A GENERAL METHOD FOR THE PREPARATION OF POLYSUBSTITUTED FURANS. A NEW SYNTHESIS OF dl-MENTHOFURAN

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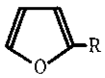
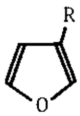
Various types of polysubstituted furans were prepared via γ-hydroxy-β-tosylacetals starting from α,β-unsaturated carbonyl compounds in fairly good yields. dl-Menthofuran was synthesized by the present method.

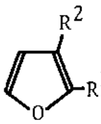
In the previous papers,[1-3] we have reported the syntheses of 2- or 3-monosubstituted (I, II) and 2,3-disubstituted furans (III) including their typical naturally occurring furans. In this paper we wish to report the synthesis of other types of polysubstituted furans (IV-IX) starting from α,β-unsaturated carbonyl compounds.



(I)



(II)



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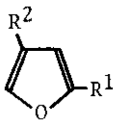
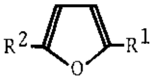
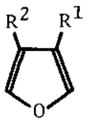


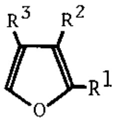
(IV)



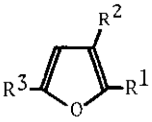
(V)



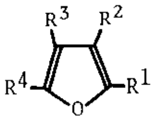
(VI)



(VII)

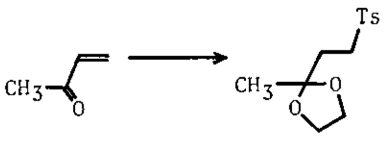


(VIII)

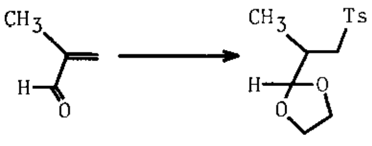


(IX)

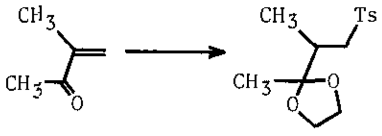
The following four kinds of β-tosylacetals (X-XIII) were prepared from the corresponding α,β-unsaturated carbonyl compounds by the similar procedure reported about 3-tosylpropanal ethylene acetal by Cooper and Dolby.[4)]



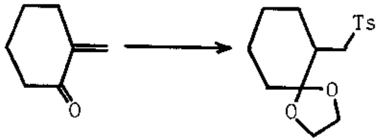
(X) 77%
mp 122-123°C



(XI) 66%
mp 44-45°C

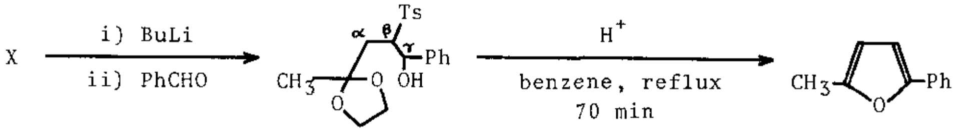


(XII) 86%
mp 88-89°C



(XIII)5)
mp 99-100°C

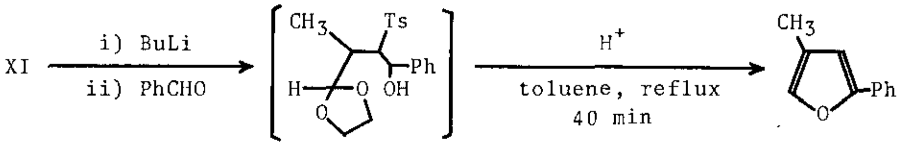
The following example shows the representative procedure for the synthesis of furan derivatives from the β-tosylacetals prepared above: 4-tosylbutan-2-one ethylene acetal (X, 135 mg, 1/2mmol) was lithiated with an equimolar amount of n-butyllithium (n-hexane solution) at − 78°C and then at room temperature under nitrogen. After cooling at − 78°C again, the lithiated X was reacted with benzaldehyde (53 mg, 1/2 mmol) and the reaction mixture was gradually raised up to room temperature followed by the treatment with pH 7 buffer solution and subsequent extraction with ether. The residue obtained by the evaporation of the ethereal extract was subjected to the preparative TLC (silica gel) to give the corresponding γ-hydroxy-β-tosylacetal (XIV, consists of two diastereoisomers) in a 94% (176 mg, oil) yield. A benzene solution of XIV was refluxed in the presence of a catalytic amount of p-toluenesulfonic acid for 70 min under nitrogen. After washing with a saturated $NaHCO_3$ solution and evaporation of the solvent, the expected 2-methyl-5-phenylfuran (Va, 49 mg) was isolated from the residue by a preparative TLC in a 62% (based on X) yield as an oily substance.



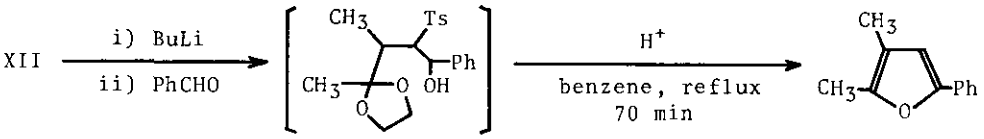
XIV, 94%

Va, 62% from X

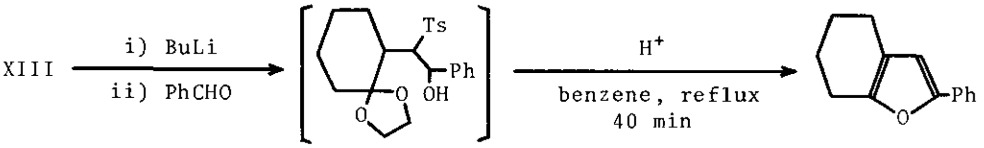
In a similar manner, IVa, VIIIa and VIIIb were prepared according to the accompanying scheme from XI, XII and XIII, respectively. In these cases, the intermediary γ-hydroxy-β-tosylacetals were not isolated.



IVa, 50%
mp 32-33°C

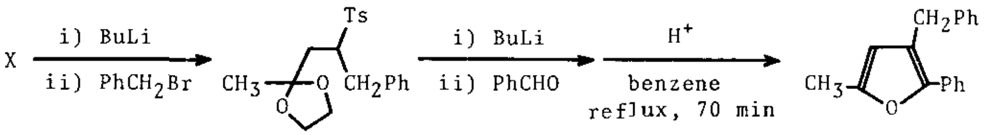


VIIIa, 76%



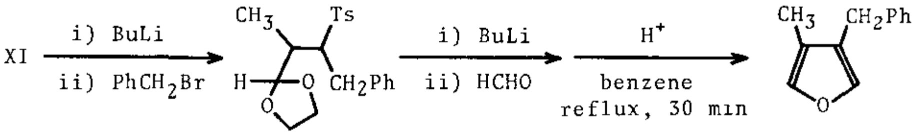
VIIIb, 70%

The lithiated β-tosylacetals reacted readily with an alkyl halide to give the alkylated products, which made further possible to prepare a variety of furan derivatives as follows:



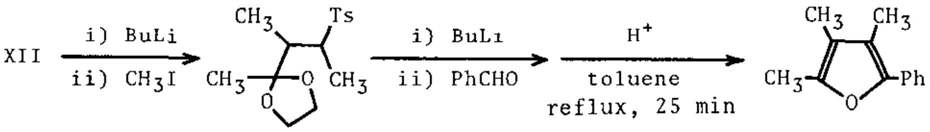
93%, mp 74-75°C

VIIIc, 61%



76%, mp 71-72°C

VIa, 58%

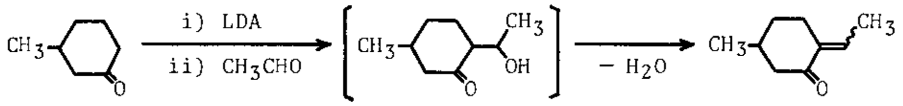


90%, oil

IXa, 66%

In order to demonstrate the utility of the present method for the preparation of polysubstituted furans, we tried to synthesize dl-menthofuran [4,5,6,7-tetrahydro-3,6-dimethylbenzofuran, VIIa] which is a typical 2,3,4-trisubstituted furan occurring in nature.

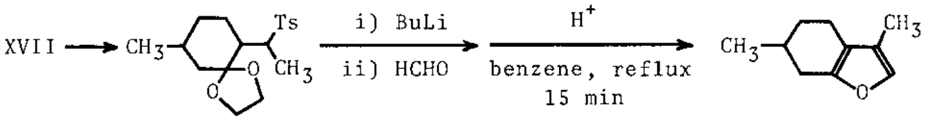
3-Methylcyclohexanone (XV) was lithiated with an equimolar amount of lithium diisopropylamide (LDA) in THF for 1 h at − 78°C under nitrogen followed by the passing excess gaseous acetaldehyde at − 78°C. After stirring for 30 min at − 78°C, the reaction mixture was treated with pH 7 buffer solution and extracted with ether. The crude β-hydroxyketone XVI obtained by evaporation of the ethereal



XV XVI XVII, 57%

extract was redissolved in dichloromethane and dehydrated by treatment with aluminium oxide and molecular sieves overnight at room temperature to give the α,β-unsaturated ketone XVII in a 57% yield (based on XV).

The β-tosylacetal XVIII derived from XVII was led to the desired dl-menthofuran (VIIa) in a similar manner above-mentioned as follows:



XVIII,6) 67% VIIa, 40%

IR and ^{13}C-NMR spectra of this compound (VIIa) were almost identical with reported ones.7,8)

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1) K. Inomata, S. Aoyama, and H. Kotake, Bull. Chem. Soc. Jpn., 1978, **51**, 930.

2) H. Kotake, K. Inomata, H. Kinoshita, S. Aoyama, and Y. Sakamoto, Heterocycles, 1978, **10**, 105.

3) K. Inomata, M. Sumita, and H. Kotake, Chem. Lett., 1979, 709.

4) G. K. Cooper and L. J. Dolby, Tetrahedron Lett., 1976, 4675.

5) The crude 2-methylenecyclohexanone derived from the corresponding Mannich base [2-(N,N-dimethylaminomethyl)cyclohexanone] was used.

6) Mixture of diastereoisomers.

7) Y. R. Naves, Compt. rend., 1953, **237**, 704. An infrared spectrum indicated a peak at ca. 1630 cm^{-1} instead of 1681 cm^{-1} reported in the literature.

8) K. Tori, M. Ueyama, I. Horibe, Y. Tamura, and K. Takeda, Tetrahedron Lett., 1975, 4583. Two carbons band at 31.5 ppm reported in the literature was split into two bands (31.4 and 31.5 ppm).

9) Satisfactory spectral data were obtained for all the compounds in this paper. For crystalline substances, satisfactory data of elemental analysis were also obtained.

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