490. (i) Song, T.; Arseniyadis, S.; Cossy, J. *Chem. Eur. J.* **2018**, *24*, 8076. (j) Kerim, M. D.; Cattoen, M.; Fincias, N.; Dos Santos, A.; Arseniyadis, S.; El

- Kaïm, L. *Adv. Synth. Catal.* **2018**, 360, 449. (k) Kerim, M. D.; Katsina, T.; Cattoen, M.; Fincias, N.; Arseniyadis, S.; El Kaïm, L. *J. Org. Chem.* **2020**, 85, 12514.
- (7) Katsina, T.; Sharma, S. P.; Buccafusca, R.; Quinn, D. J.; Moody, T. S.; Arseniyadis, S. *Org. Lett.* **2019**, 21, 9348.
- (8) (a) Lauberteaux, J.; Pichon, D.; Baslé, O.; Mauduit, M.; Marcia de Figueiredo, R.; Campagne, J. M. *ChemCatChem* **2019**, 11, 5705. (b) Mansot, J.; Vasseur, J. J.; Arseniyadis, S.; Smietana, M. *ChemCatChem* **2019**, 11, 5686.
- (9) Duchemin, N.; Cattoen, M.; Gayraud, O.; Anselmi, S.; Siddiq, B.; Buccafusca, R.; Dumas, M.; Ferey, V.; Smietana, M.; Arseniyadis, S. *Org. Lett.* **2020**, 22, 5995.