SYNTHESIS OF FURANS FROM EPOXYPROPARGYL ESTERS

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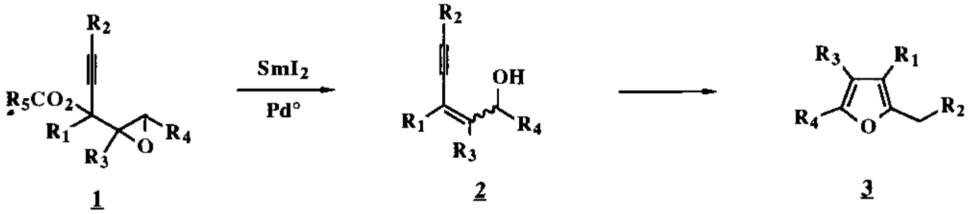
Abstract- Treatment of 1-(1,2-epoxyalkyl)-2-alkynyl esters with samarium diiodide/Pd° affords E/Z mixtures of 2-alken-4-yn-1-ols where the Z-isomers can be directly transformed into substituted furans. The method is useful for the synthesis of tetrahydroisobenzofurans. A different substitution pattern in the furan nucleus is obtained by application of the same reaction to a regioisomeric 4-(1,2-epoxyalkyl)-2-alkynyl ester *via* a cumulene alcohol intermediate.

Furans represent an important class of heterocyclic compounds. Thus, the furan ring can be found as a subunit in numerous natural products and substances of industrial importance.[1] Additionally, furan derivatives are extensively utilized as useful synthetic intermediates and building blocks.[2] Among the existing methods for the formation of furans from acyclic precursors,[3,4] those employing 2-alken-4-yn-1-ols as starting materials have received particular attention.[5] In a recent report, Marshall[5] has shown that these compounds readily cyclize in the presence of strong base to afford furan derivatives, presumably through a 5-*exo-dig* cyclization from the corresponding alkoxide. While the reaction seems of fairly general application for Z-enynols, it requires the presence of base-removable hydrogens at the α-position of the R_3 substituent in the corresponding E-isomers to effect the E to Z isomerization prior to cyclization.

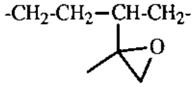
The samarium diiodide/Pd°-promoted reductive elimination of 1-(1,2-epoxyalkyl)-2-alkynyl esters[6] (Scheme 1) provides an efficient method for the preparation of 2-alken-4-yn-1-ols from simple and readily available starting materials.[7] Since this reaction actually yields a samarium alkoxide product it would seem to have potential as a direct method for the conversion of esters (1) into substituted furans.



Scheme 1

We would like to disclose here preliminary results on the realization of this idea, as well as a complementary method that affords furans from regioisomeric 4-(1,2-epoxyalkyl)-2-alkynyl esters. Since in the reported reductive eliminations of epoxypropargyl esters[6] the geometry of the newly formed double bond was necessarily E due to geometric constraints and, given the limitations of the E to Z isomerization of enynols (**2**) under basic conditions,[5] the question of the stereochemical outcome of the reductive elimination process was also addressed.

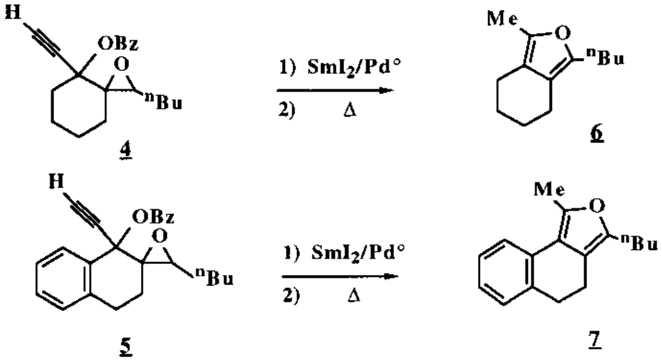
Table. Reaction of Epoxyesters (1) with SmI_2/Pd°

Epoxyester	R_1	R_2	R_3	R_4	R_5	Yield of 2 (%)	E/Z Ratio
1a	Ph	H	H	^{n}Bu	Me	83	50/50
1b	Me	H	$-(CH_2)_4-$		Ph	64	a
1c	Me	H	 $-CH_2-CH_2-CH-CH_2-$		Me	94	94/6

a E-Isomer. See text.

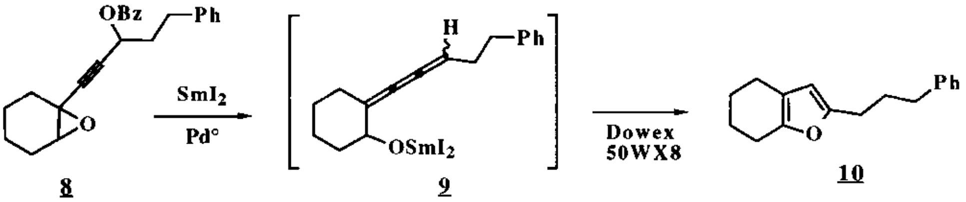
The epoxypropargyl esters (**1**) were prepared[8] and treated with SmI_2 (2 equivalents) and a catalytic (5%) amount of $Pd(PPh_3)_4$ to afford high yields of the corresponding enynols (**2**). As noted in the Table, E/Z mixtures[9] were obtained except for enynol (**2b**) which was isolated as the pure E isomer, in the indicated yield, along with a 20% yield of the highly volatile furan (**3b**) presumably arising from the direct cyclization of the corresponding Z-enynol. In contrast, the reaction of **1a** produced only the enynol (**2a**) as a 1/1 E/Z mixture. Formation of the furan (**3a**) was observed from the Z-isomer slowly by standing in the nmr tube in $CDCl_3$ solution over a period of several hours or quickly by gentle heating of the crude enynol alkoxide product previous to aqueous work-up. Trace amounts of furan (**3c**) were also detected in the reaction of **1c** probably as a result of slow Z-isomer cyclization; like in the previous case, the Z-isomer was transformed into **3a** by gentle heating. In no case was furan formation detected from E-isomers by heating of the crude enynol alkoxides previous to work-up. The failure of **E-2a** to undergo isomerization and cyclization was expected based on mechanistic considerations.[3i] The analogous results with **E-2b,c**, although not easily rationalized, were precedented by the observation that a substrate (**2**, $R_1 = R_3 = Me$) also failed to yield a furan product under basic conditions.[3i] Clearly, the usefulness of this methodology for furan syntheses will be restricted to those cases where it can be used in combination with a successful E- to Z-enynol isomerization or where geometrical constraints impede the formation of the E-product.

This later case is exemplified in Scheme 2. Thus, treatment of epoxypropargyl esters[8] (**4**) and (**5**) with $SmI_2/Pd(PPh_3)_4$ at room temperature presumably afforded enynol alkoxide intermediates which were not isolated but instead briefly heated in the same reaction medium to cleanly afford tetrahydroisobenzofuran derivatives (**6**) and (**7**) in yields of 30 and 40%, respectively.[10]



Scheme 2

A different synthetic strategy that would complement the one just described was also sought. It was expected that the treatment with SmI_2/Pd° of an epoxypropargyl ester typified by **8** (which besides the propargyl ester also includes the alkynyloxirane functionality[11]) would afford the cumulene alkoxide (**9**). This kind of species has been proposed as reactive intermediates in base-promoted furan syntheses(Scheme 3).[3g]



Scheme 3

In the event, the benzoate[12] (**8**) (Scheme 3) was reacted with SmI_2/Pd(PPh_3)$_4$ and the reaction mixture directly treated with Dowex 50WX8 resin to afford furan (**10**) in 50% isolated yield. If the reaction mixture was worked-up previous to the resin treatment, a material whose ^{1}H-nmr spectral properties were compatible with the alcohol derived from an alkoxide (**9**) could be isolated but decomposed on attempted purification.

Efforts oriented to the full development of this methodology are currently in progress.

ACKNOWLEDGEMENTS.

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REFERENCES.

1. For general reviews on its occurrence and applications see: (a) D. M. X. Donnelly and M. J. Megan, in *Comprehensive Heterocyclic Chemistry*; Vol. 3, ed. A. R. Katritzky and C. W. Rees, Pergamon, 1984, pp.

657-712; (b) A. P. Kozikowski, in *Comprehensive Heterocyclic Chemistry*; Vol. 1, ed. A. R. Katritzky and C. W. Rees, Pergamon, 1984, pp. 413-430.

2. For a review see: B. H. Lipshutz, *Chem. Rev.*, 1986, **86**, 795.
3. For some recent examples see: (a) R. L. Danheiser, E. J. Stoner, H. Koyama, D. S. Yamashita, and C. A. Klade, *J. Am. Chem. Soc.*, 1989, **111**, 4407; (b) Y. Fukuda, H. Shiragami, K. Utimoto, and H. Nozaki, *J. Org. Chem.*, 1991, **56**, 5816; (c) S. Kim and Y. G. Kim, *Tetrahedron Lett.*, 1991, **32**, 2913; (d) J. A. Marshall and X. J. Wang, *J. Org. Chem.*, 1991, **56**, 960; (e) J. A. Marshall and X. J. Wang, *J. Org. Chem.*, 1991, **56**, 4913; (f) Y. Kataoka, M. Tezuka, K. Takai, and K. Utimoto, *Tetrahedron*, 1992, **48**, 3495; (g) J. A. Marshall and W. J. DuBay, *J. Am. Chem. Soc.*, 1992, **114**, 1450; (h) A. Arcadi, S. Cacchi, R. C. Larock, and F. Marinelli, *Tetrahedron Lett.*, 1993, **34**, 2813; (i) J. A. Marshall and W. J. DuBay, *J. Org. Chem.*, 1993, **58**, 3435; (j) A. Padwa and F. R. Kinder, *J. Org. Chem.*, 1993, **58**, 21.
4. See Ref. 1a and references cited therein.
5. See Ref. 3i and references cited therein.
6. W. H. Okamura, J. M. Aurrecoechea, R. A. Gibbs, and A. W. Norman, *J. Org. Chem.*, 1989, **54**, 4072; J. D. Enas, J. A. Palenzuela, and W. H. Okamura, *J. Am. Chem. Soc.*, 1991, **113**, 1355; J. D. Enas, G. Y. Shen, and W. H. Okamura, *J. Am. Chem. Soc.*, 1991, **113**, 3873.
7. Esters (**1**) can be easily prepared from suitable alkynes and allylic alcohols.
8. Prepared from the corresponding epoxycarbonyl compounds by treatment with lithium acetylide and esterification of the resulting propargyl alcohols.
9. The stereochemical composition of the epoxypropargyl ester is of no consequence as different diastereoisomers afford the same E/Z mixture of enynols.
10. These reactions proceeded very cleanly. Therefore, the low isolated yields are probably due to volatility and/or instability of the products. Similar problems with annelated furans have been reported: B. J. M. Jansen, R. M. Peperzak, and A. de Groot, *Rec. Trav. Chim. Pays-Bas*, 1987, **106**, 549.
11. Alkynyloxiranes are also good electron acceptors in the presence of SmI_2: J.M. Aurrecoechea and M. Solay-Ispizua, unpublished work.
12. Prepared from 1-ethynylcyclohexene by the following sequence: *i*) ^{n}BuLi; *ii*) 3-phenylpropanal; *iii*) benzoyl chloride; *iv*) MCPBA.

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