

Addition of Organochromium Reagents to Heteroaryl Aldehydes. Synthesis of Heteroaryl Substituted bis-Allyl Ethers and Homoallyl Ethers

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Abstract: Heteroaryl substituted allyl and homoallyl alcohols were synthesised with two different method. Synthesis of bis-allyl ethers and homoallyl ethers were carried out via reaction of allyl bromide with allyl alcohols and homoallyl alcohols, respectively. [2,3]-Wittig Rearrangement reactions of heteroaryl substituted bis-allyl ethers were investigated using GC/MS techniques. In these reactions two unexpected products were isolated in high yield.

Keywords: Nozaki-Hiyama reaction, Organochromium reagents, Hetero-aromatic aldehydes

Introduction

A selective carbon-carbon bond forming reaction was described by Nozaki-Hiyama in 1977 based on the mild addition of alkenyl, alkynyl or vinyl chromium (III) compounds to aldehydes in an anhydrous medium. The Nozaki-Hiyama reaction is mainly applied to aldehydes but ketones can be used in some cases and the reaction can be also extended to other organochromium reagents. This reaction has been widely employed in natural product synthesis, becoming the key step in some synthesis plans and it played a key role, for example, in the highly stereocontrolled synthesis of the aliphatic segment of the antibiotic *rifamycin S* [1-5].

The [2,3]-Wittig Rearrangement of unsymmetrical bis-allylic ethers is exceedingly useful for regio- and stereoselective preparations of substituted allyl alcohols. This reaction has also

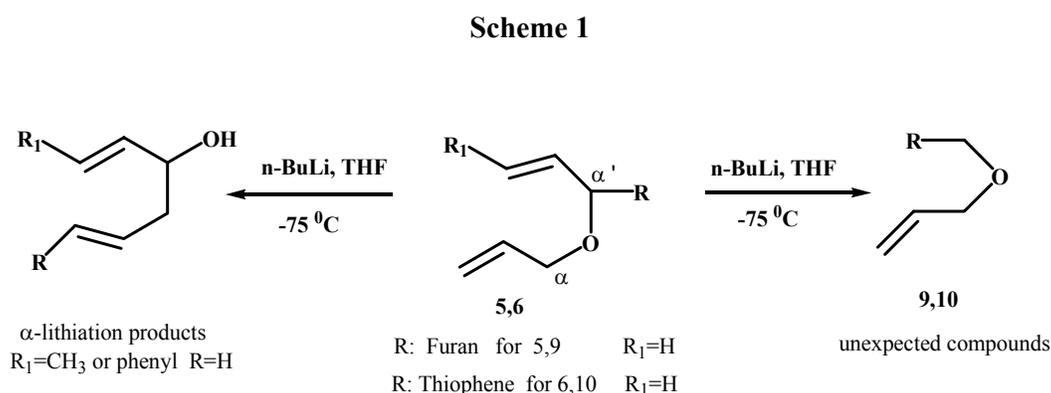
attracted the interest of chemists as the subject of mechanistic investigations and has been increasingly utilized as a useful methodology for organic synthesis [6-10].

This article reports the synthesis of heteroaryl substituted allyl and homoallyl alcohols and their ethers. Also reported are synthesis of heteroaryl substituted bis-allyl ethers and their [2,3]-Wittig Rearrangement reactions. In this reaction, two unexpected products were isolated in high yields. These compounds were characterized by using $^1\text{H-NMR}$, FT-IR and GC/MS techniques.

Results and Discussion

There are several methods for the preparation the substituted allyl and homoallyl alcohols [11-13]. In this study, heteroaryl substituted allyl and homoallyl alcohols were synthesized using the Nozaki-Hiyama reaction. This reaction was carried out with both commercial CrCl_2/DMF (Method A) and $\text{CrCl}_3/\text{LiAlH}_4/\text{THF}$ (Method B). The reaction was performed at $25\text{ }^\circ\text{C}$ in DMF for Method A, and the reaction was relatively fast with high yields compared with Method B.

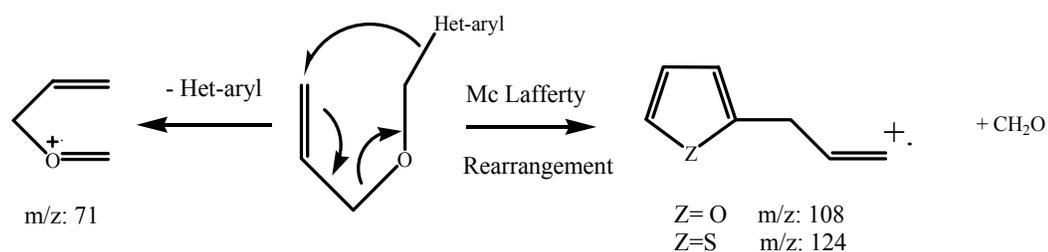
Chromium (II) chloride is a powerful reducing agent. Anhydrous chromium (II) chloride is commercially available and can be used without further purification. A suitable chromium (II) reagent is prepared by reduction of 2 equivalents of anhydrous CrCl_3 with one equivalent of LiAlH_4 in THF at $0\text{ }^\circ\text{C}$, Method B.



The [2,3]-Wittig Rearrangement reactions of 2-(1-allyloxy allyl) furan (**5**) and 2-(1-allyloxy allyl) thiophene (**6**) were carried out according to published procedures [6-10]. In all of the rearrangements of unsymmetrical substrates with different substitution patterns at the α - and α' positions of the two allylic moieties, lithiation takes place exclusively on the less substituted allylic moiety, thus leading to the exclusive formation of the [2,3]-Wittig product as a single regioisomer as shown Scheme 1.

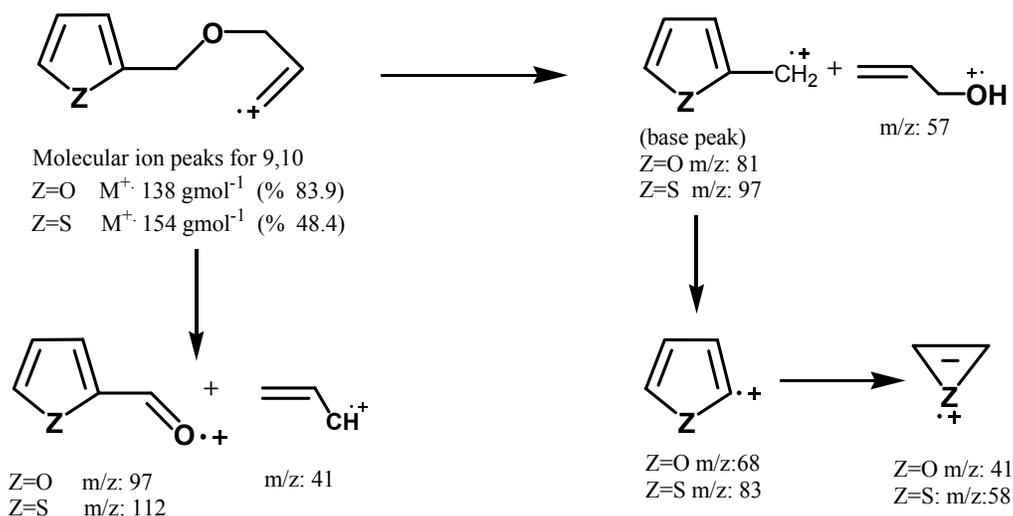
In this work, instead of the expected products of α -lithiation, compounds **9** and **10** were produced in the [2,3]-Wittig rearrangement reaction. α -Lithiation products have been obtained when in compounds **5**, **6** $\text{R}_1 = \text{CH}_3$ and phenyl and $\text{R} = \text{H}$ [6]. On the other hand, the unexpected compounds were isolated when in compounds **5**, **6** $\text{R} = \text{thiophene}$ and furan , $\text{R}_1 = \text{H}$. We are not able to suggest a reaction mechanism for to account for compounds **9** and **10**. The MS spectra of compounds **9**, **10** are explained in detail in Schemes 2, 3.

Scheme 2



α -Cleavage is reduced to a secondary process, as demonstrated by the low abundance of a m/e 71 peak in the mass spectra of compounds **9**, **10** (Scheme 2). Similarly, α -fission followed by olefin elimination is essentially absent. Instead, rupture of the carbon-oxygen linkage with charge retention on the hydrocarbon moiety (m/e 41) becomes dominant. In allyl alkyl ethers, carbon-oxygen bond cleavage yielding allylic ions are the most important fragmentation process. Instead, a series of peaks of medium intensity at even mass numbers is observed whose genesis requires rearrangement processes, but the paucity of experimental data makes structural assignments very tentative [14].

Scheme 3



Acknowledgments

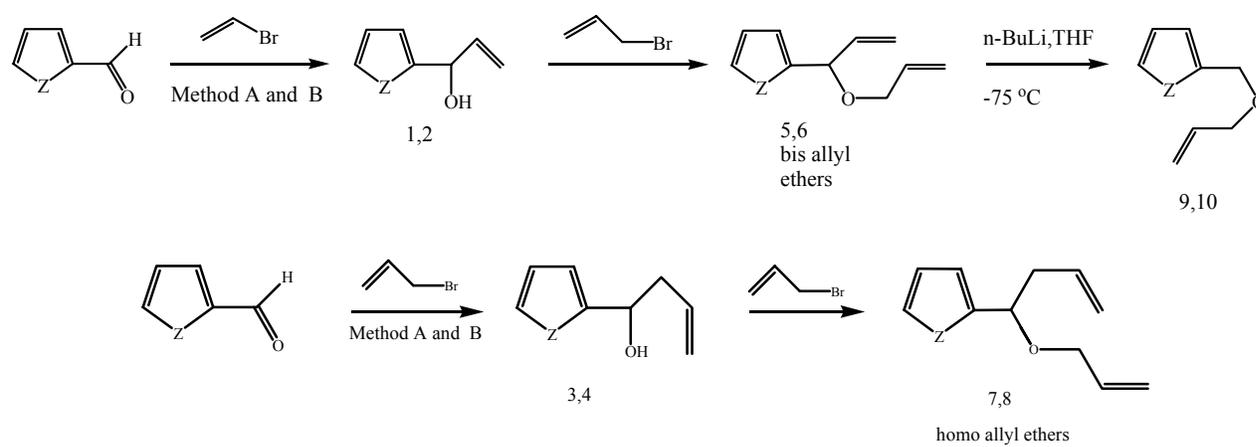
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Experimental

General

The synthetic routes followed are outlined in Scheme 4. CrCl_2 , CrCl_3 , LiAlH_4 , DMF, THF, vinyl bromide, allyl bromide, furan-2-carboxaldehyde, thiophene-2-carboxaldehyde and $n\text{-BuLi}$ were obtained from commercial sources and all the solvents were used without further purification. The products were purified by column chromatography using one of the following eluent systems: (A) 6:1 hexane-ethyl acetate; (B) 4:1 hexane-ethyl acetate; (C): 5:1:1 hexane-ethyl acetate-acetone. IR spectra (NaCl, thin film) were measured on a Mattson series FT-IR 1000 model spectrometer and $^1\text{H-NMR}$ spectra were measured on a JEOL FX-90 Q instrument at 90 MHz, using CDCl_3 as solvent. Shift values are reported in ppm relative to TMS. GC/MS (eV, EI) analysis measurement on a Micromass Zabspec model instrument was determined at The Scientific and Technical Research Council of Turkey (TUBITAK).

Scheme 4



Addition of Organochromium Reagents to Heteroaromatic Aldehydes: Synthesis of Heteroaromatic Substituted Allyl Alcohols (**1, 2**) and Homoallyl Alcohols (**3, 4**)

Method A:

Solutions of vinyl bromide (4.0 mmol) in DMF (10 mL) and heteroaromatic aldehyde (2.0 mmol) in DMF (6 mL) were added at 25 °C to a stirred suspension of CrCl_2 (0.98 gr, 8.0 mmol) in DMF (8 mL) over a period of 10 min under an argon atmosphere. After being stirred at 25 °C for 15 min, the mixture was quenched by addition of water (20 mL) and extracted with ether. The reaction mixture was filtered, the residues were washed with twice with ether, dried with MgSO_4 and concentrated under vacuum to give the crude product that was purified by column chromatography over silica gel.

Method B:

CrCl₃ (4.28 gr, 27 mmol) was reduced with LiAlH₄ (513 mg, 13.5 mmol) in THF (20 mL). After stirring at room temperature for 10 min, the heteroaromatic aldehyde (6.1 mmol) and subsequently vinyl bromide (13.5 mmol) in THF (10 mL) were added dropwise over a period of 20 min. After stirring for 3h and extracting with ether the reaction mixture was filtered, the residues were washed with twice with ether, dried with MgSO₄ and concentrated under vacuum give the crude product that was purified by column chromatography over silica gel.

1-(2-furyl) propen-1-ol (1): Yield: 81.3% (Method A), 76 %; (Method B) Rf: 0.652 (eluent system A); IR (KBr): 3706-3166, 3117, 1667 cm⁻¹. ¹H-NMR: δ 2.85 (broad, OH, 1H), 4.84 (s, CH, 1H), 5.10-6.20 (m, CH=CH₂, 3H), 6.62-7.67 (m, furan ring protons, 3H)

1-(2-thienyl) propen-1-ol (2): Yield: 85.2 % (Method A), 74.9 %; (Method B); Rf: 0.543 (eluent system A); IR (KBr): 3693-3128, 3104, 1641 cm⁻¹. ¹H-NMR: δ 3.01 (broad, OH, 1H), 4.71 (s, CH, 1H), 5.40-6.44 (m, CH=CH₂, 3H), 6.66-7.21 (m, thiophene ring protons, 3H)

1-(2-furyl)-3-buten-1-ol (3): Yield: 75.7 % (Method A), 61.9 %; (Method B); Rf: 0.611 (eluent system B); IR (KBr): 3743-3148, 3078, 1643 cm⁻¹. ¹H-NMR: δ 1.60-1.95 (m, CH₂, 2H), 2.57 (broad, OH, 1H), 3.68 (t, CH, 1H), 4.45-5.25 (m, CH=CH₂, 3H), 6.23 and 7.33 (furan ring protons, 3H)

1-(2-thienyl)-3-buten-1-ol (4): Yield: 75.5 % (Method A), 63.6%; (Method B); Rf: 0.522 (eluent system B); IR (KBr): 3610-3175, 3076, 1650 cm⁻¹. ¹H-NMR: δ 1.76-1.83 (m, CH₂, 2H), 2.85 (broad, OH, 1H), 3.68 (s CH, 1H), 4.25-5.25 (m, CH=CH₂, 3H), 6.52-7.73 (m, thiophene ring protons, 3H)

General Procedure for the Synthesis of bis-Allyl Ethers and Homoallyl Ethers (5-8):

Allyl bromide (17.0 mL, 220 mmol) or vinyl bromide (220 mmol) in THF (20 mL) was added dropwise to a vigorously stirred mixture of heteroaromatic allylic alcohols (200 mmol), n-Bu₄NHSO₄ (3.7 gr, 10 mmol), NaOH (16.0 gr, 400 mmol) and H₂O (4 mL). The resulting mixture was stirred overnight at room temperature. The solid formed was filtered off. Usual work up followed by distillation afforded the title compounds.

2-(1-Allyloxy allyl) furan (5): Yield: 63.3 %; Rf: 0.719 (eluent system D); IR (KBr); 3146, 3119, 3080, 1072, 1661, 1153 cm⁻¹. ¹H-NMR δ 3.85-4.10 (CH₂-O, 2H), 4.44 (s, CH-O, 1H), 5.05-6.00 (m, CH=CH₂, 6H), 6.30 and 7.39 (furan ring protons, 3H)

2-(1-Allyloxy allyl) thiophene (6): Yield: 71.0 %; Rf: 0.648 (eluent system C); IR (KBr); 3101, 3082, 1644, 1074 cm⁻¹. ¹H-NMR: δ 3.85-4.10 (CH₂-O, 2H), 4.67 (s, CH-O, 1H), 5.02-6.15 (m, CH=CH₂, 6H), 6.80-7.10 (m, thiophene ring protons, 3H)

2-(1-Allyloxy-3-butenyl) furan (**7**): Yield: 51%; Rf: 0.731 (eluent system A); IR (KBr); 3088, 3019, 1650, 1240, 1080 cm^{-1} . $^1\text{H-NMR}$: δ 3.65-4.10 (m, CH_2 , 2H), 4.60-5.41 (m, CH-O and CH_2 -O, 3H), 5.61-6.45(m, $\text{CH}=\text{CH}_2$, 6H), 7.15-7.55 (m, furan ring protons, 3H)

2-(1-Allyloxy-3-butenyl) thiophene (**8**): Yield: 63.1 %; Rf: 0.633 (eluent system A); IR: 3105, 3078, 1648, 1228, 1080 cm^{-1} . $^1\text{H-NMR}$: δ 3.98-4.10 (m, CH_2 , 2H), 4.50-4.65 (m, CH-O and CH_2 -O, 3H), 4.90-6.11- (m, $\text{CH}=\text{CH}_2$, 6H), 6.61-7.51 (m, thiophene ring protons, 3H)

2-Allyloxymethyl furan (**9**) and 2-allyloxymethyl thiophene (**10**) were synthesized via [2,3]-Wittig rearrangement reactions of the unsymmetrical bis-allyl ethers under an argon atmosphere and at -75°C in high yields according to literature methods [6-10].

2-Allyloxymethyl furan (**9**): Yield: 57.2 %; Rf: 0.544 (eluent system C); IR (KBr); 3146, 3119, 3080, 1068, 1663, 1157 cm^{-1} . $^1\text{H-NMR}$: δ 4.10 (s, CH_2 -O, 2H), 4.85 (s, CH_2 -O, 2H), 5.21-5.89 (m, $\text{CH}=\text{CH}_2$, 3H), 6.23 and 7.33 (furan ring protons, 3H); GC/MS: M^+ 138, base peak: 81, retention time: 16.96 min.

2-Allyloxymethyl thiophene (**10**): Yield: 61.4 %; Rf: 0.503 (eluent system C); IR (KBr); 3101, 3082, 1641, 1072 cm^{-1} . $^1\text{H-NMR}$: δ 4.13 (s, CH_2 -O, 2H), 4.63 (s, CH_2 -O, 2H), 5.17-6.09 (m, $\text{CH}=\text{CH}_2$, 3H), 6.73-7.10 (m, thiophene ring protons, 3H); GC/MS: M^+ 154, base peak: 97, retention time: 21.94 min.

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