Interrupted Oligomerization Revisited: Simple and Efficient One-Pot Multicomponent Approach to Versatile Synthetic Intermediates

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ABSTRACT
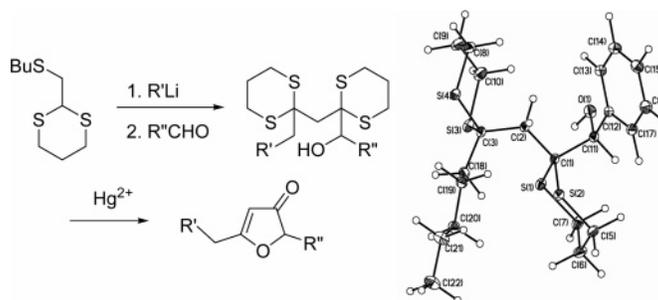
A novel multicomponent reaction allowing for a one-pot formation of three carbon−carbon bonds has been developed. It is based on in situ generation and anionic dimerization of methylenedithiane and produces a versatile synthetic equivalent of 4-hydroxy-1,3-alkanediones which, among other things, offers expeditious one-pot access to 3(*2H*)-furanones.

One-pot multicomponent reactions (MCRs) provide unmatched opportunities for the expeditious increase of complexity and diversity in synthetic outcomes. Particularly successful are the isocyanide-based approaches to heterocyclic systems, i.e., the Ugi-type reactions.[1] For practical reasons most of these reactions are limited to three to four components, as selectivity and reasonable yields are progressively more difficult to ensure in higher dimensional reagent space.

Interrupted oligomerization is an attractive alternative, which is normally controlled by a favorable formation of a 5−6-membered cyclic system—examples range from the age-old trimerization of acetone,[2] to the trimolecular formation of thiophene or selenophene ring systems,[3] to Posner's elegant interrupted anionic polymerization furnishing sub-

stituted cyclohexanes.[4] Most of these approaches rely on a strategically installed latent electrophile. To make this methodology general, i.e., not dependent on the in situ presence of the capping electrophile (or an equivalent leaving group as in the case of vicarious nucleophilic substitution), one needs to control the degree of polymerization, which conceivably can be achieved by a rapid buildup of steric hindrance as oligomerization progresses. The other objective is to install synthetically useful groups for subsequent functionalization. With this, we revisited Carlson's early studies of nucleophilic additions to 2-methylene-1,3-dithiane (MDTA).[5] Radical polymerization of MDTA is known to produce a polymer, which is a masked 1,3-polycarbonyl

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(2) Ipatieff, V.; Linn, C. B. US Patent 2419142 19470415, 1947.

(3) Nakayama, J.; Yomoda, R.; Hoshino, M. *Heterocycles* **1987**, *26*, 2215−2222.
(4) Posner, G. H.; Shulman-Roskes, E. M. *J. Org. Chem.* **1989**, *54*, 3514−3515.
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compound.[6] As alkyllithiums are known to add to MDTA, we reasoned that a controlled anionic dimerization of MDTA initiated by such addition and terminated with a synthetically useful electrophile, for example, a carbonyl compound, would constitute a multicomponent reaction in which four modules are combined to furnish a linear framework of masked 4-hydroxy-1,3-dione (Scheme 1). In many cases the

Scheme 1
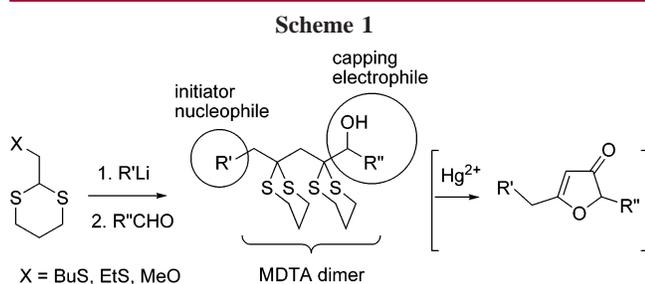
products can be simply hydrolyzed and cyclized into dihydro-3-furanones in a one-pot reaction.

In this Letter we report a successful implementation of this multicomponent strategy offering one-pot access to versatile synthons for subsequent transformations.

Our preferred precursor for MDTA is butylthiomethyl-1,3-dithiane (**1**), synthesized readily from inexpensive butanethiol, 2-bromo-1,1-dimethoxyethane, and 1,3-propanedithiol. Alternatively, alkoxymethyl-1,3-dithianes can be used,[5,7] although in our hands these precursors proved inferior to **1**.

Systematic optimization of reaction conditions with alkyllithiums showed that the yield of a dimeric anion is maximized at 20 °C in 15 min after the addition of 1.35−1.45 equiv of RLi. Scheme 2 illustrates the tetracomponent reaction of **1** initiated by alkyl- or aryllithiums and capped by benzaldehyde. X-ray crystallography of **2a** and **2b** confirmed the anticipated structures (Figure 1).

Generation of MDTA from **1** is very efficient and completed within minutes at 20 °C. Excess RLi adds at this temperature to form the initial monomeric dithianyl anion **A-1** within 5 min. The second addition of **A-1** to MDTA produces the bis-dithianyl anion **A-2**. Formation of this anion is a slower process that can be controlled by varying reaction conditions. For example, one can stop this process altogether at low temperature, i.e., formation of the anion and quenching of the reaction mixture with benzaldehyde at −30 °C → room temperature produces only *mono*-dithiane adduct **3**. Apparently the bis-dithianyl anion **A-2** is even less reactive toward MDTA, allowing for its selective accumulation in the reaction mixture. The bar graph in Figure 2 shows the results of screening for optimal reaction conditions, with the maximum yield of the bis-dithianyl adduct (67%) achieved at 20 °C by quenching the anionic reaction mixture with benzaldehyde after 15 min. Under these conditions the *mono*adduct **3** is formed in 22%. The two adducts are either

(6) Kobayashi, S.; Kadokawa, J.; Shoda, S.; Uyama, H. *Macromol. Rep.* **1991**, *A28* (Suppl. 1), 1−5.

(7) Doelling, W. *Sci. Synth.* **2006**, *24*, 461−516.

Scheme 2
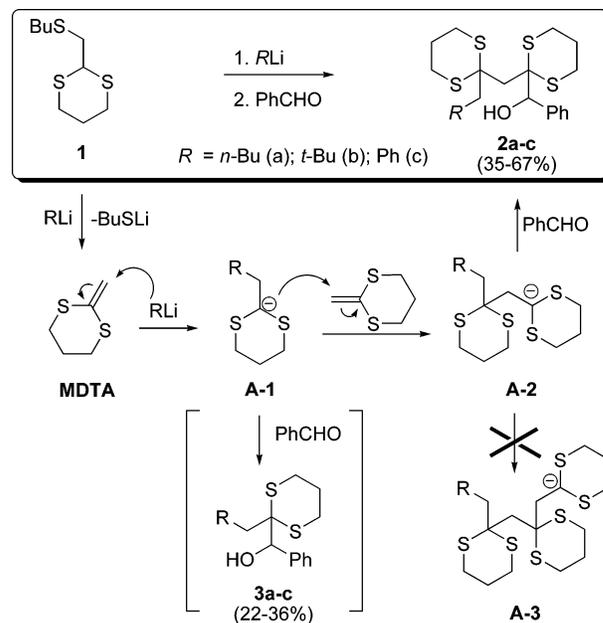
readily separated by column chromatography or subjected as a mixture to Hg^{2+}-catalyzed hydrolysis after crude gel-filtration. The ratio of bis- to monoadduct grows with time, as more of **A-1** is converted into **A-2**, but the absolute yield of the bis-adduct declines after 15 min due to the slow degradation of the anion **A-2**. We did not see any evidence for the formation of trimeric dithianyl anion **A-3**. If desired, the overall reaction can be accomplished in a stepwise manner, with MDTA generated with 1 equiv of phenyl- or butyllithium at the first step, followed by the dimerization induced with a different alkyl- or aryllithium.

A similar outcome is achieved when excess lithiated methyldithiane is treated with **1**. Thus, several experimental observations indicate that the dimerization of MDTA via carbolithiation is fairly efficient, while trimerization is either unfavorable or slow. Small amounts of bis-dithiane **4** were isolated. Interestingly, in this case we did not observe products of (mono) methyldithiane addition to aldehydes.
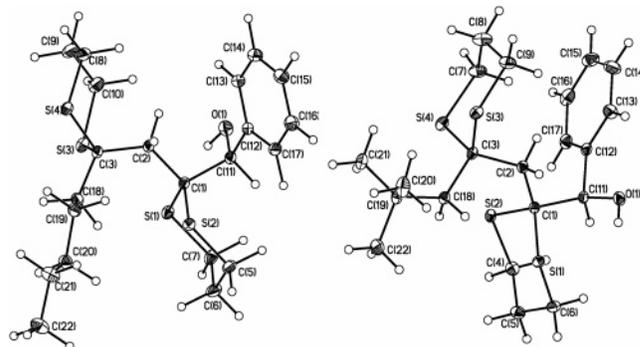
Figure 1. ORTEP drawings of bis-dithianes **2a** (left) and **2b**.
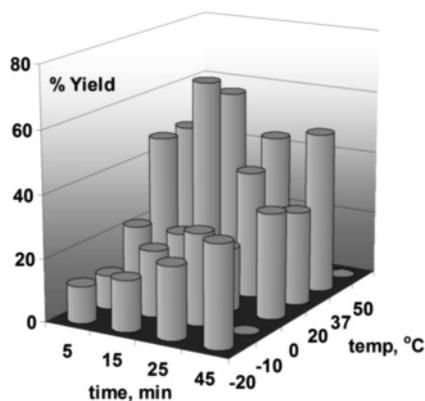
Figure 2. Optimization of the yield of **2a** as a function of temperature and the time before the quenching of the anion with benzaldehyde.

The reaction is much cleaner and the yields of adducts **2d,e** are much higher, 82−84%.

R = Ph (d); Et (e)

2d,e
(82-84%)

4
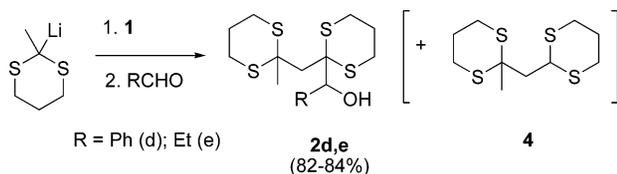
Ketones can also be used as capping electrophiles, as exemplified by acetone. However, esters and acyl chlorides undergo a more complex electron transfer initiated reaction, similar to the radical reductive ring opening described earlier for bulky dithianes.[8]

The particular synthetic significance of these findings lies in the fact that this multicomponent reaction allows for a controlled one-pot formation of three carbon−carbon bonds, furnishing a useful masked hydroxyalkanedione, which, among other things, can be utilized in a one-pot hydrolysis and cyclization into 3(2H)-furanones—a central structural element of several important natural products.[9] For example, the reaction of **1** initiated by BuLi and capped by propanal produced **5**, which was subjected to HgCl₂-catalyzed hydrolysis in aqueous acetonitrile to give furanone **6**.

1

5
(+ mono)

6
(55%)
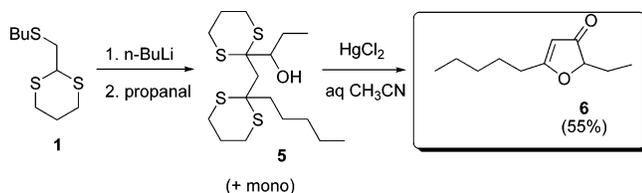
The efficiency of the second step (55%), i.e., hydrolytic cyclization, is comparable to that of a similar conversion of

β-hydroxyalkyl bis-dithiane to pyran recently described by Little.[10] In cases when benzaldehyde was used as a capping electrophile, the Hg²⁺-catalyzed reaction was accompanied by dehydrative expansion of one of the dithiane rings to furnish dithiepin enols **7**.

2a,b,d

R = n-Bu (a); t-Bu (b), H (d)

7a,b,d
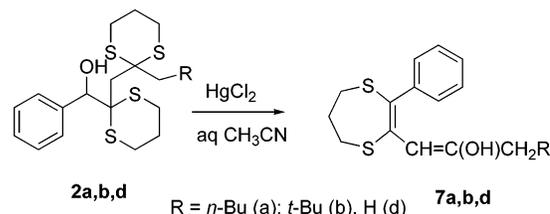
Under the same conditions monomeric adduct **3a** produced the expected product of thioacetal hydrolysis, i.e., 1-phenyl-1-hydroxy-2-heptanone. It is expected that milder methods of thioacetal deprotection[11] would allow for hydrolysis of both dithiane moieties in **2** without affecting the sensitive benzylic hydroxyls.

Attempts to induce tri- or tetramerization of MDTA by further decreasing the molar excess of phenyllithium reacting with **1** resulted only in elimination to furnish MDTA in high yield. During the column purification, the mixture of MDTA and benzaldehyde underwent a silica gel-catalyzed condensation, similar to that previously described.[12]

MDTA

8
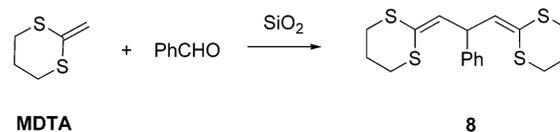
In conclusion, we have demonstrated a simple and efficient one-pot multicomponent approach to versatile synthetic intermediates based on controlled anionic dimerization of methylenedithiane.

Supporting Information Available: Synthetic procedures and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Nishiguchi, G. A.; Little, R. D. *J. Org. Chem.* **2005**, *70*, 5249−5256.
(11) For milder methods of thioacetal deprotection see: (a) Cossy, J. *Synthesis* **1987**, *12*, 1113−1115 (MCPBA-CF₃CO₂H). (b) Lucchetti, J.; Krief, A. *Synth. Commun.* **1983**, *13*, 1153−1161 (CuCl₂/CuO). (c) Varma, R. S.; Saini, R. K. *Tetrahedron Lett.* **1997**, *38*, 2623−2624 (clay). (d) Epling, G. A.; Wang, Q. *Tetrahedron Lett.* **1992**, *33*, 5909−5912 (photosensitized by Methylene Green).
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