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A Simple, Efficient Synthesis of 3-Substituted Furans

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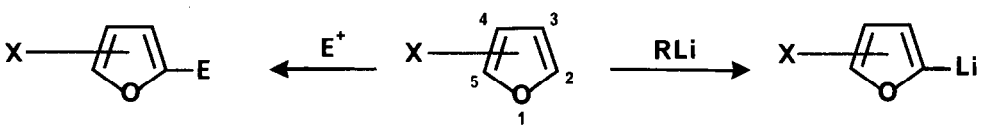
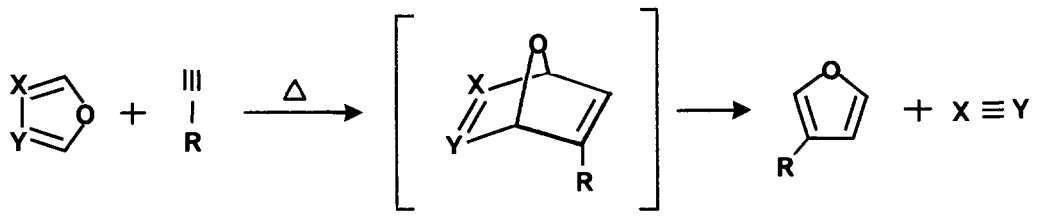
Summary: 3-Substituted furan can be readily prepared in a single step via a tandem Diels-Alder/retro Diels-Alder reaction between 4-phenyloxazole and simple alkylacetylenes.

3-Substituted furans are a somewhat difficult class of compounds to prepare. For example, the two most common methods of functionalizing furans (i.e., metallation reactions and electrophilic additions) show a marked preference for position 2 (or 5) over position 3 (or 4) (*vide infra*)[2]. Alternative synthetic approaches which do not involve furans as starting materials have also been reported. In the main these involve modifications of butyrolactone derivatives[3] or the cyclization of acyclic precursors[4]. All of these are multi-step processes and are generally not well-suited for large scale preparations of furans.



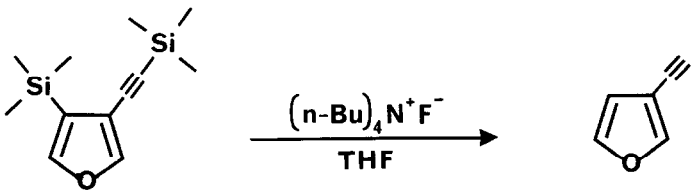
We had hoped to gain easy access to a variety of 3-substituted furans using a strategy which is well-precedented for the synthesis of many heterocyclic systems, i.e., a tandem Diels-Alder/retro Diels-Alder sequence of the type shown below. In principle, such an approach would provide us with the needed flexibility with regard to: (a) accessibility of starting materials, (b) functional group compatability, and (c) overall simplicity. Clearly, however, the success of this approach hinges on the selection of the diene. For maximum generality the diene chosen

must be capable of undergoing Diels-Alder reactions even with unactivated acetylenes. In addition, the resulting Diels-Alder adducts must undergo relatively facile retro Diels-Alder reactions to produce a stable fragment, X≡Y, and the desired furan.



Our search for a diene which satisfied the above criteria was greatly facilitated by the reports of Hutton[5] and of Graf and Konig[6] that the reaction of a 4-substituted oxazole (1, X=N, Y=CPh) with 2-butyne-1,4-diol and its derivatives produced furan 3,4-dimethanol and its derivatives in good yield. However, since the number of unactivated acetylenes reported in these studies was quite limited, the generality of this approach was unclear. This was particularly true with regard to silylacetylenes and remotely-functionalized acetylenes. We report herein that the process described above represents a simple, efficient and general method for the preparation of 3-substituted furans[7]. Our results are shown in Table I[8].

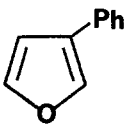
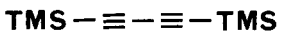
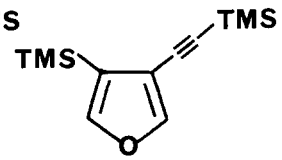
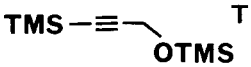
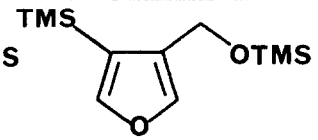
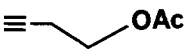
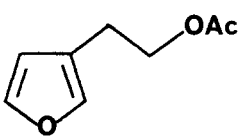
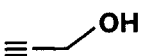
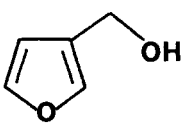
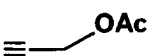
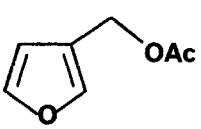
These reactions have proven to be relatively insensitive to the substitution pattern of the acetylene used. In fact, even hindered C-silylated acetylenes (e.g., 10) can be smoothly transformed to their corresponding furan derivatives. These silylated furans can also be readily desilylated with tetra-butylammonium fluoride as shown below. Finally, all of the reactions listed in Table I are quite amenable to large scale production[9].



9 **18**

A typical experimental procedure is illustrated below for the conversion of 8 to 9. A mixture of 4-phenyloxazole[5] (14.5 g, 10 mmole) and bis-trimethylsilylbuta-1,3-dyne[10] (19.4 g, 10 mmole) was heated in a sealed tube at 210°C for 16 hrs. The crude reaction mixture was first distilled (bulb-to-bulb, 89°-90°C/3 mm Hg) and chromatographed on silica gel using hexane as the eluent. Evaporation of the solvent in vacuo yields 22.6 g of pure 9 (95% yield):

Table I

Reactant (Number)	Product (Number)	Reaction Temp.(°C)	Reaction Time (hr.)	Isolated Yield (%)
 **6**	 **7**	220	20	83
 **8**	 **9**	210	16	95
 **10**	 **11**	190	48	66
 **12**	 **13**	220	48	70
 **14**	 **15**	200	24	50
 **16**	 **17**	180	16	90

^{1}H NMR (δ) ($CDCl_3$): 7.64 (d, J=2 Hz, 1), 7.18 (d, J=2 Hz, 1), 0.26 (s, 9), 0.21 (s, 9).

In summary, the method described above enables one to produce large quantities of 3-substituted furans in a single step. Further applications of this methodology will be the subject of future reports.

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References:

1. Fellow of the Alfred P. Sloan Foundation, 1980-84. Recipient of a Camille and Henry Dreyfus Teacher-Scholar Fellowship, 1981-86.

2. (a) Paquette, L. A. "Modern Heterocyclic Chemistry"; Benjamin: Reading, MA, 1968; pp 102-149. (b) Dunlap, A. P.; Peters, F. N. "The Furans"; Reinhold: New York, 1953. (c) Gschwend, H. W.; Rodriguez, H. R. Org. React. (1979) 26, 1 and references contained therein.

3. Grieco, P. A.; Pogonowski, C. S.; Burke, S. J. J. Org. Chem. (1975) 40, 542.

4. (a) Spencer, T. A.; Garst, M. E. J. Amer. Chem. Soc. (1973) 95, 250. (b) Harris, C. M.; Cleary, J. J.; Harris, T. M. J. Org. Chem. (1974) 39, 72.

5. Hutton, J.; Potts, B.; Southern, P. F. Synthetic Commun. 9, 789.

6. Graf, F.; Konig, H., Ger. Offen. 1,935,009. These authors have also reported the preparation of 17 by a similar reaction.

7. For a nice example of the use of oxazoles in intramolecular Diels-Alder reactions, see: Jacobi, P. A.; Walker, D. G. J. Amer. Chem. Soc. (1981) 103, 4611 and references contained therein.

8. Reactions were carried out neat in a sealed tube. The ratio of reactants was 1:1. Products were purified first by distillation and then by chromatography on silica gel. Products were characterized on the basis of their ir, nmr, and mass spectra.

9. For example, we routinely produce 9 in 10-20 gram quantities in a single run.

10. Ballard, D. H.; Gilman, H. J. Organometallic Chem. (1968) 15, 321.

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