

FURANNULATION STRATEGY. AN EFFICIENT SYNTHESIS OF FUSED 3-METHYLFURANS

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Abstract—A two-step synthesis of fused 3-methylfurans (furannulation) by the addition of enolate anion of cyclic 1,3-dicarbonyl compounds to allenic sulfonium salt is described.

Fused ring furans are abundantly shown in terpenoids arising from plants and marine organisms, and their structural interest and biological activities have stimulated considerable synthetic efforts.¹⁻³ Biogenetically, many of them like furanoeremophilanes possess 3-methylfuran structure (fused 3-methylfuran ring system) and that requires some devices in furanoterpenoid synthesis because of difficulty in direct introduction of methyl group at 3-position of furan ring. In 1981, Jacobi et al. have developed the facile synthesis of fused 3-methylfurans by intramolecular Diels-Alder reaction of acetylenic oxazoles (bis heteroannulation).¹ On the other hand, Srikrishna and Krishnan recently described the synthesis of 3-acyl-4-methylfurans from cyclohexane-1,3-dione based on radical cyclization reaction.⁴

Among many of efforts for the synthesis of 3-methylfurans have culminated, furannulation by the reactions of allenic sulfonium salt (**1**) with enolate anions of β -keto ester, β -keto sulfone and β -diketone affords the acyclic substituted furans in high yields in one step.⁵ We describe here a direct synthesis of fused 3-methylfurans by the reaction of **1** and enolate anions of various cyclic 1,3-dicarbonyl compounds.

A typical experimental procedure is as follows (Scheme II). To an ethanolic suspension of **1**, easily obtained by the reaction of propargyl bromide (1.8 ml, 20 mmol) and dimethyl sulfide (1.5 ml, 20 mmol) in 1.2 ml of MeCN followed by isomerization by addition of 2 ml of ethanol⁶, was added an ethanolic solution of cyclohexane-1,3-dione (1 g, 8.9 mmol) and sodium ethoxide (0.61 g, 8.9 mmol). The reaction mixture was refluxed for 1 h to give **3a**; ir (CHCl₃) 1660 cm⁻¹; ¹H-nmr (δ , CDCl₃) 5.65 (t, J=3.0 Hz, 1H), 5.06 (t, J=3.0 Hz, 2H), 4.81 (t, J=3.0 Hz, 1H), 2.64-1.94 (m, 6H). **3a** was easily isomerized to furan in acidic conditions. Thus treatment of **3a** with p-TsOH (9 g, 47 mmol) in benzene (10 ml) at room temperature for 2 h led to smooth formation of **4a** in 75% from **2a** (entry 1, Table I); ir (CHCl₃) 1660 cm⁻¹; ¹H-nmr (δ , CDCl₃) 7.07 (br s, 1H), 2.84 (t, J=6.0 Hz, 2H), 2.19 (d, J=1.2 Hz, 3H), 2.57-1.90 (m, 4H).

Scheme II

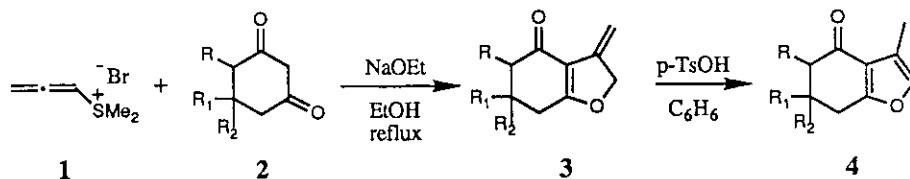


Table I. Fused 3-Methylfuran Synthesis

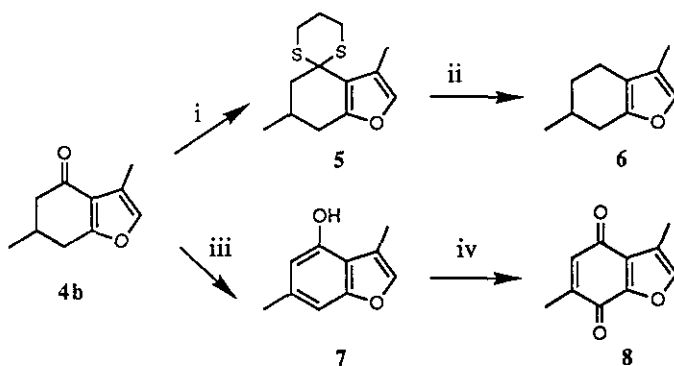
entry	1,3-dicarbonyl compound	furan (yield) ^{a)}
1		
2		
3		
4		
5		

^{a)}Isolated yield after acid isomerization without purification of the intermediacy 3

Various cyclic 1,3-dicarbonyl compounds reacted in a similar fashion to afford fused 3-methylfurans in good yields as shown in Table I. Interestingly, evodone (**4b**), a furanomonoterpene isolated from *Evonia hortensis*, was briefly synthesized in 75% from **2b** (entry 2). *Trans*-decaline-1,3-dione gave two products in 35% and 21%, respectively. Spectral data suggested both products were tricyclic

furans, and enol silyl ether of major isomer showed the signal of the olefinic proton as a broad singlet at δ 4.50 in ^1H -nmr spectrum, which indicated that the structure of major isomer to be **4f** (entry 5, Table I).

An interesting facet of our procedure is shown in Scheme III. The fused 3-methylfurans (**4**) could be transformed into some important intermediates in synthesis of furanoterpenoids by using the ketone group. For example, **4b** was converted to menthofuran (**6**), a proximate toxic metabolite of pulegone, by reduction of thioketal **5** using Raney Nickel in 54% yield. **4b** could be also converted to benzofuranquinone which actually used as a dienophile in synthesis of furanoterpenoids.² Indeed, **4b** was oxidized to phenol **7** according to Saegusa's method via silyl enol ether,⁷ which was further oxidized to 3,6-dimethylbenzofuran-4,7-quinone (**8**) by Fremy's salt.⁸



Scheme III. Reagents and conditions: i, $\text{HS}(\text{CH}_2)_3\text{SH}$, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , room temperature (100%); ii, Raney Ni, EtOH, room temperature (54%); iii, a) LDA, THF, -32°C , then $\text{TMSCl} \cdot \text{NEt}_3$, b) $\text{Pd}(\text{OAc})_2$, p-benzoquinone, MeCN, room temperature (36%); iv, Fremy's salt, EtOH- KH_2PO_4 buffer, 0°C (69%).

The method described above is simple and efficient for direct synthesis of a variety of fused 3-methylfurans and expected widespread applicability in the synthesis of furanosesquiterpenoids. Further synthetic application of a number of fused 3-methylfurans is currently underway in our laboratory.

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