Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

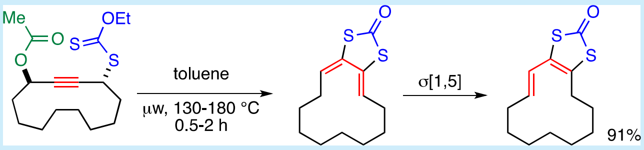
Sigmatropic Rearrangement-Based Synthesis of 4-Alkenyl-1,3-dithiol-2-ones

Pavels Ostrovskis,[†] Andrey A. Mikhaylov, and Samir Z. Zard*

Laboratoire de Synthèse Organique, Ecole Polytechnique, CNRS UMR 7652, Palaiseau 91128 Cedex, France

Supporting Information

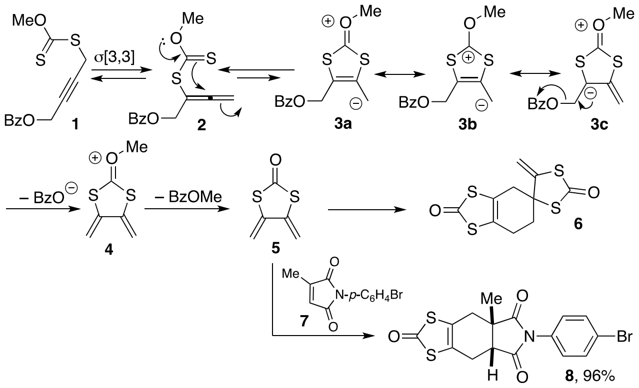
ABSTRACT: A series of conjugated 4-alkenyl-1,3-dithiol-2-ones have been prepared by microwave-assisted rearrangement of *S*-(4-acyloxy-2-alkynyl)-*O*-ethyl xanthates in moderate to good yields. The synthetic approach is based on a combination of [3,3] and [1,5] sigmatropic rearrangements as well as the intermediacy of a reactive betaine that induces the ionic elimination of the acyloxy group. The [1,5] sigmatropic rearrangement was confirmed by a deuterium-labeling experiment.



1,3-Dithiol-2-ones are 5-membered sulfur heterocycles with notable aromatic character. They are generally recognized as universal precursors to tetrathiafulvalenes upon phosphite-mediated reductive coupling with the analogous 1,3-dithiol-2-thiones.[1] The charge-transfer properties of tetrathiafulvalenes have found widespread applications in nonlinear optics and in photovoltaics.[2] Another mainstream utilization of 1,3-dithiol-2-ones consists of their base-induced cleavage into 1,2-dithiols, which are valuable bidentate ligands in molybdenum and tungsten complexes, such as in the molybdopterin cofactor.[3] Other transition-metal derivatives are found as redox switches and near-IR dyes.[4] We report herein a novel general approach for synthesis of 1,3-dithiol-2-ones conjugated with a double bond, thus opening up an unusual and straightforward route to tetrathiafulvalenes and dithiolene complexes with possibly improved electronic properties.

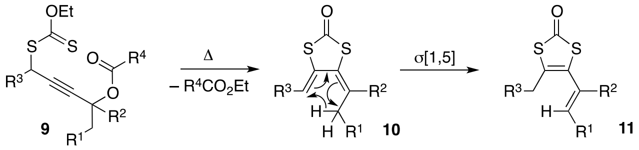
The approach is based on the thermally induced isomerization of *S*-propargyl xanthates equipped with a leaving group such as **1**, which we serendipitously discovered some years ago (Scheme 1).[5−7] This isomerization starts with the [3,3]-sigmatropic rearrangement of xanthate **1** into allenyl xanthate **2**, which we found to be in equilibrium with betaine **3**. This equilibrium strongly favors the former. Betaine **3** can be viewed as a slightly stabilized allylic anion, with perhaps some aromatic character, since the ring in canonical resonance structure **3b** contains six electrons. The build-up of electron density on the carbon adjacent to the benzoate group causes *β*-elimination to give intermediate **4**, which rapidly collapses into bis(methylidene)-1,3-dithiolan-2-one **5** and methyl benzoate. Rigid, cisoid diene **5** is highly reactive and rapidly dimerizes through a Diels−Alder cycloaddition to give compound **6**. However, it can be readily captured by a powerful dienophile such as maleimide **7** to give the corresponding Diels−Alder product **8** in high yield. The intramolecular variant of this transformation proceeds equally efficiently and allows access to highly complex polycyclic structures.[5d]

Scheme 1. Example of Diene Formation from an *S*-Propargyl Xanthate



In an attempt to expand the scope of the process to more substituted bis(alkylidene)-1,3-dithiolan-2-ones **10**, we examined the behavior of *S*-propargyl xanthates of general structure **9** (Scheme 2). In the event, we were surprised to find that dienes **10** underwent a rapid [1,5] sigmatropic rearrangement to give the much less reactive isomeric dienes **11**, which could be isolated.

Scheme 2. Sequential Thermal Sigmatropic Rearrangements

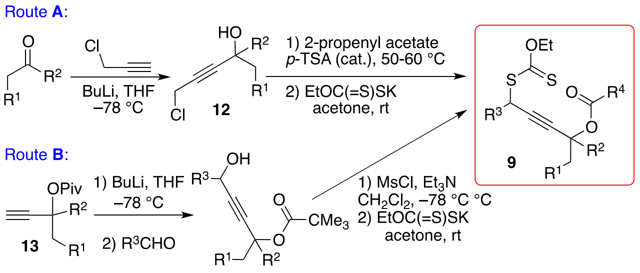


For this study, we prepared a series propargyl xanthates **9** using the two routes outlined in Scheme 3 (see the Supporting Information). Route **A** was used for the majority of the

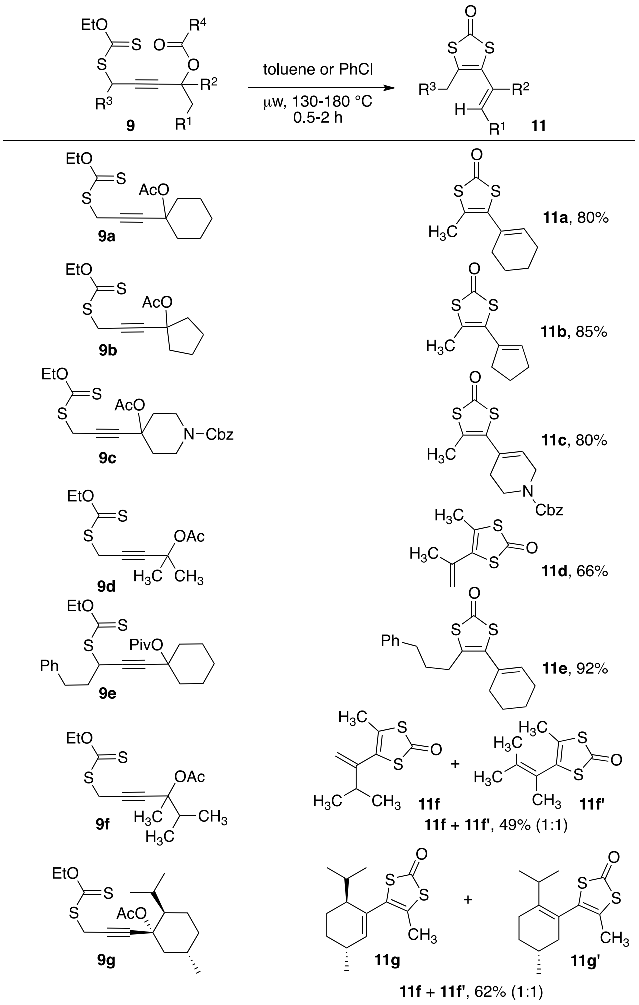
Received: April 4, 2019

DOI: 10.1021/acs.orglett.9b01157
Org. Lett. XXXX, XXX, XXX−XXX

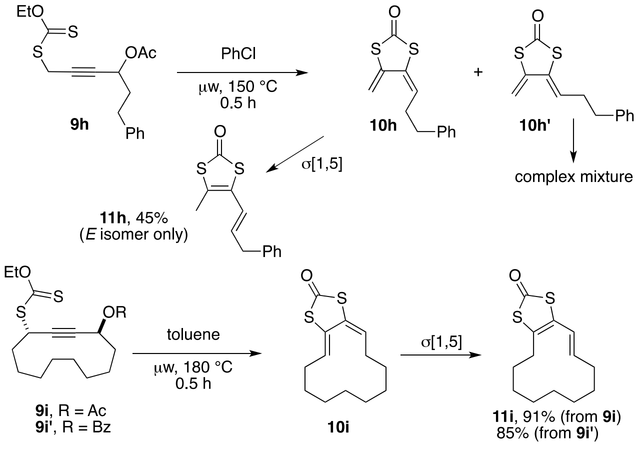
Scheme 3. Synthesis of Propargyl Xanthates



Scheme 4. Synthesis of 4-Alkenyl-1,3-dithiol-2-ones



Scheme 5. Rearrangement of Propargyl Xanthates Derived from Aldehydes



examples, giving precursors with an acetate leaving group (R^3 = H and R^4 = Me). The acetylation of the somewhat fragile tertiary chloromethyl propargylic alcohols **12** proved to be unexpectedly challenging, and numerous methods had to be screened. Ultimately, the most effective procedure was the acid-catalyzed acetyl exchange with 2-propenyl acetate.[8] Route **B** could be applied for the case where R$^3 \neq$ H through reaction of lithium acetylide derived from pivalate **13** with the appropriate aldehyde (Piv = pivalate). The use of a pivalate obviates possible complications caused by direct attack of BuLi on the ester group or by deprotonation of acidic hydrogens next to the carbonyl group, since none are present.

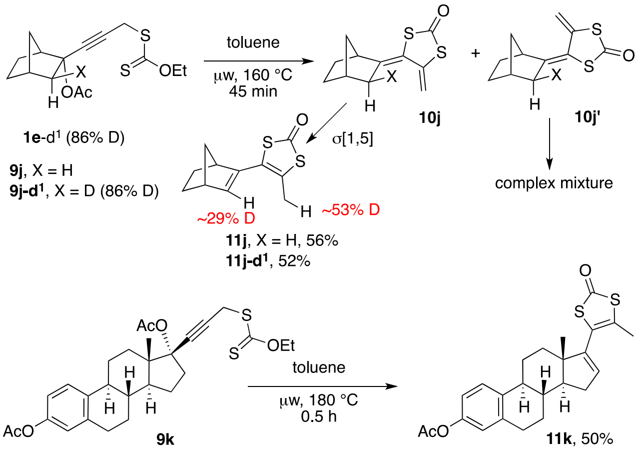
We examined initially the behavior of cyclohexanone derived xanthate **9a** in order to establish the best experimental conditions. We started by heating this compound in chlorobenzene at reflux, a procedure that had worked well for the less substituted *S*-propargyl xanthates (such as **1**) we had studied previously.[5] In this case, however, the reaction required a long time to reach completion, and significant amounts of tarry material were formed. After some experimentation, we found that heating a chlorobenzene or toluene solution in a microwave oven at 180 °C furnished 4-cycloxehenyl-5-methyl-1,3-dithiol-3-one **11a** in 80% in just 30 min (Scheme 4). Toluene is easier to eliminate and was chosen as the preferred solvent for the remainder of the study.

Other examples are displayed in Scheme 4. The first five involve substrates derived from symmetrical ketones so as to avoid complications due to isomeric intermediates (examples **11a–e**). The yield in these cases is generally good for both acetate and pivalate derivatives, and no difficulties were observed in the case of the *N*-Cbz-protected piperidine propargyl xanthate **9c**, which gave the expected dithiolone **11c** in good yield. In the case of substrates derived from unsymmetrical ketones, such as **9f** and **9g**, prepared, respectively, from methyl isopropyl ketone and menthone, the reaction produced essentially equimolar amounts of the inseparable isomeric pairs **11f** /**11f′** and **11g** /**11g′** in reduced yield. This observation indicates that the formation of diene **10** is irreversible under these conditions and that the process is under kinetic control with little selectivity.

These factors appeared to be also operating in the case of propargyl xanthates derived from aldehydes, as shown by the two examples in Scheme 5. Heating compound **9h**, prepared from dihydrocinnamaldehyde, under the usual conditions furnished dithiolone **11h** as the only isolable product. However, the reaction was not very clean, and the yield of **11h** was modest (45%). In all probability, the first rearrangement produces irreversibly isomeric dienes **10h** and **10h′**, but only the former can undergo the subsequent [1,5] sigmatropic rearrangement to give the observed dithiolone **11h** as only the *E* isomer. In contrast, the cyclododecyl derivatives **9i** and **9i′** can only rearrange into the same intermediate diene **10i**, which is ideally disposed for the [1,5] sigmatropic rearrangement leading to product **11i** in high yield in both cases. The nature of the "leaving" group, an acetate or a benzoate, hardly makes a difference.

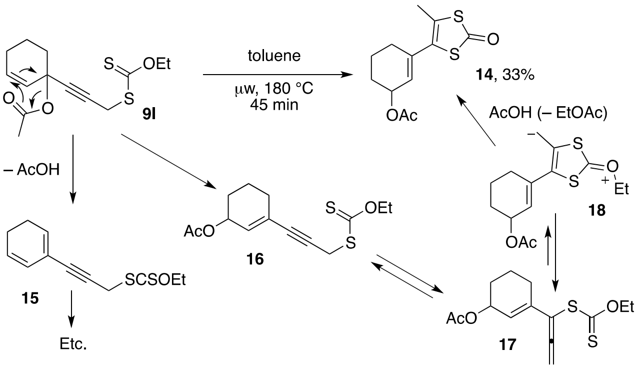
A similar behavior presumably underlies another set of propargylic xanthates derived from ketones, where only one of the corresponding isomeric dienes of general structure **10** is able to undergo the [1,5] sigmatropic rearrangement. Two examples are pictured in Scheme 6. In the first, **9j**, prepared from norbornanone, the rearrangement afforded dithiolanone **11j** in 56% yield. This compound can only arise from intermediate **10j**. The isomeric alkene **10j′** follows other pathways leading to unidentified side products. By starting with deuterated analogue **9j-d**,[1] we observed an apparent 2:1 preference for migration of the *exo* hydrogen atom. However, taking into account the primary kinetic isotope effect, which for thermal sigmatropic hydrogen migrations is estimated to be in the range of 5−8,[9] the actual preference for migration of the exo hydrogen must be much higher, of the order of 10−15:1. Incidentally, this deuteration experiment confirms the sigmatropic rearrangement proposed in Scheme 2. The second example is estrone-derived propargylic xanthate **9k**, which furnished diene **11k** in 50% yield upon heating under the usual conditions.

Scheme 6. Rearrangement of Propargyl Xanthates Derived from Unsymmetrical Ketones



We studied one case of a propargyl xanthate derived from an unsaturated ketone, namely compound **9l** obtained from 2-cyclohexenone. Microwave heating of a toluene solution did not result in a clean reaction, but a major product was isolated in 33% yield. Spectroscopic analysis indicated it to have structure **14**, where the acetate group has been retained but not in the same position (Scheme 7).

Scheme 7. Rearrangement of a Propargyl Xanthate Derived from Cyclohexenone



Upon vigorous heating, the tertiary allylic acetate can undergo elimination of acetic acid to give diene **15**, which then evolves into various products, including oxidation of the labile cyclohexadienyl system, or undergo a [3,3] sigmatropic rearrangement to furnish isomeric allylic acetate **16**. This compound can undergo a second [3,3] sigmatropic rearrangement involving this time the propagylic xanthate motif to give isomeric allene **17**, which is in equilibrium with betaine **18**. Protonation of the latter with acetic acid and concomitant loss of ethyl acetate finally generates the observed dithiolone **14**.

In summary, we have described an unusual yet inexpensive and versatile route to 4-alkenyl-1,3-dithiol-2-ones. These are rare structures. Indeed, only three synthetic routes have been described in the open literature. The first is based on a Wittig reagent prepared from 4-bromomethyl-1,3-dithiol-2-one.[10] The second is the radical addition of bis(*O*-isopropylxanthate) to enynes.[11] The last is the acid-catalyzed closure of *O*-ethyl-*S*-(4-hydroxybut-2-yn-1-yl)-xanthate.[3a] The last approach was applied to only one example but could in principle be generalized. The present procedure complements the earlier routes and provides in many instances structures that are not otherwise easily accessible.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01157.

> Experimental procedures, full spectroscopic data, and copies of ^{1}H and ^{13}C NMR for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: samir.zard@polytechnique.edu.

ORCID

Samir Z. Zard: 0000-0002-5456-910X

Notes

The authors declare no competing financial interest.
†Deceased September 5, 2014.

■ ACKNOWLEDGMENTS

We thank the ANR for financial support to two of us (P.O. and A.M.).

■ DEDICATION

This article is respectfully dedicated to the memory of Pavels Ostrovskis (1985−2014).

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