Wittig Rearrangement of 3-Furylethmethyl Ethers and Its Application to the Synthesis of Dendrolasin

Masayoshi Tsubuki,* Hiroyuki Okita and Toshio Honda*
Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa, Tokyo, 142, Japan

The Wittig rearrangement of 3-furylethmethyl ethers 1 proceeds efficiently to give 3-methyl-2-furylethanol 2 or 3-furylethanols 3 depending on the basicity of the butyllithium used; synthesis of dendrolasin is achieved with the 1,2-rearrangement of 3-furylethmethyl geranyl ether 5 as a key step.

Furan derivatives are important not only because of their widespread occurrence in natural products but also because of their role as versatile intermediates. Numerous efforts have been devoted to the synthesis of furans and functionalisation of the furan ring. As part of our continuing work on the synthesis of physiologically active natural products using furylmethanols, we were interested in developing a new method to prepare substituted furylmethanols starting from readily available 2- and 3-furylethanol. Here we report a facile synthesis of 3-methyl-2-furylethanol and 3-furylethanols based on the Wittig rearrangement of 3-furylethmethyl ethers, and its application to the synthesis of the furanoid sesquiterpene dendrolasin.

Although the Wittig rearrangement of arylmethy ethers has been extensively investigated, only one example of a 3-furylethmethyl ether has been reported in which the cyanohydrin 2,3-Wittig rearrangement proceeds to afford 2-acetyl-3-furylethuran. We therefore studied the Wittig rearrangement of 3-furylethmethyl ethers which could provide direct access to a variety of furan derivatives. (Scheme 1).

The Wittig rearrangement of allyl 3-furylethmethyl ether 1a was initially investigated under standard conditions. The results are summarised in Table 1. Compound 1a was selectively base-deprotonated at the allylic position giving the corresponding anion which underwent 2,3- and 1,2-rearrangements to afford compounds 2a and 3a. When BuLi or LDA was employed as the base in THF, the rearrangement proceeded at −30 to −20 °C, giving compounds 2a and 3a, (2–2.5: 1) respectively. Interestingly, treatment of compound 1a with BuLi in THF at −78 °C afforded compound 2a as almost the sole product.

We next examined the Wittig rearrangement of 3-furylethmethyl ethers 1b–g as shown in Table 2. Deprotonation of 1b–g with base occurred at the same position as 1a, giving the rearranged products. In substituted allylic systems, particularly 1e and 1d, the 1,2-rearrangement proceeded selectively affording 3-furylethanols 3c and 3d. Prop-2-ynyl and benzyl ethers 1e and 1f underwent 2,3-rearrangement mainly upon deprotonation with BuLi, whereas 1,2-rearrangement proceeded preferentially on treatment with BuLi at −78 to 0 °C. α-Furylethoxyacetic acid 1g rearranged expectedly to give compound 2g with excellent selectivity upon treatment with LDA. These results are in good agreement with the general rule that lower temperature favours 2,3-over 1,2-rearrangement. Treatment of allyl furylethyl ether 1h with base (BuLi or BuLi) in THF afforded mainly 1,2-product 3h as a mixture of diastereoisomers.

By use of the rearrangement, a facile synthesis of dendrolasin was achieved as follows (Scheme 2). 3-Furylethmethyl geranyl ether 5, prepared by the etherification of 3-furylethmethyl ethers with acetone, undergoes the 1,2-rearrangement with BuLi in THF at −78 °C to give compound 3i, which is then subjected to a Wittig reaction with methyltriphenylphosphonium bromide to give compound 3j. The crude product is treated with LDA in THF at −78 °C to give compound 3k, which is then subjected to a Wittig reaction with methyltriphenylphosphonium bromide to give compound 3l. The crude product is treated with LDA in THF at −78 °C to give compound 3m, which is then subjected to a Wittig reaction with methyltriphenylphosphonium bromide to give compound 3n.
methanol 4 with geranyl bromide in 70% yield, was treated with BuLi in THF at −78 to −25 °C to afford the geraniol 6 (58% yield) as the major product. None of the 2,3-rearranged product was observed in this reaction. Attempts to deoxygenate the hydroxy moiety in 6 to yield dendrolasin 8 were unsuccessful under Barton’s method. Acetylation of 6 gave the allylic acetate 7 (91% yield), which was treated with lithium in ethylamine to afford dendrolasin 8 in 39% yield with spectroscopic data identical with those reported.

Scheme 2 Reagents and conditions: i, geranyl bromide, NaH, DMF (70%); ii, BuLi (5 equiv.), THF, −78 to −25 °C (58%); iii, Ac₂O, pyridine (91%); iv, Li, EtNH₂ (39%)

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Footnote
† 3-Furylmethyl ether 1a–g were prepared by reaction of 3-furylmethyl ethers with the corresponding halides in DMF using sodium hydride (2 equiv.)

References