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[2,3]-Wittig rearrangement by a chlorine–lithium exchange

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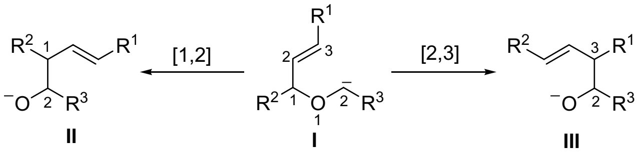
Dedicated to Professors Saverio Florio and Alfredo Ricci on occasion of their 65th birthday

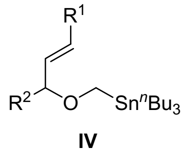
Abstract—The reaction of different allylic chloromethyl ethers **1** with an excess of lithium powder (1:7 molar ratio) and a catalytic amount of DTBB (2.5 mol %) in THF at 0 °C for 1 h gives, after hydrolysis with water, the expected alcohols **2** resulting from a [2,3]-Wittig rearrangement, in an exclusive manner. The same process can also be applied to the corresponding [1,2]-Wittig rearrangement, as it is exemplified for benzyl chloromethyl ether.

The 'Wittig rearrangement', originally reported[1] as the 1,2-migration of an alkyl group from an oxygen to a carbanion centre, was further extended to the corresponding 2,3-migration[2] and nowadays both processes are well known as the [1,2]-[3] and [2,3]-Wittig rearrangement,[4] respectively. For allylic derivatives **I**, the main difference between both reactions, has to do with the regiochemistry of the process as it is shown in Scheme 1.

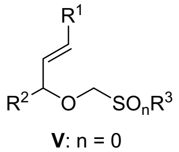


Scheme 1.

The [2,3]-rearrangement of allylic systems of type **I** to give the alkoxide **III** (which proceeds through a concerted thermally allowed sigmatropic process) is much more favoured than the corresponding [1,2] rearrangement (which is believed to occur via a radical-pair dissociation–recombination mechanism) to give the other alkoxide **II**. Apart from other interesting considerations (i.e., stereochemical details), one important aspect concerning the [2,3]-Wittig rearrangement is the generation of the corresponding α-oxygenated carbanion **I**. This operation can be carried out by deprotonation using a strong base (LDA or an alkyllithium reagent) when R^3 is an electron-withdrawing group (aryl, hetaryl, alkenyl, alkynyl, cyano, acyl, alkoxycarbonyl, carboxyl, carbamoyl) or a second-row heteroatom, such as sulfur. Under these conditions, formation of the allylic carbanion, by deprotonation at the most substituted α-position (respect to the oxygen atom) is avoided. However, this hydrogen–lithium exchange methodology fails when R^3 = H or alkyl, and consequently other alternatives must be used. Among them, tin–lithium transmetallation[5] (from compounds of type **IV**, usually with *n*-butyllithium) or sulfur–lithium exchange[6] (from sulfides **V**[7] or sulfones **VI**[8] by an arene-promoted lithiation) have been used to generate intermediates of type **I**.



IV



V: n = 0
VI: n = 2

To the best of our knowledge, the [2,3]-Wittig rearrangement has never been studied involving a chlorine–lithium exchange as the key step to access intermediate **I**. This transformation is of great interest due to the easy access to the starting materials by conventional

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Keywords: [2,3]-Wittig rearrangement; DTBB-catalysed lithiation; Chlorine–lithium exchange; Allylic chloromethyl ethers.

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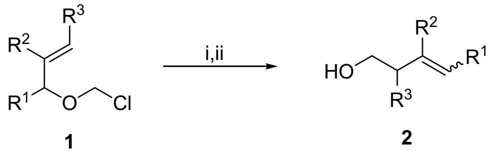


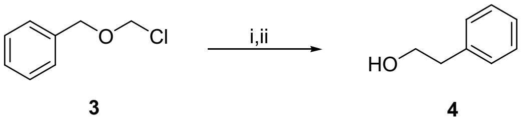
Scheme 2. Reagents and conditions: (i) Li excess, DTBB (2.5 mol %), THF, 0 °C, 1 h; (ii) H_2O, 0 °C to rt.

methodologies. However, low temperatures are required in many cases in order to avoid secondary reactions, mainly the corresponding [1,2]-rearrangement, especially in cyclic substrates. In order to solve this problem, we have developed in the last few years a lithiation methodology based on the use of an excess of lithium and a catalytic amount of an arene, mainly naphthalene and 4,4′-di-*tert*-butylbiphenyl (DTBB).[9–11] Thus, a series of new reactions, such as the preparation of organolithiums from non-halogenated materials,[12] preparation of very reactive functionalised organolithium compounds[13] (by chlorine–lithium exchange[14] or by ring opening of heterocycles[15]), generation of dilithium synthons[16] or the activation of other metals,[17] especially nickel,[18] have been carried out successfully.[19] In this letter, we report our preliminary results on the [2,3]-Wittig rearrangement from different allylic chloromethyl ethers by using the above mentioned arene-catalysed lithiation under mild reaction conditions.

The reaction of different allylic chloromethyl ethers **1** with an excess of lithium (1:7 molar ratio; theoretical 1:2) and a catalytic amount of DTBB (1:0.05 molar ratio; 2.5 mol %) in THF at 0 °C for 1 h led, after hydrolysis with water, to the expected homoallylic alcohols **2** (Scheme 2 and Table 1). In the case of starting from α-substituted materials (**1c**, **1e** and **1g**), a ca. 1:1 molar ratio of the corresponding (*Z*/*E*)-alcohols **2** was obtained (NMR; Table 1, entries 3, 5 and 7, and footnote c).[20]

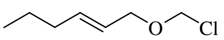
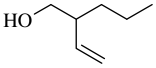
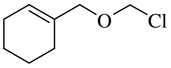
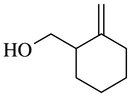
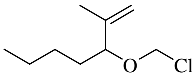
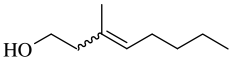
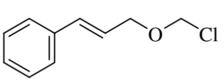
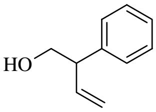
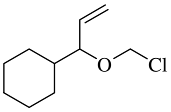
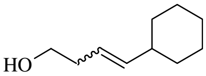
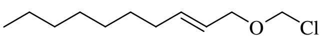
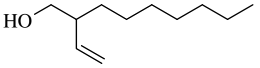
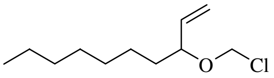
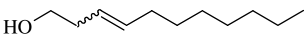
In the case of non-allylic chloromethyl ethers, such as the commercially available benzyl chloromethyl ether (**3**), the same reaction described in Scheme 2 led to a clean [1,2]-Wittig rearrangement, furnishing the corresponding 2-phenylethanol (**4**) as the only reaction product in 70% isolated yield (Scheme 3).[21]

Starting chloromethyl ethers **1** were easily prepared following two procedures: (a) reaction of the corresponding allylic alcohols with hydrogen chloride and trioxane in a benzene–toluene mixture at −10 °C (for compounds **1a**, **1f** and **1g**; 40–60% yield),[22] and (b) treatment of the same starting materials with paraformaldehyde and chlorotrimethylsilane in carbon tetrachloride at room temperature (for compounds **1b**–**e**; around 60% yield).[23,24]



Scheme 3. Reagents and conditions: (i) Li excess, DTBB (2.5 mol %), THF, 0 °C, 1 h; (ii) H_2O, 0 °C to rt.

Table 1. Preparation of homoallylic alcohols **2**

Entry	Starting material		Product[a]		
	Structure	No.	Structure	No.	Yield (%)[b]
1		**1a**		**2a**	82
2		**1b**		**2b**	78
3		**1c**		**2c**	60[c]
4		**1d**		**2d**	80
5		**1e**		**2e**	70[c]
6		**1f**		**2f**	81
7		**1g**		**2g**	75[c]

[a] All compounds **2** were >95% pure (GLC and/or 300 MHz ^1H NMR) and were fully characterised by spectroscopic means (IR, ^1H and ^{13}C NMR and MS).

[b] Isolated yield after vacuum distillation (Kugelrohr) based on the starting chloromethyl ether **1**.

[c] A ca. 1:1 mixture of (*Z*/*E*) diastereomers was obtained (NMR).

In conclusion, we have described herein the simplest way to perform the [2,3]-Wittig rearrangement from non-activated substrates by an arene-catalysed chlorine–lithium exchange starting from easily available allylic chloromethyl ethers.[25] This new and versatile methodology can be applied to the total synthesis of interesting naturally occurring complex molecules.[4]

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.06.160.

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24. Chloromethyl ethers **1** are stable compounds that can be kept for months at 0 °C, except compound **1b**, which begins to decompose after one month at the same temperature.
25. General procedure: To a suspension of lithium powder[26] (49 mg, 7 mmol) and DTBB (13 mg, 0.05 mmol) in THF (3 mL) was added the corresponding chloromethyl ether (1 mmol) at 0 °C. The resulting mixture was stirred for 1 h at the same temperature and then it was hydrolysed with water (5 mL) allowing the temperature to rise to room temperature. The resulting mixture was extracted with ether (3 × 5 mL), the organic layer dried with anhydrous $MgSO_4$ and evaporated (15 Torr). The resulting residue was purified by vacuum distillation in a Kugelrohr apparatus to give the corresponding homoallylic alcohols **2**. Yields are given in Table 1. Characterisation of compounds **2** was made by spectroscopic means (IR, ^{1}H and ^{13}C NMR and MS).
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