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Wittig rearrangement of allyl and propargyl furfuryl ethers leading to 2-furylmethanol derivatives

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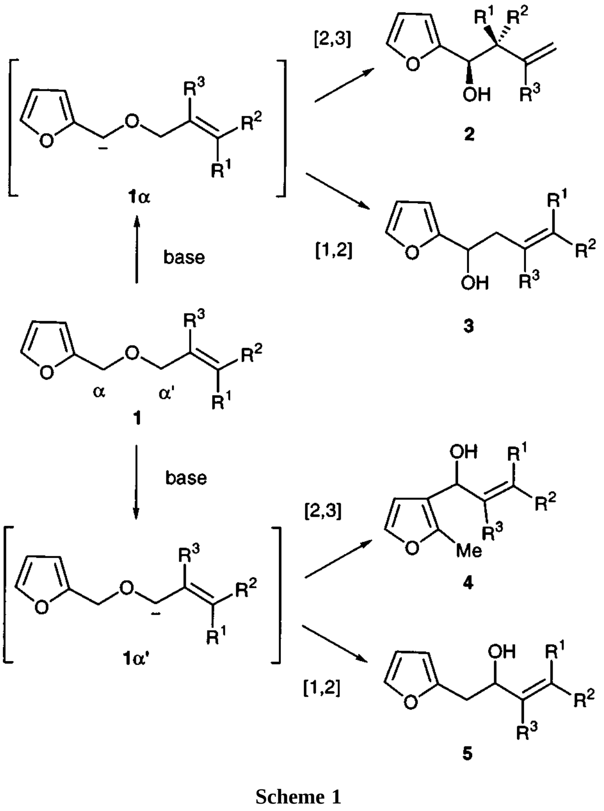
The first example of the Wittig rearrangement of furfuryl ethers is presented and its application to the preparation of 3-(2-furyl)-3-hydroxy-2-methylpropionates is described.

We have recently shown that the Wittig rearrangement of 3-furylmethyl ethers could proceed to give 2,3- and 1,2-rearrangement products.[1] An advantage of this Wittig rearrangement is that the deprotonation occurred selectively at the allylic position, and either 2,3- or 1,2-rearrangement occurred preferentially depending on the base used. Our interest in defining the scope, limitations and utility of this rearrangement in furylmethyl ethers has directed our attention to Wittig rearrangement of furfuryl ethers. Although the Wittig rearrangement of arylmethyl ethers has been widely studied,[2] there has been no successful report on the rearrangement of a furfuryl ether.[3] Herein, we report the first example of the Wittig rearrangement of allyl and propargyl furfuryl ethers to provide a variety of furyl alcohols, especially 2-furylmethanol derivatives.

The Wittig rearrangement of allyl furfuryl ethers **1a**–**e**†‡ was initially investigated under the conditions[1] described before. Allyl furfuryl ether **1** can theoretically produce both 2,3-rearrangement products **2** and **4** and 1,2-rearrangement products **3** and **5** depending on the position, α and α′, of deprotonation[4] (Scheme 1). The results are summarised in Table 1. Selective deprotonation at the α position was generally effected by Bu^{t}Li in THF at −78 °C, thus providing 2,3-rearrangement products **2a**–**e** as major isomers. In contrast, weaker bases, such as BuLi and Bu^{s}Li, favoured α′ over α deprotonation in the reactions of **1a**–**d**, giving 2,3-rearranged products **5a**–**d** together with 1,2-rearranged products **4a**,**b**. (*Z*)-Crotyl furfuryl ether **1d** afforded *syn* product[5] **2d** with high diastereoselectivity, whereas (*E*)-crotyl ether **1c** yielded *anti* isomer[5] **2c**, albeit in moderate selectivity. It is noteworthy that the (*E*)-crotyl ether **1c** underwent [2,3] Wittig rearrangement furnishing the *anti* isomer **2c** as a major compound, while the corresponding (*E*)-crotyl benzyl ether afforded a mixture in which the *syn* isomer was favoured.[2]



Scheme 1

In order to gain an understanding of the relative thermodynamic stabilities of **1α** and **1α′** anions, we undertook *ab initio* calculations involving full optimisations using the GAUSSIAN 92 quantum mechanical package.§ As one might expect, the calculations suggest that the energy minimums of the **1a**–**e** α anions were favoured by 12.0-28.5 kJ mol^{-1} over the energy minimums of the **1a**–**e** α′ anions at the RHF/6-31+G* level. It became apparent that the energy minimum of the prenyl ether **1e** α anion was predicted to be 9.7 kJ mol^{-1} lower than that of the allyl ether **1a** α anion. These results support the idea that the Wittig rearrangement of allyl furfuryl ethers **1a**–**e** proceeded through deprotonation mainly at the α position, giving 2,3-rearrangement products **2a**–**e**.

Table 2 shows that the diastereoselectivity in the Wittig rearrangement of crotyl ethers **1c**,**d** was influenced by the solvent used. Surprisingly, changing the solvent from THF to Et$_2$O caused the opposite diastereoselectivity in the reaction of

Table 1 Wittig rearrangement of furfryl ethers **1a**–**e**

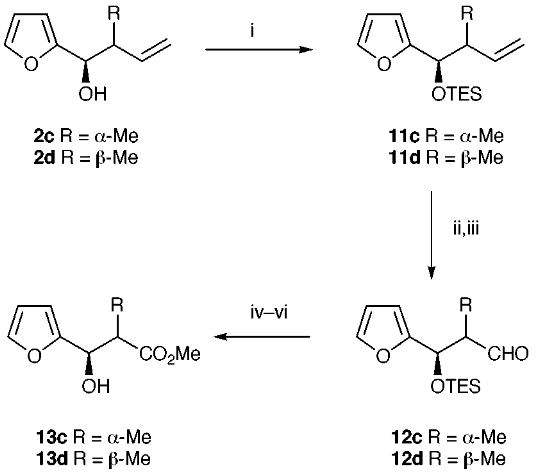
Substrate	Base[a]	Yield (%)	Product Distribution[b] (%) 2	3	4	5
1a R^1 = R^2 = R^3 = H	BuLi	53	31[c]		19	50
	Bu^{s}Li	61	30[c]		16	54
	Bu^{t}Li	61	63[c]		17	20
1b R^1 = R^2 = H, R^3 = Me	BuLi	71	23[c]		23	54
	Bu^{s}Li	55	23[c]		15	62
	Bu^{t}Li	69	67[c]		14	19
1c R^1 = R^3 = H, R^2 = Me	BuLi	79	74 (66/34)[d]	—	—	26
	Bu^{s}Li	66	45 (75/25)[d]	—	—	55
	Bu^{t}Li	73	93 (73/27)[d]	—	—	7
1d R^1 = Me, R^2 = R^3 = H	BuLi	59	82 (9/91)[d]	—	—	18
	Bu^{s}Li	70	52 (10/90)[d]	—	—	48
	Bu^{t}Li	64	90 (10/90)[d]	—	—	10
1e R^1 = R^2 = Me, R^3 = H	BuLi	57	82	5	—	13
	Bu^{s}Li	57	56	39	—	5
	Bu^{t}LI	79	91	2	—	7

[a] Reactions were carried out with base in THF at −78 °C. BuLi (10 equiv.) was employed and the reaction was allowed to warm to −20 °C. Bu^{s}Li (3 equiv.) was employed.Bu^{t}Li (5 equiv.) was employed. [b] Determined by 270 MHz NMR analysis of the crude products. [c] [2,3] Rearranged products **2a**,**b** are equal to [1,2] rearranged products **3a**,**b**. [d] In parentheses: the ratio of the *anti* to the *syn* product.

Table 2 Wittig rearrangment of crotyl furfuryl ethers **1c**,**d** with Bu^{t}Li in different solvents at −78 °C

Substrate	Solvent	*syn*:*anti*	Yield (%)
1c	THF[a]	27:73	73
1c	Et_2O	87:13	72[b]
1c	toluene	74:26	69
1c	hexane	78:22	58[b]
1d	THF[a]	90:10	64
1d	Et_2O	94:6	66
1d	toluene	92:8	51
1d	hexane	>99:<1	60[b]

[a] The results from Table 1. [b] Based on the recovery of the starting material.



Scheme 2 *Reagents and conditions*: i, TESCl, Pr$^i_2$EtN, CH_2Cl_2 (87% for **11c**, 89% for **11d**); ii, OsO_4, NMO, acetone–H_2O; iii, $NaIO_4$, CH_2Cl_2–H_2O (2 steps: 54% for **12c**, 47% for **12d**); iv, $NaClO_2$, 2-methylbut-2-ene, NaH_2PO_4, Bu^{t}OH, H_2O; v, MeI, $NaHCO_3$, DMF; vi, TsOH, MeOH (3 steps: 65% for **13c**, 59% for **13d**).

(*E*)-crotyl ether **1c**. The same trend was observed even in a non-polar solvent. On the other hand, better results were found in Et_2O, toluene and hexane, where 84–98% de was obtained in the reactions of (*Z*)-crotyl ether **1d**. A trace amount of **5c,d** was formed in all cases.

The promising results for the Wittig rearrangement of allyl furfuryl ethers prompted us to examine the rearrangement of propargyl ethers **6a**,**b** (Table 3). For propargyl ether **6a** deprotonation with Bu^{s}Li or Bu^{t}Li proceeded through the dianion at the α and terminal alkyne positions to give 1,2-rearrangement product **8a** preferentially. In contrast, propargyl ether **6b** was deprotonated at the α′ position to produce mainly 2,3-rearrangement product **9b**.

Employing *anti* and *syn* alcohols **2c**,**d** we prepared 3-(2-furyl)-3-hydroxy-2-methylpropionates **13c**,**d**, key intermediates for the synthesis of several natural products.[6] Protection of the hydroxy group in **2c**,**d** as a TES ether afforded **11c**,**d**, which were oxidised to aldehydes **12c**,**d** by dihydroxylation of the alkene followed by glycol cleavage in 47 and 42% yield, respectively. Oxidation of **12c**,**d** with sodium chlorite gave the carboxylic acids, which were esterified and then deprotected with TsOH to furnish propionates **13c**,**d** in 65 and 59% yield, respectively.

In summary, Wittig rearrangement of furfuryl ethers offers a new route for the synthesis of furyl alcohols, especially 2-furylmethanol derivatives.

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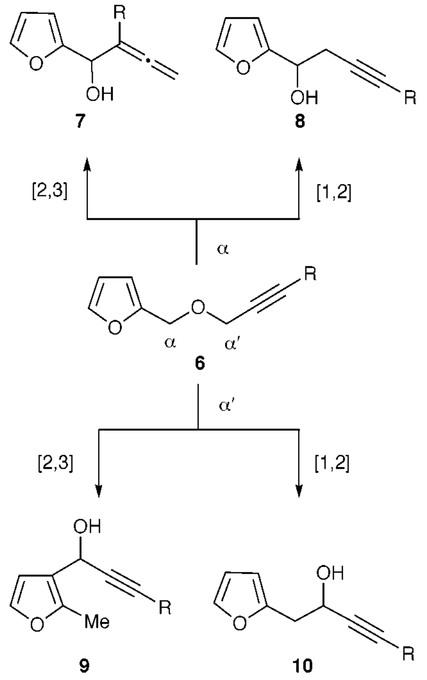
Table 3 Wittig rearrangement of furfuryl propargyl ethers **6a**,**b**



Substrate	Base[a]	Yield (%)	Product Distribution[b] (%) 7	8	9	10
6a R = H	BuLi	73	—	45	6	49
6a R = H	Bu^{s}Li	62	—	65	14	21
6a R = H	Bu^{t}Li	61	—	89	—	11
6b R = Me	BuLi	67	9	—	70	21
6b R = Me	Bu^{s}Li	64	12	—	85	3
6b R = Me	Bu^{t}Li	52	9	—	82	9

[a] Reactions were carried out with base in THF at −78 °C. BuLi (10 equiv.) was employed and the reaction was allowed to warm to −20 °C. Bu^{s}Li (3 equiv.) was employed. Bu^{t}Li (5 equiv.) was employed. [b] Determined by 270 MHz NMR analysis of the crude products.

Notes and references

† Furfuryl ethers **1a–e** and **6a**,**b** were prepared by reaction of furfuryl alcohol with the corresponding halides in DMF using 2 equiv. of sodium hydride (ref. 7).

‡ All new compounds exhibited satisfactory elemental analyses and/or HRMS and ^1H and ^{13}C NMR and IR spectral data. In general furans with low molecular weight are volatile.

§ MO calculations were performed using the IBM RS/6000 version of the GAUSSIAN 92 suite of programs.

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