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# Mercuric Chloride and Iodide Mediated Cyclization of Tethered Alkynedithioacetals as a General Route to Five- and Six-Membered Rings: Tuning of Regioselectivity by Alkyne Substitution

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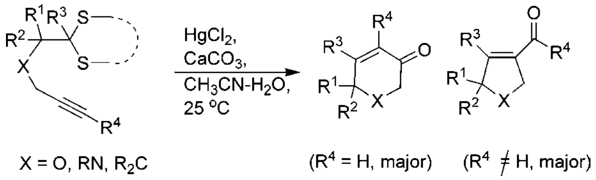
## ABSTRACT



**Mercuric chloride mediated cyclization of tethered alkynedithioacetals has been established as a general route to five- and six-membered carbocycles and heterocycles. Substitution at the alkyne terminus leads to preferential formation of five-membered rings, whereas unsubstituted alkynedithioacetals give six-membered rings as the major products. Mercuric iodide interrupts the reaction at the intermediate dithioacetal stage.**

The use of mercury compounds as reagents in organic synthesis is well established.[1] Apart from different mercuration reactions involving alkenes and alkynes, Hg(II) compounds have been extensively used in a variety of carbocyclization and heterocyclization reactions.[1,2] The majority of these ring-forming reactions have led to the formation of five- and six-membered rings. Recently we reported a unique reaction of *O*-propargylglycolaldehyde dithioacetals **1** (X = O, Scheme 1) in the presence of mercuric chloride, $CaCO_3$ in $CH_3CN-H_2O$, which results in the formation of 6*H*-pyran-3-ones **3** (3-pyranones, X = O, $R^3$ = H, $R^4$ = H, Scheme 1) along with dihydrofuran-3-aldehydes **4** (X = O, $R^3$ = H, $R^4$ = H) in some cases (Scheme 1).[3] The most noteworthy feature of this cyclization was the intermediacy of the 3-pyranone dithioacetals **2** (X = O, $R^3$ = H, $R^4$ = H) during the reaction. The utility of this novel reaction lies in the fact that the end result is intramolecular carbon−carbon bond formation leading to six- and five-membered rings. The reaction attains greater significance if it can accommodate substrates having all

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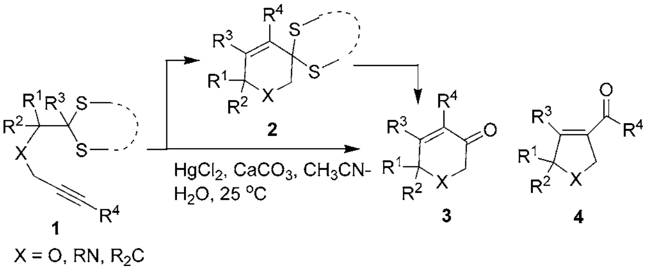
(1) (a) Larock, R. C. *Solvomercuration/Demercuration Reactions in Organic Synthesis*; Springer-Verlag: Berlin, Germany, 1986. (b) Larock, R. C. *Tetrahedron* **1982**, *38*, 1713−1754.

(2) (a) Imagawa, H.; Iyenaga, T.; Nishizawa, M. *Org. Lett.* **2005**, *7*, 451−453. (b) Imagawa, H.; Kurisaki, T.; Nishizawa, M. *Org. Lett.* **2004**, *6*, 3679−3681. (c) Nishizawa, M.; Yadav, V. K.; Skwarczynski, M.; Takao, H.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 1609−1611. (d) Nishizawa, M.; Takao, H.; Yadav, V. K.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 4563−4565. (e) Nishizawa, M.; Skwarczynski, M.; Imagawa, H.; Sugihara, T. *Chem. Lett.* **2002**, 12−13. (f) Frederickson, M.; Grigg, R. *Org. Prep. Proc. Int.* **1997**, *29*, 63−116. (g) Larock, R. C.; Harrison, L. W. *J. Am. Chem. Soc.* **1984**, *106*, 4218−4227. (h) Riediker, M.; Schwartz, J. *J. Am. Chem. Soc.* **1982**, *104*, 5842−5844. (i) Bates, D. K.; Jones, M. C. *J. Org. Chem.* **1978**, *43*, 3775−3776. (j) Thyagarajan, B. S.; Majumdar, K. C.; Bates, D. K. *J. Heterocycl. Chem.* **1975**, *12*, 59−66. (k) Balasubramanian, K. K.; Reddy, K. V.; Nagarajan, R. *Tetrahedron Lett.* **1973**, *14*, 5003−5004.

(3) Ghorai, S.; Bhattacharjya, A. *Org. Lett.* **2005**, *7*, 207−210.

10.1021/ol0527274 CCC: $33.50

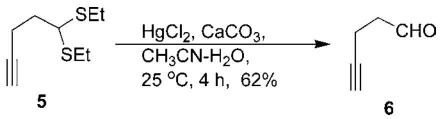
**Scheme 1.** General $HgCl_2$ Mediated Carbocyclization of Three-Atom Tethered Alkynedithioacetals



carbon tethers or tethers containing other heteroatoms such as nitrogen resulting in the formation of both carbocyclic and heterocyclic rings. Moreover the reaction depicted in Scheme 1 was also observed to afford five-membered rings as minor products in some cases.[3] The scope of the reaction could be expected to increase if the regioselectivity could be tuned so as to preferentially afford either six- or five-membered rings. The realization of the aforementioned two goals would greatly expand the scope of the reaction and increase the diversity in the products obtained. We report herein that the reaction is indeed applicable to alkynedithioacetals **1** (Scheme 1) having tethers comprising all carbon atoms or containing heteroatoms such as nitrogen and oxygen. Also described below is an interesting and useful tuning of the regioselectivity by substitution at the alkyne terminus, which makes the reaction preferentially favor the five-membered ring-systems **4** (Scheme 1).

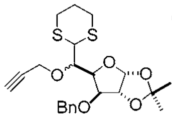
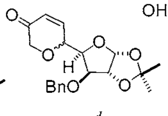
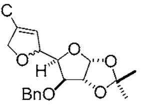
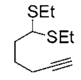
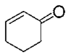
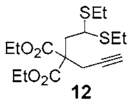
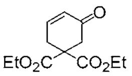
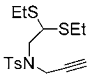
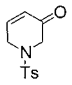
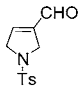
It was observed earlier that the mercuric chloride induced reaction of these tethered alkyne dithioacetals did not occur when the tether contained more than three atoms.[3] The necessity of a three-atom tether was evident from the hydrolytic cleavage of the dithioacetal **5** with a two-atom tether under the aforementioned conditions; this led to the aldehyde **6**[4] (Scheme 2) rather than the anticipated cyclization product.

**Scheme 2.** $HgCl_2$ Mediated Reaction of a Two-Atom Tethered Alkynedithioacetal



The applicability of the reaction to chiral substrates was demonstrated by the cyclization of the diastereomerically pure **7** (entry 1, Table 1; stereochemistry unknown), which afforded 3-pyranone **8** (28%) along with the dihydrofuran aldehyde **9** (14%) (Table 1), both as single diastereomers. The simplest all carbon tethered alkynedithioacetal **10** (entry 2, Table 1), on treatment with $HgCl_2$ and $CaCO_3$ in $CH_3CN-H_2O$ at 25 °C, resulted in the formation of cyclohex-2-enone (**11**) as the exclusive product in 42% isolated yield. The $^1H$ NMR spectrum of **11** was identical with the reported $^1H$ NMR spectrum of cyclohex-2-enone.[5] The malonate derivative **12** (entry 3, Table 1) under similar conditions gave rise to the cyclohexenone **13** in 45% yield. No five-membered compound was detected in these reactions. The nitrogenous substrate **14** (entry 4, Table 1) also successfully underwent cyclization, affording a mixture of the 2,3-dihydro-1*H*-pyridin-4-one **15** (41%) and the 2,5-dihydro-1*H*-pyrrole-3-carbaldehyde **16** (7%). Formation of five-membered rings as minor components was also previously observed with oxygen analogues.[3] The results cited in Table 1 established that the mercuric chloride mediated cyclization of tethered alkynedithioacetals containing an unsubstituted alkyne moiety is a general reaction giving rise primarily to six-membered rings. The structures of the aforementioned compounds were established on the basis of IR, NMR, and mass spectral analyses. The results presented in Table 1 established that the $HgCl_2$ mediated alkynedithioacetal cyclization is generally applicable for the construction of six- and five-membered carbocycles and heterocycles.

**Table 1.** Generalized $HgCl_2$ Mediated Cyclization of Tethered Alkynedithioacetals Containing Terminal Alkynes[a]

| entry | alkyne dithioacetal[b] | products (% yield)[c] | |
|---|---|---|---|
| 1 |  **7**[d] |  **8**[d] (28) |  **9**[d] (14) |
| 2 |  **10** |  **11** (42) | |
| 3 |  **12** |  **13** (45) | |
| 4 |  **14** |  **15** (41) |  **16** (7) |

[a] All reactions were performed at 25 °C in $CH_3CN-H_2O$ (4:1) for 4 h in the presence of 3.0 equiv of $HgCl_2$ and 4.0 equiv of $CaCO_3$. [b] Preparation of the starting materials is described in the Supporting Information. [c] Chromatographically isolated yields. [d] Compounds **7**, **8**, and **9** are diastereomerically pure; however, their stereochemistry could not be established.

The reaction of substrates, in which the terminal alkyne moieties are substituted, showed a drastic change in regioselectivity. In this regard, our results are presented in Table 2. The substituted alkyne substrates **17**, **19**, **21**, and **23** (entries 1−4, Table 2) all gave exclusively five-membered

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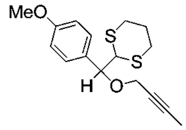
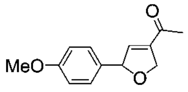
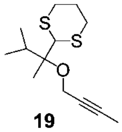
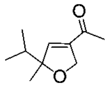
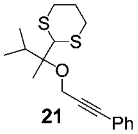
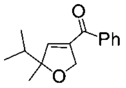
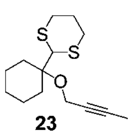
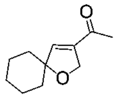
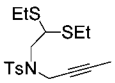
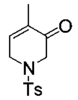
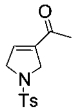
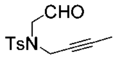
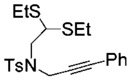
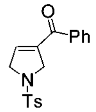
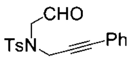
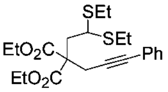
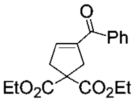
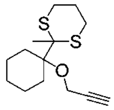
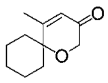
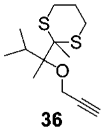
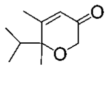
(4) Kulkarni, B. A.; Sharma, A.; Gamre, S.; Chattopadhyay, S. *Synthesis* **2004**, 595−599.

(5) *Handbook of Proton-NMR Spectra & Data*; Edited by Asahi Research Centre, Academic Press: Orlando, FL, 1985; Vol. 2, p 67, compound number 929.

**Table 2.** Effect of Substitution on the $HgCl_2$ Mediated Cyclization of Tethered Alkynedithioacetals[a]

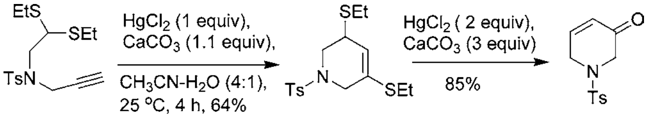
| entry | alkyne dithioacetal[b] | products (% yield)[c] |
|---|---|---|
| 1 |  **17** |  **18** (34) |
| 2 |  **19** |  **20** (32) |
| 3 |  **21** |  **22** (37) |
| 4 |  **23** |  **24** (53) |
| 5 |  **25** |  **26** (27)<br> **27** (31)<br> **28** (13) |
| 6 |  **29** |  **30** (38)<br> **31** (16) |
| 7 |  **32** |  **33** (52) |
| 8 |  **34** |  **35** (46) |
| 9 |  **36** |  **37** (51) |

[a] All reactions were performed at 25 °C in $CH_3CN-H_2O$ (4:1) for 4 h in the presence of 3.0 equiv of $HgCl_2$ and 4.0 equiv of $CaCO_3$. [b] Preparation of the starting materials is described in the Supporting Information. [c] Chromatographically isolated yields.

3-acyl-2,5-dihydrofurans **18**, **20**, **22**, and **24** on treatment with $HgCl_2$ under the standard conditions, which stood in sharp contrast to our earlier reported reactions, which afforded the six-membered enones exclusively or as the major products.[3] The dithioacetal **25** (entry 5, Table 2) gave a 1:1 mixture of the dihydropyridone **26** (27%) and the pyrrolidine **27**[6] (31%). The aldehyde **28**[6] (13%) formed via the cleavage of the dithioacetal was also obtained from this reaction albeit in poor yield. The pyrrolidine **30**[6] (38%) was the exclusive product of cyclization from **29** (entry 6, Table 2), along with deprotected aldehyde **31**[6] (16%), which was obtained as a minor product. The all-carbon tethered malonate **32** (entry 7, Table 2) gave exclusively the cyclopentene **33**[6] (52%). Substitution at the dithioacetal carbon atom did not lead to any change in the regioselectivity as is evident from the reactions of **34** and **36** (entries 8 and 9, Table 2), which gave rise to the six-membered rings **35** (46%) and **37** (51%), respectively, as exclusive products.

The results (entries 1−7) in Table 2 indicate that a useful and interesting tuning of the regioselectivity of the cyclization can be achieved with alkyne substitution. The reasons for this change in regioselectivity are not known. Although the exact mechanism of mercuration reactions is not known,[1] it is proposed that Hg(II) reacts with a terminal alkyne to form a vinyl carbonium ion or complex, in which the Hg is attached to the terminal carbon atom. The situation is more complex for a disubstituted alkyne where the carbonium ion may be formed at any of the two alkyne carbon atoms. This is probably why mixtures of products are formed from such reactions,[1] although there are cases where the preferential formation of one product has been observed.[1,2h] In our earlier study 1,3-propanedithioketals of the corresponding 3-pyranones were isolated as intermediates in some reactions of *O*-propargylgylcolaldehyde dithioacetals.[3] In the present work a related but different intermediate **38** was isolated from the reaction of alkyne diethyldithioacetal **14** with 1.0 equiv of $HgCl_2$. The structure of **38** was secured by NMR and mass spectral data, and it was found that the ketone **15** could be generated from **38** by treatment with excess $HgCl_2$. A tentative mechanism for the formation of **38** is presented in Scheme 4. It should be mentioned that this mechanism has close similarity with the one proposed earlier for the formation of pyranones.[3]

**Scheme 3.** Formation of Vinylsulfide Intermediate during Hg(II) Reaction of Alkyne Ethanedithioacetal **14**



**14** **38** **15**

The yields of the $HgCl_2$ mediated reactions are not particularly high, although it should be mentioned that alternative routes to the products would require multistep synthesis. It is possible that a substantial part of the starting material undergoes polymerization, because appreciable quantities of insoluble residues are obtained in all the reactions.

A remarkable observation was made when $HgI_2$ was used as the reagent in the reaction of the *O*-propargylglycolalde-

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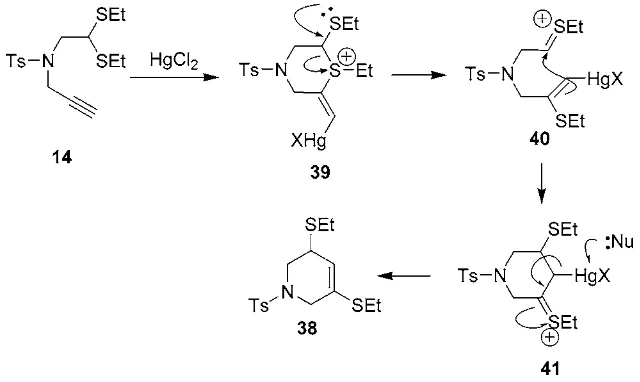
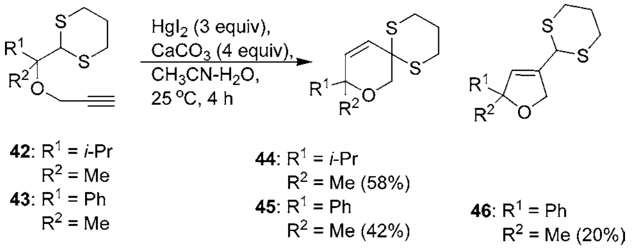
(6) Rhee, J. U.; Krische, M. J. *Org. Lett.* **2005**, *7*, 2493−2495.

**Scheme 4.** Tentative Mechanism for the Formation of **38**



hyde dithioacetal **42** (Scheme 5). The known[3] intermediate dithioacetal **44** was isolated as the exclusive product even when excess $HgI_2$ was used. Similar behavior of $HgI_2$ was also encountered in the reaction of the dithioacetal **43**, where a mixture of the known[3] 3-pyranone dithioacetal **45** and the dithioacetal **46** was obtained (Scheme 5). The particular ability of $HgI_2$ to interrupt the reaction at the intermediate stage is expected to be useful, because the dithioacetals can undergo further transformations such as desulfurization giving rise to unsaturated rings. So far all attempts to catalyze the above-mentioned reactions by mercuric triflate, which has been successfully used for other mercuration reactions,[2a−e] have so far proven unsuccessful. Treatment of **43** with $Hg(OTf)_2$ in $CH_3CN-H_2O$ resulted in hydration of the alkyne without affecting the thioacetal group, and this observation was in agreement with the reported hydration of alkynes in the presence of $Hg(OTf)_2$.[2e]

**Scheme 5.** $HgI_2$ Mediated Cyclization of Alkynedithioacetals



In conclusion, $HgCl_2$ has been established as an effective reagent for mediating the general cyclization of tethered alkynedithioacetals to obtain five- and six-membered rings. A remarkable aspect of this reaction is the tuning of the regioselectivity of the reaction by alkyne carbon atom substitution. In addition, $HgI_2$ has been found to interrupt the reaction so that the intermediate dithioacetal is formed exclusively. Future work on this potentially important reaction will focus on the dependence of the mechanism on the nature of dithioacetals as well as its application to the synthesis of complex ring systems.

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**Supporting Information Available:** Experimental procedure and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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