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A CONVENIENT METHOD FOR THE PREPARATION OF 3-ACYLFURANS. A NEW SYNTHESIS OF PERILLA KETONE

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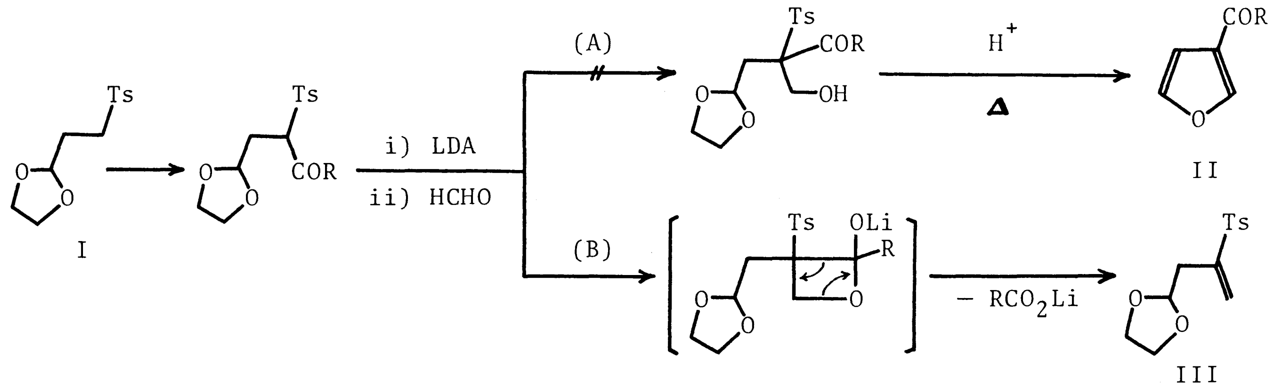
It was found that 3-(phenylthio)propanal ethylene acetal (IV) is a useful starting material for the preparation of 3-acylfurans. Some 3-acylfurans, including perilla ketone [3-(4-methylpentanoyl)furan], were prepared by the use of IV from an aziridide or aldehydes.

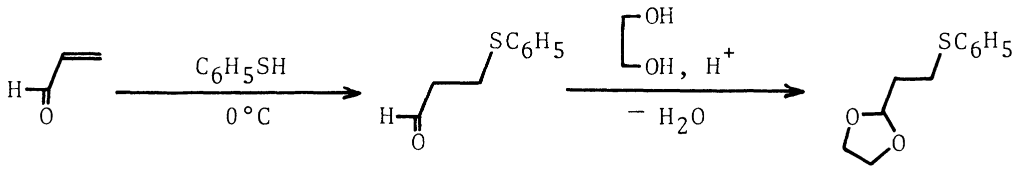
A considerable number of 3-acylfurans have been discovered in nature,1) however, only a few methods of their syntheses have been reported2) except those starting from 3-furyl type synthons,3) which are usually not easy to prepare.

Recently we have reported the general methods for the preparation of 2- or 3-alkylated and 2,3-dialkylated furans starting from 3-tosylpropanal ethylene acetal (I),4,5) but attempt to extend the method to the preparation of 3-acylfurans (II) according to the following scheme (A) was unsuccessful because of the unexpected formation of vinyl sulfone (III) via deacylation (B).6) All another attempts for the syntheses of 3-acylfurans starting from I under various conditions were fruitless.



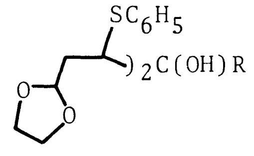
We have now found that the use of 3-(phenylthio)propanal ethylene acetal (IV) in the place of I could supress such a deacylation reaction and gave the desired 3-acylfurans in fairly good yields.

The starting material IV (bp 113-117°C/0.003 Torr) was prepared by the reaction of 3-(phenylthio)propanal, which was easily obtained from equimolar quantities of acrylaldehyde and benzenethiol at 0°C and used without further purification, with ethylene glycol (1.2 equiv.) in benzene containing a trace of p-toluenesulfonic acid with azeotropic removal of water in a 75% yield.

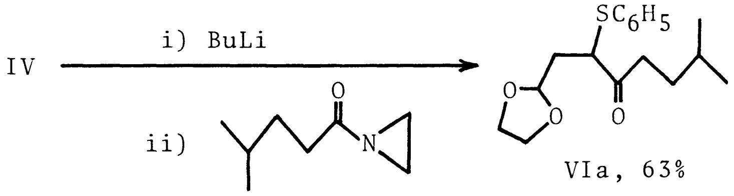


IV

Acylation of IV was first tried by the reaction of a lithiated IV with acyl chloride or methyl ester in the similar manner reported by Bartlett and his co-worker about alkyl sulfones,7) but unfortunately satisfactory result was not obtained because of the formation of tertiary alcohols (V). The acylation was achieved by the reaction of the lithiated IV with an aziridide in THF as follows: to a THF solution (3 ml) of IV (219 mg, 1.04 mmol) was added an equimolar amount of BuLi (in hexane) under nitrogen at – 50°C and the temperature was gradually raised up to – 20°C (required ca.1 h). After addition of a THF solution (3 ml) of N-(4-methylpentanoyl)aziridine (197 mg, 1.5 mmol) at – 50°C, the reaction mixture was allowed to warm to room temperature and kept overnight followed by treatment with pH 7 buffer solution. The crude residue obtained after the usual work-up was subjected to preparative TLC (silica gel) to give the desired acylated product VIa (203 mg) as an oily substance in a 63% yield.

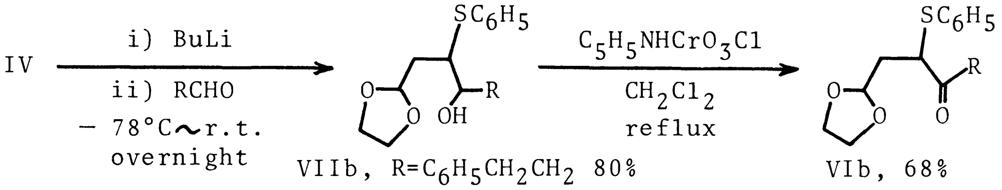


V



VIa, 63%

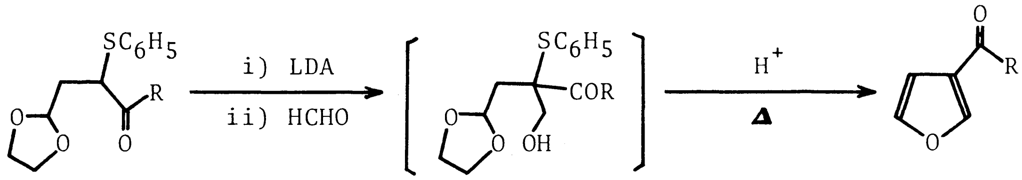
Further, it was found that the acylated product (VI) could also be given by oxidation of an alcohol (VII), prepared by the reaction of the lithiated IV with an aldehyde, with pyridinium chlorochlomate (1.66 equiv.) by refluxing in dry CH_2Cl_2 for about 40 h.



VIIb, R=$C_6H_5CH_2CH_2$ 80% VIb, 68%

VIIc, R=$CH_3(CH_2)_7$ 63% VIc, 65%

The 3-acyl-3-(phenylthio)propanal ethylene acetal (VIa-c) obtained above was treated with an equimolar amount of lithium diisopropylamide (LDA) in THF at $-$ 50°C~r.t. followed by bubbling gaseous formaldehyde through the solution at room temperature. After stirring overnight, the reaction mixture was filtered to remove a precipitate, and the filtrate was treated with pH 7 buffer solution and extracted with ether. The organic layer was dried over sodium sulfate and evaporated. The resulting keto-alcohol (VIIIa-c) was dissolved in dry benzene and refluxed in the presence of a catalytic amount of p-toluenesulfonic acid for 1-2 h. After neutralization with aqueous sodium bicarbonate, the solvent was removed under reduced pressure and the residue was subjected to preparative TLC to afford an expected 3-acylfuran (IIa-c) in a good yield. 3-(4-Methylpentanoyl)furan (IIa) derived from VIa is a naturally occurring 3-acylfuran named perilla ketone originally isolated from Perilla frutescens Brit.[8)]



VIa-c VIIIa-c

IIa, R=$(CH_3)_2CHCH_2CH_2$ 62%

IIb, R=$C_6H_5CH_2CH_2$ 72%

IIc, R=$CH_3(CH_2)_7$ 81%

From the above results, it is evident that 3-(phenylthio)propanal ethylene acetal (IV) is synthetically useful starting material for 3-acylfurans. We are now investigating further to elucidate the scope and limitation of this method.

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9) The spectral data of the products are as follows.

IIa: IR 1670, 1562, 1152, 868, 738 cm^{-1}; NMR$^{2a)}$ (CDCl$_3$) δ 0.91 (d, 6H, J=5 Hz), 1.3-1.8 (m, 3H), 2.68 (t, 2H, J=7 Hz), 6.68 (m, 1H), 7.35 (m, 1H), 7.95 (m, 1H).

IIb: IR 1675, 1562, 1152, 870, 740 cm^{-1}; NMR (CDCl$_3$) δ 2.97 (s, 4H), 6.66 (m, 1H), 7.15 (m, 5H), 7.30 (m, 1H), 7.86 (m, 1H).

IIc: IR 1660, 1568, 1160, 880, 740 cm^{-1}; NMR (CDCl$_3$) δ 0.6-2.0 (m, 15H), 2.70 (t, 2H, J=7 Hz), 6.70 (m, 1H), 7.34 (m, 1H), 7.93 (m, 1H).

IV: IR 1580, 1130 cm^{-1}; NMR (CDCl$_3$) δ 1.75-2.20 (m, 2H), 2.98 (t, 2H, J=8 Hz), 3.81 (m, 4H), 4.90 (t, 1H, J=4 Hz), 7.18 (m, 5H).

VIa: IR 1710 cm^{-1}; NMR (CDCl$_3$) δ 0.85 (d, 6H, J=6 Hz), 1.2-1.7 (m, 3H), 2.0-2.3 (m, 2H), 2.4-2.7 (m, 2H), 3.65-3.98 (m, 5H), 4.94 (t, 1H, J=4 Hz), 7.30 (m, 5H).

VIb: IR 1710 cm^{-1}; NMR (CDCl$_3$) δ 1.9-2.3 (m, 2H), 2.85 (m, 4H), 3.60-3.95 (m, 5H), 4.88 (t, 1H, J=5 Hz), 7.13 (m, 10H).

VIc: IR 1710 cm^{-1}; NMR (CDCl$_3$) δ 0.6-1.7 (m, 15H), 1.95-2.33 (m, 2H), 2.33-2.70 (m, 2H), 3.55-3.95 (m, 5H), 4.89 (t, 1H, J=5 Hz), 7.21 (m, 5H).

VIIb and VIIc consist of two diastereoisomers, respectively.

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