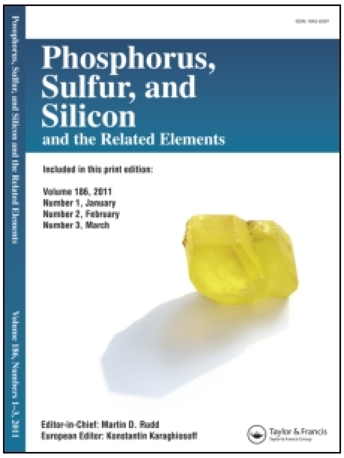

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IN-SITU SYNTHESES OF ALKYLLITHIUM COMPOUNDS UNDER ULTRASONIC IRRADIATION

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The syntheses of organometallics such as alkyllithium compounds are performed. Furan and thiophene derivatives were prepared. Parameters which influence the yield have been optimized. The more important were the physical states of lithium and its sodium content and the nature of the substrate.

INTRODUCTION

Organolithium compounds are widely used in organic syntheses because of the ionic character of the Li-C bond. The bond polarity $Li^{\delta+}$ $C^{\delta-}$ leads to carbanionic character which means behavior as base or nucleophile like Grignard reagents. Thus many alcohols can be obtained by addition of alkyllithium to C-O double bonds.

However organoalkali compounds such as alkyllithium are air and moisture sensitive and therefore require to be handled under dry inert atmosphere and in dry solvents.

To avoid these difficulties we attempted to generate alkyllithium in-situ by using the couple alkylhalide / lithium. In fact metallic lithium reacts with oxygen slower than alkyllithiums and is easier to handle.

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As metallic lithium is not soluble in the solvents used we decided to use the molecular activation by ultrasound which is suitable for heterogenous reaction media.

Ultrasound by its mechanical effect corrodes the metal and prevents it from being coated by products and impurities. Its electrochemical effect helps formation of radical anion.

As reactions involving alkali and alkaline earth metals proceed by a single electron transfer mechanism, they are expected to be sensitive to sonication[1]. The first step of such a process involves a transfer of an electron from the metal to the carbon halogen bond.

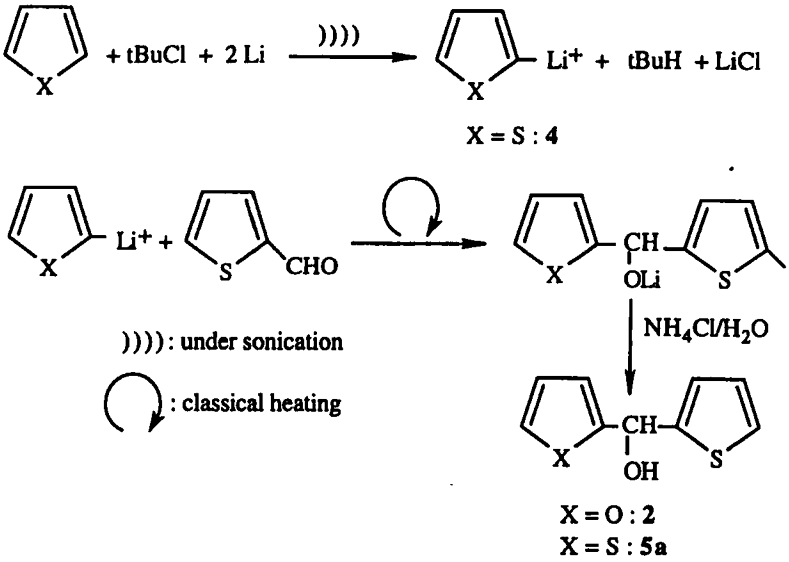
The radical ion formed is not sensitive to ultrasound but the rate of its cleavage is a function of temperature[3]. The resulting radical R can get an electron from the remaining metal to give the organolithium R^-Li^+.

We focused our work on the preparation of butyllithium derivatives which are the most used among organometallic compounds. Classical syntheses of these compounds require complicated and lasting procedures. Moreover temperature adjustements are necessary[4]. These syntheses become simple, fast and efficient under ultrasound irradiation. The yields depend on the nature of the starting materials. As alkylhalides are concerned alkylchlorides give the best yields. On the other hand the yields depend on the kind of lithium for a given substrate[6]. The present survey begins with optimization of the reaction of a butyllithium with furan under ultrasonic irradiation. Thereafter attempts will be made to optimize reactions involving thiophene. The influence of parameters such as lithium quality, halogenoalcane and electrophilic nature will be assessed.

RESULT AND DISCUSSION

Reaction of furan

The reaction involving furan is shown in scheme 1. Furan, t-butyl chloride and lithium are mixed prior to ultrasonic irradiation. Furan is in three fold excess relative to t-butyl chloride. It will be readily removed by evaporation for its boiling point is low (e_b: 32°C). A flat bottom flask is used for better propagation of ultrasonic waves. Under ultrasound t-butyllithium forms and reacts immediately with furan by abstracting the hydrogen atom at the α position relative to oxygen.



SCHEME 1 Reactions with furan or thiophene

Two physical states of lithium were used: wire and sand (table I). Lithium wire with 1 % sodium content purchased from aldrich is used in two experiments. In the first it is used as purchased while in the second it is flattened and washed with absolute ethanol in order to remove nitrides which coat it. In both cases the reaction does not go to completion. The first experiment does not afford the expected product in contrast to the second experiment which yields 10 % of it. The results can be explained by two facts. First, as the metal becomes flat its contact surface with waves increases. Secondly, ethanol removes the nitrides coats from the metal surface allowing it to react faster.

The expected product 2 – (2′.thienylhydroxymethyl) furan is a carbinol which is unstable in acidic media. Thus it rearranges to cyclopentenone. The by-product **3** is 2-hydroxymethyl furan. In a third experiment lithium sand with 2 % sodium content was made to react with furan in a flat bottom flask under ultrasound. The results were better than for the former experiments but we could not determine accurately the yield of pure product as it was difficult to separate it from the by products. Therefore thiophene was chosen as the substrate for another optimization.

TABLE I Physical states of lithium with furan

Lithium species	*Sonication time*	*Products*	*Yield*[a] *(%)*
Lithium wire used as purchased	3 H	Expected product **2**	0
		2-formylthiophene **1**	45
		2-hydroxymethylfuran **3**	5
Activated lithium wire	1 H 30	Expected product **2**	10
		2-formylthiophene **1**	22
		2-hydroxymethylfuran **3**	18
Activated lithium wire 1 % sodium content (aldrich)	1 H 30	Expected product **2**	10
		2-formylthiophene **1**	22
		2-hydroxymethylfuran	18
Lithium sand suspension in hexane 2% sodium content (Fluka)	0,25 h	Expected product **2**	38
		2-formylthiophene **1**	27
		2-hydroxymethylfuran **3**	3

a. The yield is determined by ^1H NMR integration. Zero denotes material not detectable.

Reaction of thiophene

Reaction of t-butyllithium with furan or thiophene always leads to ortholithiation relative to the heteroatom (scheme 1 x = s).

The reaction is faster (15 nm) when lithium sand is used (see table II). However the yield is low (44 %) because of the high content of sodium which does not seem to help reaction with thiophene. The highest yield is obtained when lithium wire is used. It will be selected for the other experiments.

The reaction is faster with t-butylchloride than with n-butylchloride (71 % yield in 45 min versus 45 % in 1h 45 min). This difference can be explained by the fact that t BuCl is more basic than n BuCl, so it abstracts the hydrogen from thiophene faster. On the other hand because of its bulkiness t-BuCl alkylate thiophene slower than n-BuCl. Thus the yield of the expected product must be high with respect to t-BuCl.

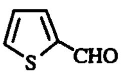
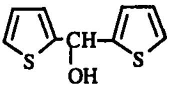
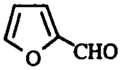
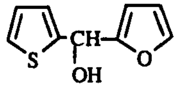
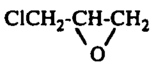
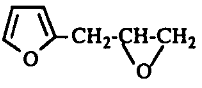
TABLE II Physical states of lithium with thiophene

Lithium species	*Sonication time*	*Yield of isolated product %*
Activated lithium wire 1% sodium content	45 min	71,5
Lithium sand suspension in hexane 2 % sodium content	15 min	44
Activated lithium bar 1% sodium content	45 min	54

Therefore t-BuCl will be used to assess the influence of the electrophile.

It can be inferred from table III that the best yield is obtained with 2-formyl thiophene (71,5 %). In conclusion, we noticed that alkyllithiums could be prepared in good yield under ultrasonic irradiation. The yield depends on several parameters. Some are difficult to control, for example the energy input in the reaction media under ultrasonic irradiation. On the other hand the physical state of lithium and it's sodium content is highly important. This remark is frequently reported but never explained. The nature and the amount of alkylhalide used are also determinant. Systematic optimization of these parameters is necessary for each substrate.

TABLE III Influence of the electrophile with thiophene

Electrophile	*time of sonification*	*Product*		*yield %*
	45 min		**5a**	71,5
	45 min		**2**	58
	45 min		**5b**	30

EXPERIMENTAL SECTION

General procedure

The source of ultrasound is a 5,75 1 ultrasonic cleaning bath (kery ultrasound). It is a 38 KHz, 1–2 W/cm^2 apparatus with acoustic threshold of 85 dB. The bath is thermostated at 18°C by using water through copper coils PMR (80 MHz) and CMR (62,89 MHz) were taken on Bruker AC80 and AC250 instrument respectively. Infrared spectra were recorded on a Perkin Elmer 257 spectrometer. Elemental analyses were performed by the microanalysis service of the "Ecole Nationale Supérieure de Chimie de Toulouse".

Synthesis of 2 (2′-thienylhydroxymethyl) furan: 2

3 to 5 ml of a 15 % suspension of lithium in hexane is introduced to a flat bottom flask filled with argon.

Hexane is evaporated through a vacuum line to get the exact weight of lithium (eg: 0.042 g; 0.006 mol.: 2 eq.). Then 10 mL of anhydrous THF is added to it; subsequently 0.009 mol of furan in 5 ml of THF and 0.003 mol of t-butylchloride in 5 mL of THF are added dropwise. The mixture is sonicated until all the lithium has disappeared (ca. 15 min). Afterwards 2-formyl thiophene (0.003 mol.) is added to the reaction medium which is then stirred classicaly for 1 hour. The mixture is treated with 20 mL of a saturated solution of ammonium chloride in water. After separation the aqueous phase is extracted with methylene chloride. The organic phase is dried over magnesium sulfate and the solvents are evaporated to give an oily residue Yield 38 %, IR (meat): 3415 cm^{-1} (OH); PMR ($CDCl_3$) = 3.05 (s, 1H, OH); 6.03 (s, 1H, CHOH); 6.28.6.33 (m, 2H, H_3H_4 fur.); 6.94–7.00 (m, 2H, H_3, H_4, thio), 7–23–7.31 (m, 1H, H_5fur.); 7–37 – 7–40 (m, 1H, H_5, Thio).

Synthesis of 2 – lithiothiophene: 4

0.033 g (0.00 48 mol) of lithium wire (1 % sodium content) is flattened under an inert atmosphere and washed with absolute ethanol. Then anhydrous THF (10 ml) is added to the reaction flask previously filled with argon. Then a solution of 0.002 mol of thiophene in 5 ml of THF and a solution of 0.0024 mol of t-butyl chloride in 5 ml of THF are added dropwise. The mixture is sonicated up to complete disappearance of lithium (ca. 45 min).

Synthesis of compound 5a and 5b

To the previous mixture containing **4** is added 0.002 mol of the electrophile leading to **5a** or **5b**. Then, the mixture is stirred mechanically 1 hour and 2h for **5a** and **5b** respectively. It is subsequently treated with a saturated solution of NH_4Cl in water (20 ml). The aqueous phase is extracted with CH_2Cl_2. The organic layer is dried with $MgSO_4$ and evapored to dryness. The oily residue is chromatographed on a silica column with a mixture of cyclohexane and ethyl acetate (9/1) to yield the pure product.

2- (2′ – thienylhydroxymethyl) thiophene: 5a

yield: 71,5 %; IR (neat): 3414 cm^{-1} (OH), PMR ($CDCl_3$): 2.85 (s, 1H, OH); 6.26 (s, 1H, CHOH); 6.26 (s, 1H, CHOH); 6.90–7.01 (m, 4H, H_3 H_4 (thio); 7.24 (dd, 2H, $^4J = 1.8$, $^3J = 4.5$, H_5 thio). NMR ^{13}C ($CDCl_3$): 68.5 (CHOH); 125.1 (CH thio); 125.6 (CH thio); 126.7 (CH thio); 147.2 (C thio). Anal. Calc for $C_9H_8OS_2$ C, 55.07; H, 4.11; Found C, 55.29 H, 3.94

3-(2′-thienyl) 1,2-epoxypropane 5b

yield: 30 %; IR (neat): 3490 cm^{-1}(OH); PMR ($CDCl_3$): 2.54–3.2 (m, 5H, CH_2, CH); 6.90–7.0 (m, 2H, H_3, H_4, thio); 7.13 – 7.21 (m, 1H, H_5 thio); NMR ^{13}C ($CDCl_3$): 33.0 (CH_2); 47.0 (CH_2O); 52-2 (CH); 124.3 (CH thio); 125.8 (CH thio); 127.0 (thio); 138.9 (C thio). Anal. Calc for $C_7H_8O_5$ C, 59.96 H, 5.75; Found C, 60.30; H, 5.89

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