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A New Synthesis of γ-Butyrolactones via $AuCl_3$- or Hg(II)-Catalyzed Intramolecular Hydroalkoxylation of 4-Bromo-3-yn-1-ols†

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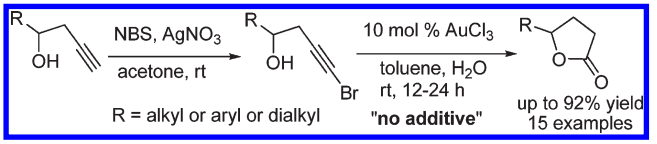
ABSTRACT



An efficient conversion of 4-bromo-3-yn-1-ols to γ-butyrolactones via $AuCl_3$-catalyzed electrophilic cyclization (hydroxyl-assisted regioselective hydration) in wet toluene is described. Various secondary and tertiary alcohols including benzylic systems were found to be equally reactive with moderate to excellent yields obtained in all cases.

Cycloisomerization via intramolecular hydroalkoxylation and hydroamination of alkynes with tethered hydroxyl or amino groups is currently an emerging method for the synthesis of various heterocycles such as pyrroles, furans, quinolines, spiroketals, and many new frameworks which are not otherwise readily accessible.[1,2] Various metal ions including Au(I), Au(III), Hg(II), Fe(III), Zn(II), Ag(I), Pd(0), Pd(II), Cu(II), Ni, Co, and Ir have been employed to functionalize alkynes.[1,2] In particular, the recent explosion of interest in gold catalysis has not only made the several existing methods easier but also led to the synthesis of a variety of novel heterocyclic architectures.[1] The popularity of such chemistry stems from the easy access to alkyne intermediates and the brevity of approach and because the alkyne intermediates are inert to various reagents and reaction conditions and, hence, can be used to conceal the required subunit until an appropriate point is reached in a long total synthesis. We herein report for the first time the conversion of 4-bromo-3-yn-1-ols to butyrolactones using $AuCl_3$ in aqueous toluene (Scheme 1, eq 3). The starting substrates, bromoalkynols, can be easily accessed from alkynes, alkynylsilanes, and dibromoolefins

(1) For some recent examples, see: (a) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164–11165. (b) Kothandaraman, P.; Rao, W.; Foo, S. J.; Chan, P. W. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 4619–4623. (c) Belting, V.; Krause, N. *Org. Lett.* **2006**, *8*, 4489–4492. (d) Patil, N. T.; Kavthe, R. D.; Shinde, V. S.; Sridhar, B. *J. Org. Chem.* **2010**, *75*, 3371–3380. (e) Fang, C.; Pang, Y.; Forsyth, C. J. *Org. Lett.* **2010**, *12*, 4528–4531. (f) Nishizawa, M.; Imagawa, H.; Yamamoto, H. *Org. Biomol. Chem.* **2010**, *8*, 511–521. (g) Carney, M. M.; Donoghue, P. J.; Wuest, W. M.; Wiest, O.; Helquist, P. *Org. Lett.* **2008**, *10*, 3903–3906. (h) Sandelier, M. J.; DeShong, P. *Org. Lett.* **2007**, *9*, 3209–3212 and the references therein.

(2) (a) Ravindar, K.; Reddy, M. S.; Deslongchamps, P. *Org. Lett.* **2011**, *13*, 3178–3181. (b) Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *J. Org. Chem.* **2011**, *76*, 1269–1284. (c) Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *Org. Lett.* **2010**, *12*, 4420–4423.

(3) (a) Gallagher, P. W.; Terstiege, I.; Maleczka, R. E. *J. Am. Chem. Soc.* **2001**, *123*, 3194–3204. (b) Boden, C. D. J.; Pattenden, G.; Ye, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2417–2419. (c) Gonzalez, I. Cl.; Forsyth, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 9099–9108. (d) Lu, W.; Zheng, G.; Cai, J. *Tetrahedron* **1999**, *55*, 7157–7168.

(4) (a) Bandichhor, R.; Nosse, B.; Reiser, O. *Top. Curr. Chem.* **2005**, *243*, 43–72. (b) Miyabe, H.; Fujji, K.; Goto, T.; Naito, T. *Org. Lett.* **2000**, *2*, 4071–4074. (c) Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2001**, *3*, 675–678. (d) Koch, S. S. C.; Chamberlin, A. R. *Enantiomerically Pure γ-Butyrolactones*; Atta-ur-Rahman, Ed.; Elsevier Science: Amsterdam, 1995; pp 687–725. (d) Fernandez, A.-M.; Plaquevent, J.-C.; Duhamel, L. *J. Org. Chem.* **1997**, *62*, 4007–4014. (e) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1869–1888.

(5) For a few examples of synthesis of lactones, see: (a) Huang, L.; Jiang, H.; Qi, C.; Liu, X. *J. Am. Chem. Soc.* **2010**, *132*, 17652–17654. (b) Dohi, T.; Takenaga, N.; Goto, A.; Maruyama, A.; Kita, Y. *Org. Lett.* **2007**, *9*, 3129–3132. (c) Schomaker, M. M.; Travis, B. R.; Borhan, B. *Org. Lett.* **2003**, *5*, 3089–3092. (d) Seitz, M.; Reiser, O. *Curr. Opin. Chem. Biol.* **2005**, *9*, 285–292. (e) Ogliaruso, M. A.; Wolfe, J. F. In *Synthesis of Lactones and Lactams*; John Wiley & sons: New York, 1993. (f) Trost, B. M.; Rhee, Y. H. J. *Am. Chem. Soc.* **1999**, *121*, 11680–11683. (g) Nosse, B.; Chhor, R. B.; Jeong, W. B.; Bohm, C.; Reiser, O. *Org. Lett.* **2003**, *5*, 941–944. (h) Compain, P.; Gore, J.; Vatele, J. –M. *Tetrahedron* **1996**, *52*, 10405–10416. (I) Gutierrez, J. L. G.; Jimenez-Cruz, F.; Espinosa, N. R. *Tetrahedron Lett.* **2005**, *46*, 803–803.

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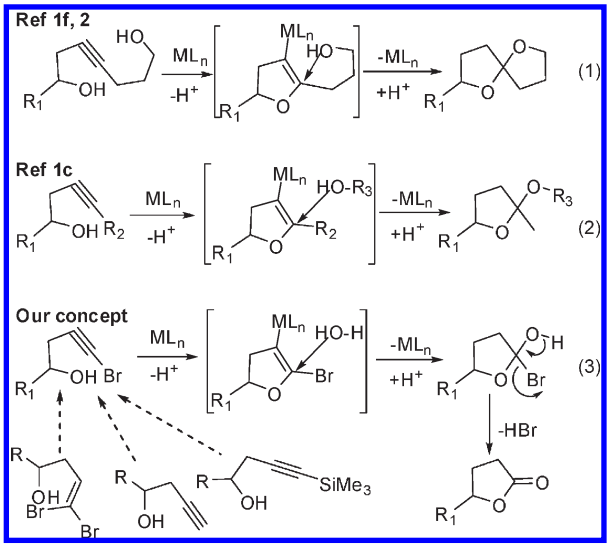
using well-established literature precedents (Scheme 1, eq 3).[3]

γ-Butyrolactones are very common structural units in many biologically active compounds and natural products.[4] Consequently, the development of efficient syntheses of lactone rings has been an important objective.[5] In continuation of our interest in the electrophile-initiated cycloisomerization of alkynols via hydroalkoxylation,[2] we were curious to know the reactivity of bromoalkynes. Based on previous mechanistic work,[1c,f,2a] we conceived

Scheme 1. Concept for the Synthesis of γ-Butyrolactones Based on the Previous Mechanistic Studies



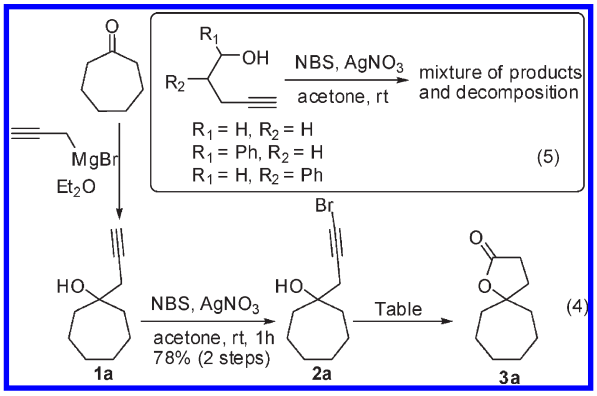
a new synthesis of γ-butyrolactones from 4-bromo-3-yn-1-ols as described in the Scheme 1 (eq 3 based on eqs 1 and 2).

Thus, we initiated our study (Table 1) on **2a**, which was obtained from cycloheptanone via propargylation[6] and bromination[3] using literature precedents (eq 4). Bromination of **1a** to give **2a** was not adversely affected by the presence of the free hydroxyl group, and hence its protection was not necessary. Various secondary and tertiary unprotected 3-alkyn-1-ols were converted to the corresponding terminal bromides in high yield (*vide infra,* Table 2). The reason for emphasizing the bromination of unprotected 3-alkyn-1-ols[7] is that a similar process on 4-alkyn-1-ols leads to the formation of a mixture of products and decomposition of the substrates (Table 1, eq 5).

Initially, we treated **2a** with 0.1 equiv of $HgCl_2$ (entries 1 and 2) in CH_3CN/H_2O (9/1). After 30 h at 50 °C, the expected product **3a** was obtained in only 5% yield while most of the starting material remained unaffected. No significant improvement was observed either in yield of product or in reaction speed with increased catalyst loading and with extended reaction times. $Hg(OAc)_2$ and $Hg(OTFA)_2$ were found to be ineffective, with most of the

(6) Njardarson, J. T.; Wood, J. L. *Org. Lett.* **2001**, *3*, 2431–2434.
(7) One example of conversion of unprotected homopropargyl alcohol to corresponding bromoalkyne was reported in ref 3a.

Table 1. Optimization Studies for the synthesis of butyrolactone **3a** from **2a**



entry	catalyst	mol %	solvent[a]	temp	time	yield(%)
1	$HgCl_2$	10	$MeCN/H_2O$ (9/1)	50 °C	30 h	5[b]
2	$HgCl_2$	25	-do-	50 °C	30 h	9[b]
3	$Hg(OAc)_2$	20	-do-	50 °C	24 h	--[b]
4	$Hg(OTFA)_2$	20	-do-	50 °C	24 h	--[b]
5	$Hg(OTf)_2$	10	-do-	50 °C	48 h	25
6	$Hg(OTf)_2$	25	-do-	50 °C	24 h	37
7	$Hg(OTf)_2$	50	-do-	40 °C	0.5 h	62
8	$HgBr_2$	20	-do-	50 °C	30 h	10
9	**$Hg(OTf)_2$/AgOTf**	**10/50**	**-do-**	**rt**	**12 h**	**66**
10	AgOTf	20	-do-	rt	18 h	--[b]
11	TfOH	20	-do-	50 °C	12 h	--[c]
12	PPTS	20	-do-	50 °C	12 h	--[c]
13	$FeCl_3$	20	-do-	50 °C	12 h	--[b]
14	$Bi(OTf)_3$	20	-do-	50 °C	12 h	--[b]
15	$Pd(CH_3CN)_2/CuCl_2$	5/100	-do-	rt	12 h	5[d]
16	$Pd(OAc)_2$	5	THF/H_2O	rt	12 h	5[d]
17	**$AuCl_3$**	**10**	**toluene/H_2O**	**rt**	**12 h**	**87**

[a] All reactions were conducted with 1 mmol of substrate in 0.25 M concentration. [b] Most of the starting material was recovered. [c] Unidentified mixture of products obtained. [d] Rest of the starting material decomposed.

starting material being recovered after several hours of reaction (entries 3 and 4). Use of CH_2Cl_2, THF, acetone, and toluene with any of the above catalysts did not change the outcome.

Employment of $Hg(OTf)_2$, however, produced better results (entries 5, 6, and 7). Initially, when 10 mol % of catalyst was used in wet acetonitrile at 60 °C, the reaction proceeded over 6 h until ~20% of starting material was consumed, but thereafter it became sluggish, remaining incomplete even after 2 days giving **3a** in 25% yield, with 55% of the recovered starting material. Increased catalyst loading to 25 mol % led to consumption of approximately half of the starting material (TLC) to afford 37% of **3a**. Use of 50 mol % of $Hg(OTf)_2$, although an unacceptable loading of a catalyst, led to complete reaction in 0.5 h at 40 °C to produce **3a** in 62% yield. Overall, it appears that each equivalent of $Hg(OTf)_2$ is reacting with ~2 equiv of the substrate. Based on this observation, we propose the reaction pathway shown in Figure 1.

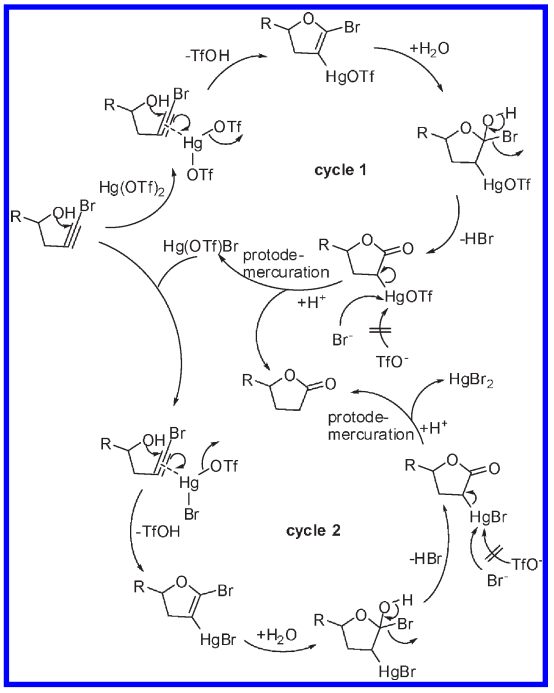


Figure 1. Proposed pathway for the synthesis of lactones using $Hg(OTf)_2$ as catalyst.

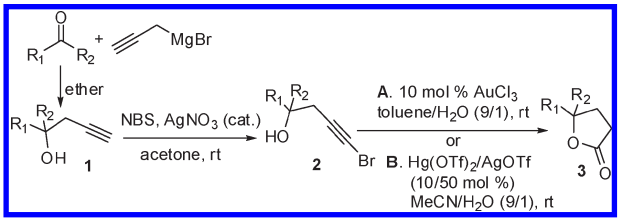
Accordingly, the Hg(II) species expelled in the first catalytic cycle was HgBrOTf which, in the second catalytic cycle, converted to $HgBr_2$, probably because the bromide ion is a stronger nucleophile and the triflate ion is a better leaving group. $HgBr_2$ might be less efficient, and hence the reaction became very slow after all of the $Hg(OTf)_2$ and HgBrOTf were converted to $HgBr_2$.

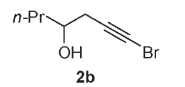
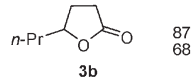
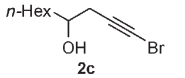
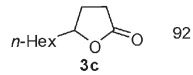
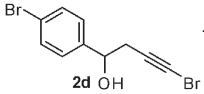
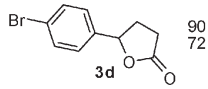
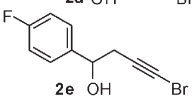
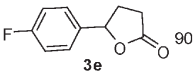
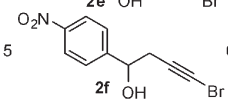
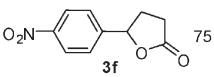
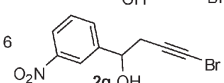
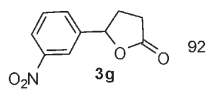
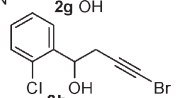
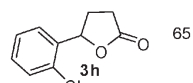
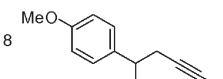
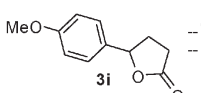
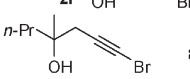
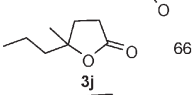
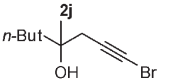
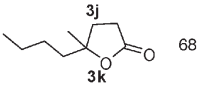
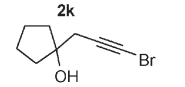
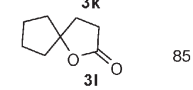
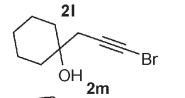
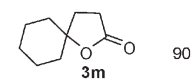
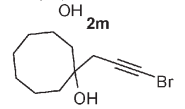
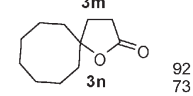
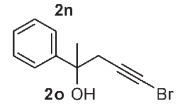
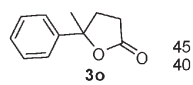
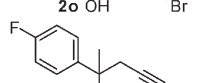
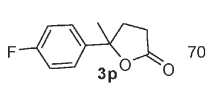
In support of this, when we employed $HgBr_2$ as the catalyst for the conversion of **2a** to **3a**, the reaction was observed to be sluggish and far less productive, irrespective of catalyst loading and reaction temperature (entry 8). Further support for the postulated mechanism came when we used AgOTf as a cocatalyst, which could trap the bromide counterion and increase the triflate ion concentration. The reaction was faster and was complete at room temperature affording **3a** in 66% yield (entry 9). AgOTf alone was not reactive (entry 10). CH_3CN was found to be the better choice of solvent compared to CH_2Cl_2, THF, acetone, and toluene.

Next, we examined other alkynophilic catalysts, e.g. $FeCl_3$ and $Bi(OTf)_3$, and Brønsted acids, e.g. TfOH and PPTS, but none of them were fruitful giving back mostly starting material or a mixture of unidentified products (entries 11–14). $Pd(CH_3CN)_2/CuCl_2$ and $Pd(OAc)_2$, which were earlier used to convert 4-(trimethylsilyl)-3-yn-1-ols to corresponding lactones,[3d] also proved ineffective.[8] Finally, we were delighted to identify an exciting lead in the form of $AuCl_3$ (10 mol %) in wet toluene (a better choice of solvent compared to CH_3CN), which led to the clean

(8) Starting material decomposed from the beginning of the reaction.

Table 2. Synthesis of γ-Butyrolactones **3** from **2** via Au(III) or Hg(II) Catalyzed Cycloisomerization



entry	2	yield (%) of 2 (in two steps)[a]	method[b]	time (h)	3	yield[a] (%)
1	 **2b**	82	A B	15 12	 **3b**	87 68
2	 **2c**	80	A	15	 **3c**	92
3	 **2d**	75	A B	20 7	 **3d**	90 72
4	 **2e**	78	A	20	 **3e**	90
5	 **2f**	64	A	5	 **3f**	75
6	 **2g**	68	A	20	 **3g**	92
7	 **2h**	75	A	20	 **3h**	65
8	 **2i**	68	A B	15 12	 **3i**	--[c] --[c]
9	 **2j**	84	A	15	 **3j**	66
10	 **2k**	80	A	15	 **3k**	68
11	 **2l**	80	A	15	 **3l**	85
12	 **2m**	85	A	15	 **3m**	90
13	 **2n**	82	A B	15 12	 **3n**	92 73
14	 **2o**	68	A B	15 12	 **3o**	45 40
15	 **2p**	74	A	17	 **3p**	70

[a] Isolated yields. [b] All reactions were conducted with 1 mmol of substrate in 0.25 M concentration. [c] Starting material decomposed.

conversion of **2a** to **3a** at room temperature in 87% yield. Elevating the reaction temperature to 60 °C reduced the reaction time from 12 to 4 h but with a drop in yield to 68%. Use of 5 mol % of the catalyst caused the reaction to slow (28 h) and be lower yielding (74%).

With this exciting result, we set out to investigate the scope of the transformation. Thus, several secondary and tertiary 4-bromo-3-alkyn-1-ols along with benzylic hydroxyl systems were subjected to $AuCl_3$- and $Hg(OTf)_2$-catalyzed cascade cycloisomerizations, and the results are summarized in Table 2. As is apparent from the table, secondary alcohols **2b**−**g**, which include benzylic systems **2d**−**g**, consistently produced the corresponding lactones in 75−92% yields. A significant effect of electron density in the phenyl ring attached to the carbinol was observed on the reaction speed and yield (affecting the nucleophilicity of the hydroxyl group). Thus, *o*-chlorophenyl substrate **2h** reacted in a lower yield compared with **2d** and **2e** due to a negative inductive effect and steric hindrance created by the proximity of chlorine to the carbinol carbon. Similarly, *p*-nitrophenyl substrate **2f**, which has a strong withdrawing effect on carbinol attached to the phenyl carbon, required a higher temperature (65 °C) to ensure the completion of the reaction and reacted in a lower yield compared with its meta-counterpart **2g** (75% compared to 92%). Surprisingly, *p*-OMe-substituted benzylalcohol **2i** decomposed with both Hg(II) and $AuCl_3$ catalysts and no product was isolated. That was probably due to benzylic oxygen cleavage, with the help of the extended conjugation from the methoxy group in one of the intermediates involved that had a positive charge on the oxygen. Tertiary alcohols **2l**−**n** also reacted smoothly to give the required products in 85−92% yield. Notably, methyl tertiary carbinols **2j**−**k** and **2o**−**p** reacted in lower yields compared with their other counterparts. $Hg(OTf)_2$ along with the AgOTf cocatalyst was also tested with a few of the substrates (**2b**, **2d**, **2i**, **2n**−**o**) in Table 2. Somewhat lower yields were obtained with $Hg(OTf)_2$ compared to $AuCl_3$ (entries 1, 3, 8, 13, and 14).

Lastly, we propose that $AuCl_3$ catalysis follows a similar pathway to that explained in Figure 1. Of course the bromide counterion interference, in this case, does not slow the reaction, as bromide is a better leaving group and a better nucleophile than chloride.

In conclusion, we have demonstrated that 4-bromo-3-alkyn-1-ols can be cyclized to butyrolactones under extremely mild conditions in the presence of $AuCl_3$. The reactions were carried out under aqueous and open air conditions, and no supportive catalysts or additives were required. The corresponding lactones were isolated in high yield. The process constitutes an easy and efficient access to highly valuable building blocks of natural products or biologically active compounds. Our next aim is to extend the method to γ-lactams and higher lactones.

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Supporting Information Available. Experimental procedures and copies of ^1H and ^{13}C NMR spectra of all compounds (**2a**−**p**, **3a**−**p**). This material is available free of charge via the Internet at http://pubs.acs.org.

[†] CDRI Communication number: 8192.
The authors declare no competing financial interest.