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Mercury(II) Chloride-Mediated Cyclization–Rearrangement of *O*-Propargylglycolaldehyde Dithioacetals to 3-Pyranone Dithioketals: An Expeditious Access to 3-Pyranones

Subir Ghorai and Anup Bhattacharjya*

Indian Institute of Chemical Biology, 4, Raja S. C. Mullick Road, Kolkata 700032, India

anupbh@hotmail.com

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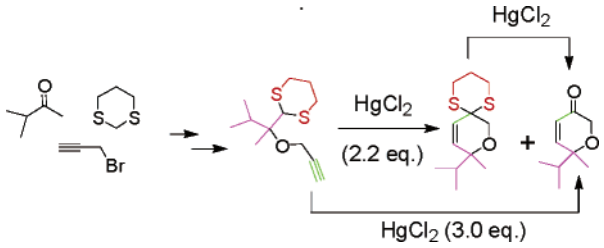
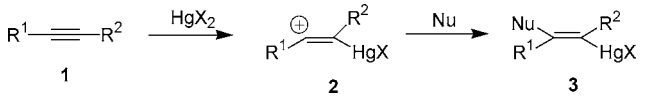
ABSTRACT



***O*-Propargyl glycolaldehyde dithioacetals undergo a unique cyclization–rearrangement in the presence of mercuric chloride and calcium carbonate to afford 3-pyranones exclusively or along with 2,5-dihydrofuran-3-carboxaldehydes via their dithioketals and dithioacetals.**

Electrophilic mercury salts are important reagents in organic synthesis. Examples of reactions involving mercury salts with alkenes and alkynes in the presence of various nucleophiles giving rise to varied types of products abound in the literature.[1] Intramolecular cationic cyclizations of olefinic and acetylenic substrates having aromatic rings, alkene moieties, and heteroatoms in the neighborhood are also well documented.[1,2] The Hg(II)-mediated reaction of an alkyne **1** generally occurs via the formation of a vinylmercurial carbonium ion **2** followed by the attack by a nucleophile leading to the formation of the organomercury species **3** (Scheme 1). The formation of benzofurans, benzothiophenes, and indoles from ortho-substituted arylalkynes,[2a] 2-methylene tetrahydrofurans and dihydropyrans from hydroxy alkynes,[2b] dihydronaphthalenes from arylalkynes,[2a,c] benzopyrans from arylalkynyl ethers,[2a,d−f] furans from alkynyl ketones,[2g] and carbocyclization of 1,6-enynes are some of the examples of the above process.[2h] Although most of the Hg(II)-mediated

Scheme 1. Hg(II)-Mediated Reaction of an Alkyne in the Presence of a Nucleophile



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

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

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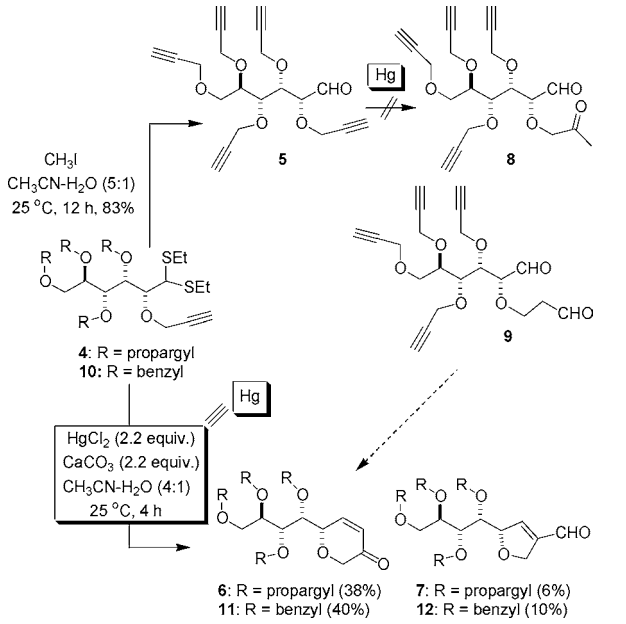
reactions involve the employment of the mercury salts in stoichiometric quantities, in a major development in this area, catalytic amounts of the reagent, especially Hg(II) triflate, have been successfully used in some of the above reactions as well as hydration of alkynes.[2c,g−i]

Another common application of Hg(II) salts is found in the cleavage of dithioacetals or ketals leading to carbonyl compounds;[3] in this regard, we now disclose herein a unique carbocyclization of dithioacetals derived from *O*-propargylglycolaldehydes in the presence of mercuric chloride, which is apparently initiated by the electrophilic attack of Hg(II) but takes a hitherto unknown course thereafter leading to the formation of 6*H*-pyran-3-ones (3-pyranones) via their dithioketals. It should be mentioned in this context that there have been several synthetic exercises directed toward pyran-3-ones due to their importance as useful synthons.[4] Most of these methods use 2-furyl alcohols, glycals, or dipropargyl ethers as the key building blocks.

To generate the aldehyde **5** (Scheme 2) following a common procedure of dithioacetal cleavage,[5] the penta-*O*-propargyl glucose diethyldithioacetal **4**, prepared according to a known method,[6] was treated with 2.2 equiv each of $HgCl_2$ and $CaCO_3$ in CH_3CN-H_2O (4:1) at 25 °C for 4 h.

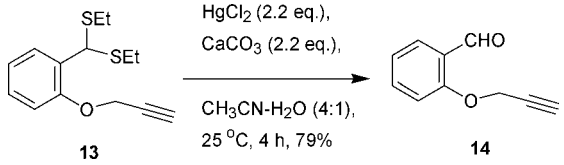
Scheme 2. Hg(II)-Mediated Reaction of 2-*O*-Propargyl Glucose Diethyldithioacetals



We were surprised to find that the products were the 3-pyranone **6** (38%) and the dihydrofuryl aldehyde **7** (6%) rather than the expected aldehyde **5** (Scheme 2). The structures of **6** and **7** were secured from NMR, mass, and IR spectral data. A simple explanation for the formation of these compounds appeared to be a sequence of reactions consisting of the cleavage of the dithioacetal to **5**, a nonregioselective Hg(II)-catalyzed hydration of the alkyne to give **8** and **9**, followed by the intramolecular aldol condensation and dehydration to **6** and **7**, respectively (Scheme 2). This possibility was ruled out by the observation that the aldehyde **5** generated by an alternative method[7] did not afford **6** and **7** under identical conditions (Scheme 2) and was recovered unchanged. In contrast, no such reaction occurred with the corresponding penta-*O*-allyl glucose diethyldithioacetal, which could be cleaved smoothly giving rise to the parent aldehyde.[6]

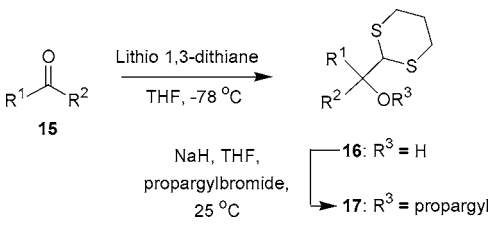
These observations clearly indicated that the presence of both the dithioacetal and the alkyne functionalities was necessary for the formation of **6** and **7**. To our knowledge, such a cyclization in an alkyne-dithioacetal system has not been encountered previously. That the above cyclization was not an isolated example was evident from the formation of the pyranone **11** and the furan aldehyde **12** under identical conditions from the structurally similar glucose-derived dithioacetal **10**. However, the cyclization failed when the tether between the alkyne and the dithioacetal moieties was longer than that present in **4** and **10**.

O-Propargylsalicylaldehyde diethyldithioacetal (**13**), which has one more carbon atom in the tether, underwent cleavage rather than any cyclization, and *O*-propargylsalicylaldehyde (**14**) was isolated as the exclusive product. These results led to the hypothesis that the above cyclization required the presence of an *O*-propargyl glycolaldehyde dithioacetal system in the substrate.



With the dual purpose of establishing the generality of the reaction, an alternative method for assembling the aforementioned skeleton was devised as shown in Scheme 3. A two-step method involving the reaction of an aldehyde or ketone **15** with lithio 1,3-dithiane,[8] followed by *O*-propar-

Scheme 3. Synthesis of *O*-Propargyl Dithioacetals from Aldehydes and Ketones

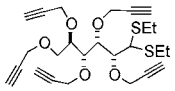
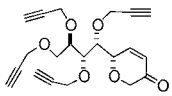
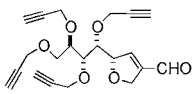
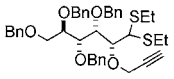
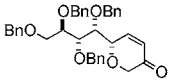
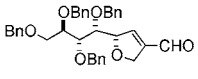
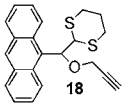
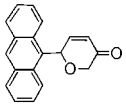
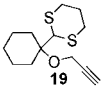
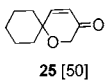
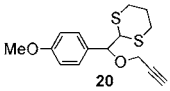
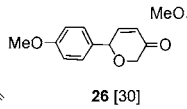
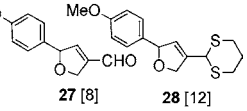
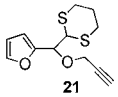
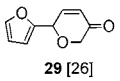
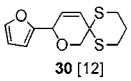
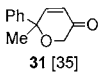
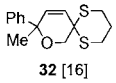
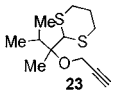
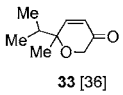
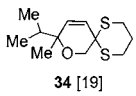


(3) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999; pp 329−344.

(4) (a) Krishna, U. M.; Deodhar, K. D.; Trivedi, G. K. *Tetrahedron* **2004**, *60*, 4829−4836 and references therein. (b) Jung, M. E.; Pontillo. J. *J. Org. Chem.* **2002**, *67*, 6848−6851. (c) Sugawara, K.; Imanishi, Y.; Hashiyama, T. *Tetrahedron: Asymmetry* **2000**, *11*, 4529−4535. (d) van der Deen, H.; van Oeveren, A.; Kellogg, R. M.; Feringa, B. L. *Tetrahedron Lett.* **1999**, *40*, 1755−1758 and references therein. (e) Dauben, W. G.; Kowalczyk, B. A.; Lichtenthaler, F. W. *J. Org. Chem.* **1990**, *55*, 2391−2398 and references therein. (f) Hepworth, J. D. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., McKillop, A., Eds.; Pergamon: Oxford, 1984; Vol. 3, pp 843−844.

gylation of the resulting alcohol **16** in the presence of sodium hydride, gave the alkyne dithioacetal **17** (Scheme 3). The 1,3-propanedithioacetals prepared in this way were subjected to the $HgCl_2$-mediated reaction using the conditions adopted for **4** and **10**, i.e., stirring with 2.2 equiv of each of $HgCl_2$ and $CaCO_3$ in CH_3CN-H_2O (4:1) for 4 h at 25 °C, and the results are presented in Table 1.

Table 1. Hg(II) Chloride-Mediated Reaction of *O*-Propargyl Glycolaldehyde Dithioacetals[a]

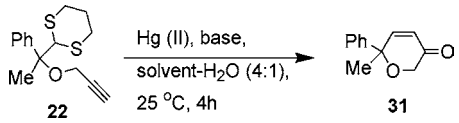
Entry	Substrate	Product [%][b] (%)[b]		
1	 **4**	 **6** [38] **6** (40)	 **7** [6] **7** (8)	
2	 **10**	 **11** [40] **11** (42)	 **12** [10] **12** (13)	
3	 **18**	 **24** [40]		
4	 **19**	 **25** [50]		
5	 **20**	 **26** [30] **26** (35)	 **27** [8] **27** (14) **28** [12]	
6	 **21**	 **29** [26] **29** (40)	 **30** [12]	
7	 **22**	 **31** [35] **31** (53)	 **32** [16]	
8	 **23**	 **33** [36] **33** (63)	 **34** [19]	

[a] All reactions were performed at 25 °C in CH_3CN-H_2O (4:1) for 4 h in the presence of either (A) 2.2 equiv each of $HgCl_2$ and $CaCO_3$ or (B) 3.0 equiv of $HgCl_2$ and 4.0 equiv of $CaCO_3$. [b] [%] denotes % yield under conditions A, and (%) denotes % yield under conditions B.

The most noteworthy feature of the above cyclization was discovered in the reaction of **23**, in which the pyranone **33** was isolated in 36% yield along with a minor compound in 19% yield (entry 8). The minor compound was identified as the dithioketal **34** by NMR and mass spectral analyses. Additional evidence for its structure was provided by its conversion to the parent pyranone **33** by $HgCl_2$ and $CaCO_3$ in CH_3CN-H_2O. Under similar conditions, the dithioacetal **28** and dithioketals **30** and **32** were also obtained in varying yields from the reactions of **20**, **21**, and **22** respectively (entries 5−7). Interestingly, the reaction of **23** in the presence of 1.0 equiv each of $HgCl_2$ and $CaCO_3$ for 2.5 h afforded **33** and **34** in yields of 17 and 53%, respectively, whereas under these conditions **22** gave a mixture of **32** and unchanged starting material but no pyranone, as evident from the ^1H NMR spectrum of the product.

The optimized conditions for preparing the pyranones and dihydrofuryl aldehydes uncontaminated with dithioacetals involved the use of 3.0 equiv of the mercury salt and 4.0 equiv of $CaCO_3$ in CH_3CN-H_2O (4:1) at 25 °C for 4 h. The other products besides the pyranones and the dihydrofuryl aldehydes were found to be unidentified materials insoluble in organic solvents or water. Variation in mercury(II) salts, bases, and solvents either led to the formation of intractable products or did not improve the yields (Table 2).

Table 2. Hg(II)-Mediated Cyclization of **22**



22 **31**

entry	Hg(II) (equiv)	base (equiv)	solvent	yield (%)[a]
1	$HgCl_2$ (3.0)	$CaCO_3$ (4)	CH_3CN-H_2O	53
2	$HgCl_2$ (2.2)	DIPEA (3.3)	CH_3CN-H_2O	0
3	Hg $(OTFA)_2$ (2.2)	$CaCO_3$ (3.3)	CH_3CN-H_2O	0
4	$HgCl_2$ (3.0)	$CaCO_3$ (4)	$THF-H_2O$	42
5	$HgCl_2$ (3.0)	$CaCO_3$ (4)	$(CH_3)_2CO-H_2O$	39

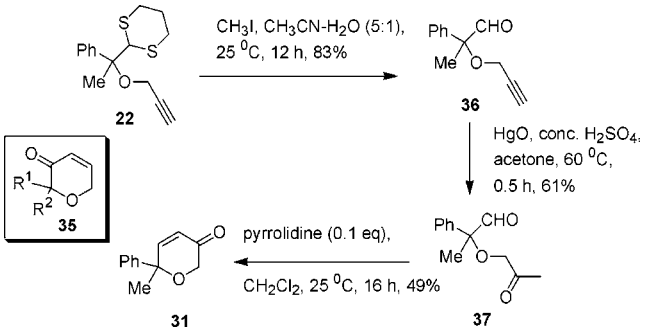
[a] Yields refer to chromatographed material. In the cases of 0% yields, only intractable materials were obtained.

The formation of dihydrofuryl aldehydes was not general and was observed from some of the substrates (entries 1, 2, and 5, Table 1) in which the carbon atoms bearing the *O*-propargyl group were monosubstituted.

The above results indicate that the primary products of this unusual cyclization are the dithioacetals or the ketals, which are subsequently cleaved by excess mercuric chloride to the parent aldehydes and ketones.[9] An alternative structure **35** for the 3-pyranone skeleton was ruled out by an unambiguous synthesis of **31** in 25% overall yield from **22** as shown in Scheme 4.[10] The higher yield of **31** (53%) obtained in the Hg(II)-mediated cyclization also established its superiority over the stepwise synthesis shown in Scheme

(5) Meyers, A. I.; Comins, D. L.; Roland, D. M.; Henning, R.; Shimizu, K. *J. Am. Chem. Soc.* **1979**, *101*, 7104−7105.
(6) Mukhopadhyay, R.; Kundu, A. P.; Bhattacharjya, A. *Tetrahedron Lett.* **1995**, *36*, 7729−7730.
(7) Fetizon, M.; Jurion, M. *J. Chem. Soc., Chem. Commun.* **1972**, 382−383.
(8) Page, P. C. B.; van Niel, M. B.; Proger, J. C. *Tetrahedron* **1989**, *45*, 7643−7677.
(9) In the cases of **4**, **10**, **18**, and **19**, the intermediate dithioacetals did not survive when 2.2 equiv each of $HgCl_2$ and $CaCO_3$ was used, and only the carbonyl compounds were isolated.

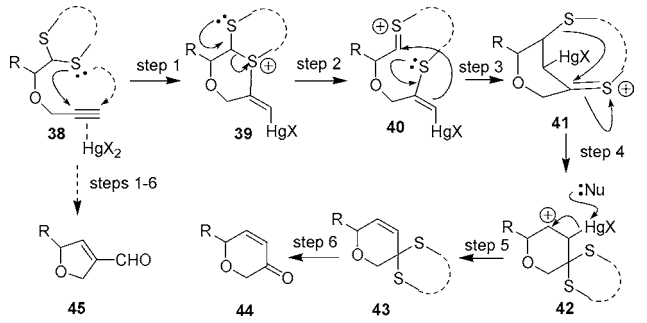
Scheme 4. Alternative Synthesis of **31** from **22**



4. The present method provides a rapid assemblage of this skeleton from an aldehyde or a ketone, 1,3-dithiane, and propargyl bromide.[11]

A tentative mechanism for the reaction is presented in Scheme 5. The reaction leading to a pyranone is initiated

Scheme 5. Proposed Pathway for the Formation of 3-Pyranone Dithioketals from *O*-Propargyl Glycolaldehyde Dithioacetals



by the *exo* attack of a sulfur atom on the alkyne−Hg(II) complex in **38** (step 1, solid arrow).[12] The organomercurial species **39** then undergoes C−S bond cleavage, and the carbocation formed is stabilized by the adjacent sulfur atom (step 2).[12] After the formation of the C−C bond (step 3), migration of the sulfur atom takes place with concomitant expulsion of the Hg(II) (steps 4 and 5). Subsequent cleavage of the thioketal in the presence of $HgCl_2$ gives rise to the pyranone **44** (step 6). An *endo* attack of the sulfur atom on the alkyne−Hg(II) complex in **38** (step 1, dashed arrow) followed by analogous steps 2−6 can explain the formation of a dihydrofuryl aldehyde **45**. We believe that the length of the tether between the dithioacetal and the alkyne moieties is critical for the occurrence of step 1. The cyclization itself appears to be specific for a three-atom-tethered alkyne dithioacetal like the *O*-propargyl glycolaldehyde dithioacetals described above.

In conclusion, the work presented here describes a unique Hg(II)-mediated reaction of *O*-propargyl glycolaldehyde dithioacetals and an expedient general route to 6*H*-pyran-3-ones. The application of this potentially useful reaction to the synthesis of other heterocyclic and carbocyclic skeletons as well as efforts toward a better understanding of its mechanism are underway.

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

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(10) ^{1}H and ^{13}C NMR spectra of the pyranones were consistent with the assigned structures. In the alternative structure **35**, at least one of the *O*-CH_2 protons is expected to be vicinally coupled to the olefinic proton. No such vicinal coupling is observed in the ^{1}H NMR spectra. The IR and mass spectral data also agreed well with the structures.

(11) Examples of preparing 6*H*-pyran-3-ones from aldehydes and ketones are scarce. In one example, a pyranone having the same skeleton as the ones reported in this work has been synthesized from a methyl ketone via a multistep sequence (ref 4b).

(12) Capture of the electrophilic vinyl carbonium ion formed after complexation with Hg(II) by a neighboring sulfur (ref 2a) as well as oxygen atoms (refs 1, 2a, 2b, and 2g) is well precedented. In some of these instances, a substituent attached to the heteroatom is cleaved in the next step, affording sulfur and oxygen heterocycles.