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Unexpected Facile Sequential Halolactamization–Hydroxylation of 2,3-Allenamides with CuX_2 for the Efficient Synthesis of 4-Halo-5-hydroxypyrrol-2(5*H*)-ones†

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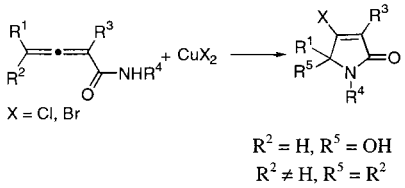
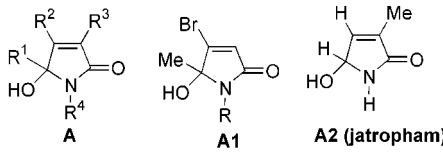
ABSTRACT



4-Halo-5-hydroxypyrrol-2(5*H*)-ones were synthesized from the efficient sequential halolactamization–hydroxylation reaction of 4-monosubstituted 2,3-allenamides with CuX_2 (X = Br, Cl) in high yields. Halolactamization of fully substituted 2,3-dienamide (1f) afforded 4-halo-pyrrol-2(5*H*)-ones.

5-Hydroxypyrrol-2(5*H*)-ones **A** exhibit a wide range of interesting biological activities.[1,2] For example, compound **A1** has been evaluated for antineoplastic activity in tumor cells of white mice,[3] and compound **A2** (jatropham), isolated from tatropha macrorhiza, shows antitumor activity (Scheme 1).[4] Although 5-hydroxypyrrol-2(5*H*)-ones derivatives have been prepared by the oxidative bromination reaction of nicotine,[5] amination of corresponding lactones,[6] metal-catalyzed condensation−cyclization reaction of acyl cyanides with 3-oxoamides,[7] and Ni-catalyzed cyanation of α-keto-alkynes in H_2O,[8] development of a highly efficient meth-

Scheme 1



† China patent pending (00125758.7).

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(1) Wooldridge, T. A.; Lightner, D. A. *J. Heterocycl. Chem.* **1977**, *14*, 1283.

(2) Vitillo, B.; Buniva, G.; Bernareggi, A.; Assandri, A.; Perazzi, A.; Fuccella, L. M.; Palumbo, R. *Int. J. Clin. Pharmacol. Ther. Toxicol.* **1984**, *22*, 273.

(3) Semonský, M.; Černý, A.; Kotva, R.; Zikán, V.; Kakáč, B. *Collect. Czech. Chem. Commun.* **1968**, *33*, 2698.

(4) For isolation and testing, see: Wiedhopf, R. M.; Trumbull, E. R.; Cole, J. R. *J. Pharm. Sci.* **1973**, *62*, 1206. For the revision of the structure, see: Yakushijin, K.; Kozuka, M.; Ito, Y.; Suzuki, R.; Furukawa, H. *Heterocycles* **1980**, *14*, 1073.

(5) McKennis, H.; Bowman, E. R.; Quin, L. D.; Denney R. C. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2046.

(6) Shiraki, R.; Sumino, A.; Tadano, K.-I.; Ogawa, S. *J. Org. Chem.* **1996**, *61*, 2845. Zihán, V.; Kakáč, B.; Holubek, J.; Veselá, H.; Semonský, M. *Collect. Czech. Chem. Commun.* **1976**, *41*, 3113. Fariña, F.; Martin, M. V.; Paredes, M. C. *Heterocycles*. **1984**, *22*, 1733. Gill, G. B.; James, G. D.; Oates, K. V.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2567.

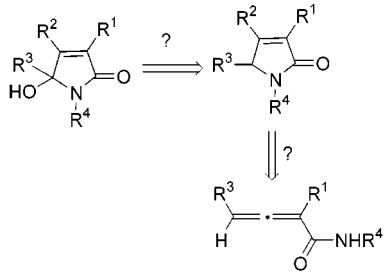
(7) Veronese, A. C.; Callegari, R.; Basato, M.; Valle, G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1779.

(8) Arzoumanian, H.; Jean, M.; Nuel, D.; Garcia, J. L.; Rosas, N. *Organometallics* **1997**, *16*, 2726.

odology for the synthesis of 5-hydroxypyrrol-2(5*H*)-ones with diversity is still of high interest.

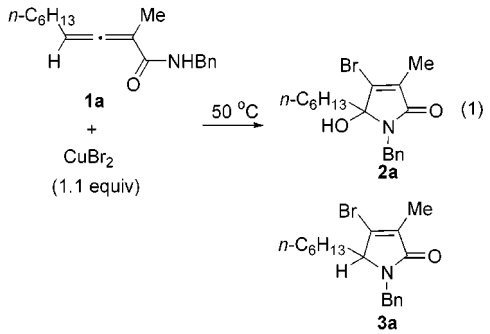
Recently, during the course of our study on the chemistry of functionalized allenes,[9] we have developed efficient methodologies for the synthesis of butenolides,[10] furans,[11] and vinylic oxiranes.[12] With the notion that the γ-hydroxylation can be accomplished via the treatment of pyrrol-2(5*H*)-ones with bubbling oxygen,[13] we envisioned that 5-hydroxypyrrol-2(5*H*)-ones may be synthesized by a sequential lactamization−hydroxylation process of 2,3-dienamides (Scheme 2). The substituent-loading capability of 2,3-

Scheme 2



dienamides (R^1, R^3, and R^4) will provide the diversity. In this communication, we wish to report our recent observation on the CuX_2-mediated halolactamization reaction of 2,3-allenamides, which was unexpectedly followed by facile oxidation to afford 4-halo-5-hydroxypyrrol-2(5*H*)-ones.

We initiated this study with the reaction of *N*-benzyl 2-methyl-2,3-decadienamide with $CuBr_2$ (eq 1). The corre-



sponding results under different conditions were summarized in Table 1. From the results in Table 1, it should be noted

Table 1. Bromolactamization−Hydroxylation Reaction of *N*-Benzyl 2-Methyl-2,3-decadienamide with $CuBr_2$

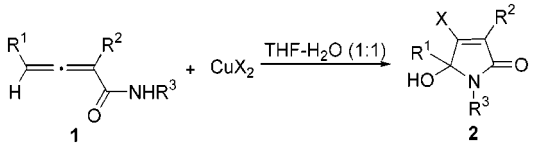
entry	solvent	time (h)	yield of **2a** (%)
1	H_2O	22	10[a]
2[b]	THF−H_2O (1:1)	22	38[c]
3[d]	THF−H_2O (1:1)	17.5	*e*
4	DMF	19	60
5	acetone−H_2O (3:2)	19	70
6[f]	THF−H_2O (1:1)	16	65
7	**THF−H_2O (1:1)**	**18.5**	**72**

[a] 68% of **1a** was recovered. [b] Et_3N (1 equiv) was used. [c] 43% of **1a** was recovered. [d] K_2CO_3 (1 equiv) was used. [e] No reaction. [f] Two equivalents of $CuBr_2$ was used.

that (1) instead of the normal bromolactamization product **3a**, the reaction unexpectedly afforded the bromolactamization−hydroxylation product **2a** in just "one-shot".[14] The reaction in pure water is slow (entry 1, Table 1). The reaction went smoothly in DMF, acetone/H_2O, and THF/H_2O to afford **2a** in 60−72% yield (entries 4−7, Table 1). However, it is interesting to observe that the reaction was inhibited by the presence of a base (entries 2 and 3, Table 1).

The results for the halolactamization−hydroxylation reaction of differently substituted 2,3-dienamides with CuX_2 in THF/H_2O (1:1) are summarized in Table 2. From Table 2,

Table 2. Halolactamization−Hydroxylation Reaction of 2,3-Allenamides with CuX_2



entry	1 R^1	1 R^2	1 R^3	CuX_2 X (equiv)	temp (°C)	time (h)	yield of **2** (%)
1	*n*-C_6H_{13}	Me	Bn (**1a**)	Br (1.1)	50	18.5	72 (**2a**)
2	*n*-C_6H_{13}	Me	Bn (**1a**)	Cl (1.1)	reflux	21	57 (**2b**)
3[a]	H	Me	Bn (**1b**)	Br (2)	50	19	78 (**2c**)
4[a]	H	Me	Bn (**1b**)	Cl (2)	50	22	60 (**2d**)
5	Ph	Me	*n*-C_4H_9 (**1c**)	Br (2)	reflux	24	94 (**2e**)
6	Ph	Me	*n*-C_4H_9 (**1c**)	Cl (4)	reflux	5 d	71 (**2f**)
7	*n*-C_7H_{15}	H	H (**1d**)	Br (1.1)	50	22	69 (**2g**)
8	*n*-C_7H_{15}	H	Bn (**1e**)	Br (1.1)	50	32	78 (**2h**)
9	*n*-C_7H_{15}	H	Bn (**1e**)	Cl (2)	50	3 d	78 (**2i**)

[a] Solvent was EtOH−H_2O 3:2; when solvent was THF−H_2O 1:1 and 1.1 equiv of $CuBr_2$ was used, yield of **2c** was 48%.

it can be concluded that this halolactamization−hydroxylation reaction can be realized with both $CuCl_2$ and $CuBr_2$. The reaction is pretty general: R^1 can be H, alkyl, or phenyl; R^2 can be H or alkyl; and R^3 can be H, alkyl, or benzyl. The yields range from 57% to 94%.

(9) Ma, S.; Shi, Z.; Li, L. *J. Org. Chem.* **1998**, *63*, 4522. Ma, S.; Li, L.; Xie, H. *J. Org. Chem.* **1999**, *64*, 5325. Ma, S.; Wei, Q. *Eur. J. Org. Chem.* **2000**, 1939. Ma, S.; Wei, Q. *J. Org. Chem.* **1999**, *64*, 1026. Ma, S.; Wang, G. *Chin. J. Chem.* **1999**, *17*, 545.

(10) Ma, S.; Shi, Z. *J. Org. Chem.* **1998**, *63*, 6387. Ma, S.; Duan, D.; Shi, Z. *Org. Lett.* **2000**, *2*, 1419. Ma, S.; Shi, Z.; Yu, Z. *Tetrahedron Lett.* **1999**, *40*, 2393. Ma, S.; Shi, Z.; Yu, Z. *Tetrahedron* **1999**, *55*, 12137. Ma, S.; Wu, S. *J. Org. Chem.* **1999**, *64*, 9314.

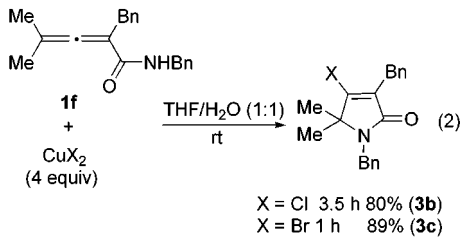
(11) Ma, S.; Zhang, J. *Chem. Commun.* **2000**, 117. Ma, S.; Li, L. *Org. Lett.* **2000**, *2*, 941.

(12) Ma, S.; Zhao, S. *J. Am. Chem. Soc.* **1999**, *121*, 7943.

(13) For the oxidation of pyrrol-2(5*H*)-ones with bubbling oxygen to afford 5-hydroxypyrrol-2(5*H*)-ones, see: Anselmi, C.; Camparini, A.; Scotton, M. *J. Heterocycl. Chem.* **1983**, *20*, 687.

(14) The structure of the halolactamization−hydoxylation product **2** was identified with IR, ^1H NMR, and ^{13}C NMR spectra and elemental analysis. The structure was further confirmed by the X-ray diffraction study of **2c**.

With only one substituent at the 4-position of 2,3-allenamides being H, 4-halo-5-hydroxypyrrol-2(5*H*)-ones **2** are always the products, which may be formed by the Cu^{2+}-mediated oxidation of 4-halopyrrol-2(5*H*)-ones **3**.[13] When fully substituted 2,3-allenamide **1f** was reacted with CuX_2, the normal halolactamization products, i.e., 4-halopyrrol-2(5*H*)-ones **3b,c**, were obtained in high yields (eq 2).



In conclusion, we have observed an interesting sequential halolactamization−hydroxylation reaction. As a result of the easily availablity of starting materials,[15] simple procedure, and high efficiency, this methodology will show utility in organic synthesis. Further study on the scope, mechanism, and synthetic application of this methodology is being carried out in our laboratory.

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Supporting Information Available: Typical experimental procedure and analytical data for all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Allenamides were conveniently prepared by the reaction of acyl chlorides with amines in ether using Et_3N as the base or the DMAP-catalyzed reaction of 2,3-allenoic acid, amine, and DCC in dry CH_2Cl_2, see: (a) Himbert, G.; Schlindwein, H.-J. *Z. Naturforsch.* **1992**, *47b*, 1785. (b) Himbert, G.; Schlindwein, H.-J. *Liebigs Ann. Chem.* **1997**, 435. (c) Wotiz, J. H. *J. Am. Chem. Soc.* **1950**, *72*, 1639.