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# A FACILE ELABORATION OF ALDEHYDES TO 2-ALKYL-3-THIOPHENYLFURANS

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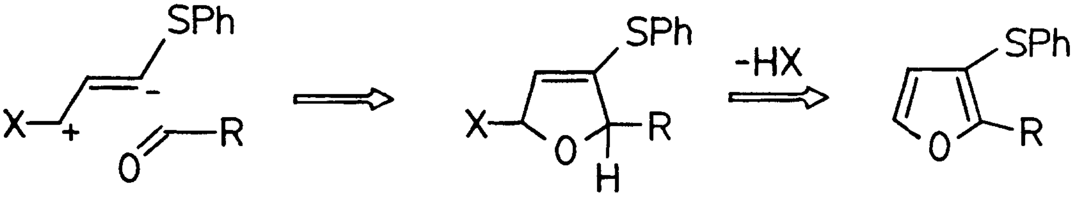
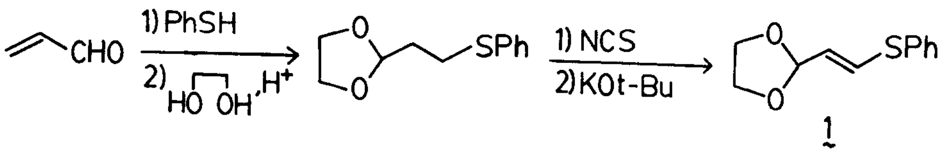
Abstract: A two-step procedure for the elaboration of aldehydes to 2-substituted 3-thiofurans has been developed. The key step involves a site-selective deprotonation of a substituted vinyl sulfide.

In connection with an ongoing project in our laboratories, we had need for 2-substituted 3-thiofurans. Inspection of the literature revealed that while a number of 3-thiofuran syntheses were known, they all suffered limitations in overall yield and/or in the scope of the reaction[1]. In general furans substituted at the 3-position are less available than their 2-substituted analogs due to the propensity of furan to undergo electrophilic substitution at the 2 position.[2] An additional requirement for our purpose was that the thiofuran could be elaborated from an aldehyde as shown in Scheme 1. While annulations of this type are known to furan chemistry[3], this approach has not been used for the construction of 3-thiofurans.



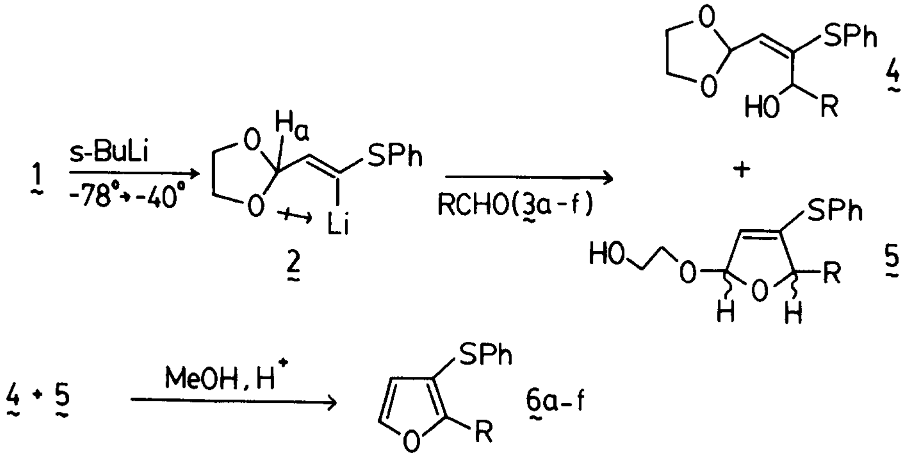
Scheme 1

We have found that vinyl sulfide **1** serves as an excellent conjunctive reagent for the elaboration of an aldehyde to a 3-thiofuran. The preparation of the vinyl sulfide (Scheme 2) is straightforward and high yielding. None of the intermediates need to be purified and the final product can be isolated by simple bulb to bulb distillation. The base catalyzed elimination leading to **1** is highly stereoselective, yielding an E/Z mixture of 95 to 5[4,5].



Scheme 2

Site-selective deprotonation of the vinyl sulfide **1** was accomplished with s-BuLi in dimethoxyethane (DME). While allylic deprotonation ($H_a$ structure 2) could be envisioned to compete with vinyl deprotonation, only products arising from vinyl deprotonation were

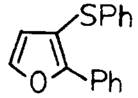
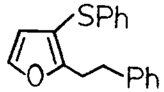
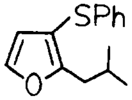
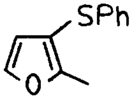
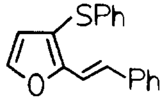
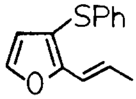


Scheme 3

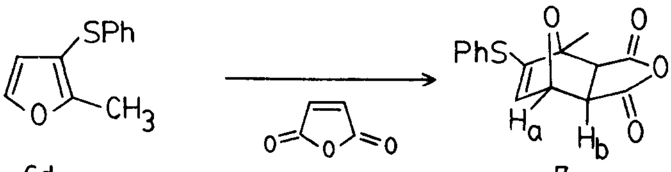
observed. This result contrasts with mono- γ-oxyvinyl sulfides which are reported to undergo allylic deprotonation[6,7]. The additional oxy-substituent in our sulfide must act to diminish the acidity of the allylic proton while maintaining a chelating environment for vinyl deprotonation as depicted in structure 2[8]. Quenching anion **2** with an appropriate aldehyde (**3a-f**, Table I) yielded a mixture of products. Although complete identification of this mixture was impossible due to the lability of the products toward silica gel, spectroscopic evidence supported structures **4** and **5** as logical intermediates. Whatever this mixture, simple acid treatment produced the desired thiofurans **6a-f** in good yield[9,10]. Inspection of Table I shows that this two pot sequence is suitable for the elaboration of aromatic, aliphatic, and α,β-unsaturated aldehydes. To our knowledge the production of **6e** and **6f** represents the first synthesis of a 2-vinyl-3-thiofuran[11].

In order to assure that the acid catalyzed cyclization had occured without concomitant isomerization[1a], **6d** was subjected to a Diels-Alder reaction with maleic anhydride. The exo

Table I. Preparation of 3-Thiofurans from Aldehydes.

| Aldehyde | 3-Thiofuran | | Yield [a] |
|---|---|---|---|
| PhCHO (**3a**) | **6a** |  | 62% |
| $PhCH_2CH_2CHO$(**3b**) | **6b** |  | 69% |
| $(CH_3)_2CHCH_2CHO$(**3c**) | **6c** |  | 65% |
| $CH_3CHO$(**3d**) | **6d** |  | 59% |
| PhCH=CHCHO(E) (**3e**) | **6e** |  | 57% |
| $CH_3CH=CHCHO$(E)(**3f**) | **6f** |  | 56% |

[a] all yields are for isolated furans.



6d                                        7

$J_{a,b}$=0 Hz

adduct **7** was formed cleanly (95%) establishing that the orientation of the methyl and the thiophenoxy groups on the furan ring was as expected. Only two isolated examples of the Diels-Alder reaction involving 3-thiofurans have been reported.[1a,b] We are presently exploring the reactivity of these species in the Diels-Alder reaction, and, in analogy to the 3-oxafurans expect to see enhanced reactivity relative to furan.[12]

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9. A typical experiment is as follows: To the vinyl sulfide 1 (800 mg, 3.85 mmoL) in DME (8 ml) at -78° was added s-BuLi(4.4 ml of a 1.3 M solution in cyclohexane, 5.7 mmoL). After warming to -40° for 15 min the reaction was recooled to -78° and dihydrocinnamaldehyde (773 mg, 5.7 mmol) was added neat. Upon warming to 0° the reaction was diluted with hexane-ether (9:1, 100 ml), washed with aqueous $K_2CO_3$(2 x 50 ml), dried ($MgSO_4$) and concentrated. The resulting yellow oil was dissolved in methanol (14 ml) and stirred in the presence of d-camphorsulfonic acid (40 mg) for 16 hr at room temperature (other examples have shown that 3 hr is sufficient to complete the reaction). Dilution with hexane (100 ml) followed by washing with 10% aqueous $K_2CO_3$(2 x 40 ml), drying ($MgSO_4$)and concentrating gave a yellow oil. This residue was purified by flash chromatography (2 x 15 cm) using ethyl acetate hexane (2:98) as the eluent to yield **6b** (740 mg, 69%) as a colorless oil.
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