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A Mild Synthesis of Substituted Furans from γ-Hydroxy-α,β-Unsaturated Ketones

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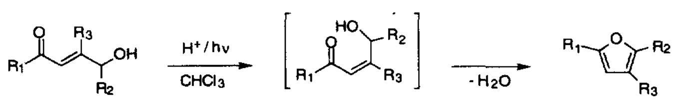
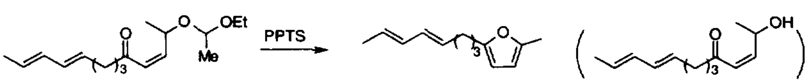
Abstract: The acid-catalyzed cyclodehydration of (*Z*)- and (*E*)-γ-hydroxy-α,β-unsaturated ketones to furans is described. In the case of E olefins, photochemical trans- to cis- olefin isomerization was found to accelerate the reaction. Copyright © 1996 Elsevier Science Ltd

Furans are important functional groups that can be found in many natural products and have been used as building blocks for the synthesis of others.[1] A number of methods for the synthesis of furans have been reported,[2] including the cyclization of 1,4-dicarbonyl compounds,[3] the isomerization of allenyl ketones and aldehydes,[4] the addition of allenylsilanes to acylium ions,[5] the condensation of α-halocarbonyls with 1,3-dicarbonyl compounds[6] and the acid-catalyzed cyclization of β,γ-epoxyketones.[7] Most of these methods require the use of strong acids and/or elevated temperatures and may not be suitable for substrates containing sensitive functionality. In this communication we report a mild new approach for the preparation of substituted furans from γ-hydroxy-α,β-unsaturated ketones (eq 1).[8]



(1)

This method was discovered in the course of the attempted synthesis of compound **3**, which contains a γ-hydroxy-α,β-unsaturated ketone (eq 2). This compound was to be prepared from the corresponding ethoxy ethyl acetal protected alcohol **1**; however, attempted deprotection of **1** with PPTS in CH_2Cl_2 cleanly provided furan **2** and none of the desired alcohol **3** (eq 2). The facility of this reaction prompted us to investigate it in greater detail, and we therefore prepared the TBS protected γ-hydroxy-α,β-unsaturated ketones listed in Table 1. The TBS group was chosen because it can be deprotected under very mildly acidic conditions with



(2)

1 **2** (observed) **3** (Desired)

triethylamine trihydrofluoride (TREAT).[9] We first examined Z olefins **4** and **6**[10] (entries 1 and 2), and, as expected, these compounds cleanly produced furans **5** and **7** upon deprotection with TREAT (method A).[11,12] No hydroxyenone was observed in the crude product of either reaction. The corresponding E olefins shown in entries 3 - 5 were then examined.[13] In these cases, we were able to deprotect and isolate the alcohol with TREAT. E to Z olefin isomerization and cyclodehydration were accomplished by irradiation of a chloroform solution of the hydroxyenone in a quartz tube for the time indicated in the table (method B).[14] Trisubstituted olefin **14** (entry 6) was prepared as a mixture of Z and E isomers[15] and, as expected, the Z isomer cyclized upon deprotection, while the E isomer required irradiation to effect cyclization.

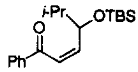
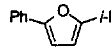
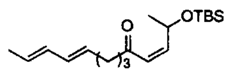
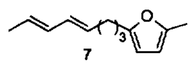
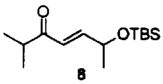
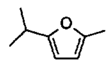
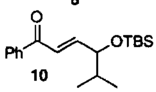
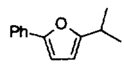
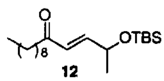
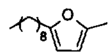
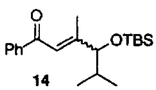
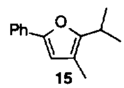
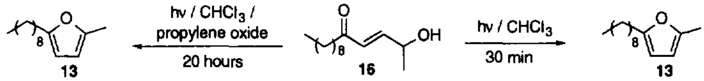
Entry	Substrate	Method [a]	Time (min)	Product	Yield (%)[b]
1	 **4**	A	45	 **5**	71
2	 **6**	A	15	 **7**	65
3	 **8**	B	15	 **9**	92 [c]
4	 **10**	B	60	 **11**	97
5	 **12**	B	30	 **13**	91
6	 **14**	B	60	 **15**	98

Table 1 (a) Method A: acetonitrile / TREAT; Method B: i) acetonitrile / TREAT, ii) hν / chloroform; (b) Isolated yield based on chromatographed product, except for entry 3 (c) Due to the volatility of the product, this yield was determined by NMR, using thioanisole as an internal standard.

We have performed some experiments in order to elucidate the mechanism of this transformation. The acid dependence of the reaction was examined by irradiation of substrate **16** in a 1:1 solution of chloroform and propylene oxide (eq 3).[16] Under these conditions, the time required for conversion to the furan increased from 30 minutes to 20 hours, consistent with our hypothesis that traces of protic acid are liberated and facilitate the reaction. We have also found that irradiation of the E olefins is not required if an acid is present. Thus, 5% TsOH in chloroform will catalyze the cyclodehydration of **16** in 1.5 hours in the dark. It therefore appears that this reaction is an acid-catalyzed process that is accelerated by the photochemical E to Z isomerization of the olefin.



In conclusion, we have described a mild method for the preparation of differentially substituted furans from readily accessible starting materials. This method should be useful for the preparation of furans containing functional groups that are incompatible with strong acids and elevated temperatures.

Acknowledgment: We thank the National Institutes of Health (GM48498) for financial support of this research. T. S. is a recipient of an American Cancer Society Junior Faculty Development Award and is an Alfred P. Sloan Research Fellow. We thank Professor Tad Koch for discussions concerning the photochemistry, and Professor Fred West for discussions and for disclosing his results prior to publication.

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1 For recent reviews, see: (a) Joule, J. A.; Mills, K.; Smith, G. F. *Heterocyclic Chemistry*, Chapman & Hall: London, 1995, p. 278; (b) Dean, F. M. In *Advances in Heterocyclic Chemistry*; Katrizky, A. R., Ed.; Academic Press: New York, 1982; Vol. 30, pp 167 - 238; (c) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795.

2 (a) Seyfarth, H. E. *Chem. Ber.* **1968**, 101, 619; (b) Miller, D. *J. Chem. Soc. C* **1969**, 12; (c) Garst, M. E.; Spencer, T. A. *J. Am. Chem. Soc.* **1973**, *95*, 250; (d) Kotake, H.; Inomata, K.; Kinoshita, H.; Aoyama, S.; Sakamota, Y. *Heterocycles* **1978**, *10*, 105; (e) Hutton, J.; Potts, B.; Southern, P. F. *Synth. Commun.* **1979**, *9*, 789; (f) Liotta, D.; Saindane, M.; Ott, W. *Tetrahedron Lett.* **1983**, *24*, 2473; (g) Minami, I.; Yuhara, M.; Watanabe, H.; Tzuji, J. *J. Organomet. Chem.* **1987**, *334*, 225; (h) McCombie, S. W.; Shankar, B. B.; Ganguly, A. K. *Tetrahedron Lett.* **1987**, *28*, 4123; (i) Srikrishna, A.; Pullaiah, K. C. *Tetrahedron Lett.* **1987**, *28*, 5203; (j) Hiroi, K.; Sato, H. *Synthesis* **1987**, 811; (k) Davies, H. L. M.; Romines, K. R. *Tetrahedron* **1988**, *44*, 3343; (l) Seiller, B.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron* **1995**, *51*, 13089.

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4 (a) Sheng, H.; Lin, S.; Huang, Y. *Tetrahedron Lett.* **1986**, *27*, 4893; (b) Marshall, J. A.; Wang, X. *J. Org. Chem.* **1991**,*56*, 960.

5 Danheiser, R. L.; Stoner, E. J.; Koyama, H.; Yamashita, D. S. *J. Am. Chem. Soc.* **1989**, *111*, 4407.

6 Bisagni, E.; Marquet, J. -P.; Bourzat, J. -D.; Pepin, J. -J. , André-Louisfert, J. *Bull. Chem. Soc. Fr.* **1971**, 4041.

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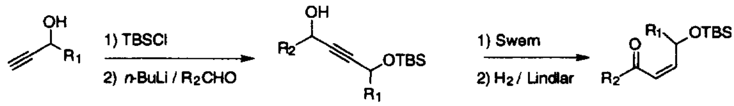
8 Professor Fred West (University of Utah) has independently discovered and utilized this method in the

synthesis of a furan containing substrate. We thank Professor West for disclosing his results prior to publication.

9 (a)Pirrung, M. C.; Shuey, S. W.; Lever, D. C.; Fallon, L. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1345; (b) Westman, E.; Stromberg, R. *Nucl. Acids Res.* **1994**, *22*, 2430. For a recent review, see: McClinton, M. A. *Aldrichimica Acta* **1995**, *28*, 31-36. Hydrogen fluoride in acetonitrile can also be utilized for the deprotection and cyclization, however, TREAT is equally effective and milder.

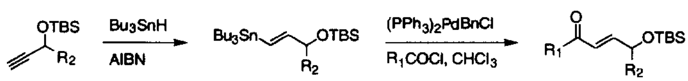
10 These substrates were prepared according to the following scheme:



11 Representative procedure A: A solution consisting of the silyl ether (0.2 mmol) and a 2:1 mixture of acetonitrile / TREAT (3 mL) was allowed to stir at reflux for the time indicated in the table. Once TLC indicated that starting material had been consumed, the reaction was quenched by the addition of sat. $NaHCO_3$ solution. The organic layer was washed with water then brine, dried over $MgSO_4$, and concentrated under reduced pressure. The product was purified by flash chromatography (hexanes / ethyl acetate) to provide the pure furan in the yield indicated in the table.

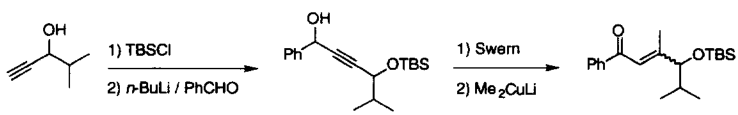
12 New compounds gave satisfactory spectral data (^{1}H, ^{13}C, and IR).

13 These substrates were prepared according to the following scheme:



14 Representative procedure B: A solution consisting of the silyl ether (0.2 mmol) and a 2:1 mixture of acetonitrile / TREAT (3 mL) was allowed to stir at reflux for the time indicated in the table. Once TLC indicated that starting material had been consumed, the reaction was quenched by the addition of sat. $NaHCO_3$ solution. The organic layer was washed with water then brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude reaction product was then dissolved in chloroform (3 mL) and placed in a quartz tube. The tube was placed approximately 1 inch from a low pressure mercury vapor lamp, and the solution was irradiated for 20 minutes. The reaction was concentrated under reduced pressure and the product was purified by flash chromatography (hexanes / ethyl acetate) to provide the pure furan in the yield indicated in the table.

15 This substrate was prepared according to the following scheme:



16 Propylene oxide was added to scavenge any HCl which may be formed under the reaction conditions. In the presence of triethylamine, no reaction is observed upon irradiation.

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