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Dichloromethane as a Source of the CH_2^{2-} Synthon: A Combination of an Arene-Catalysed Lithiation and a Barbier-Type Reaction

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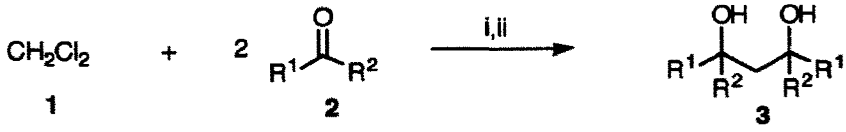
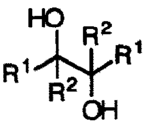
Abstract: The reaction of dichloromethane **1** with an excess of lithium powder (1:7 molar ratio) and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (5 mol %) in the presence of a carbonyl compound **2** (1:2 molar ratio) in tetrahydrofuran at -40°C yields, after hydrolysis, the corresponding 1,3-diols **3** in moderate yields. The process can be also applied to more complicated *gem*-dichloro derivatives such as 7,7-dichlorobicyclo[4.1.0]heptane **6** or methyl dichloromethyl ether **9**.

Organolithium compounds are ones of the most powerful reagents in synthetic organic chemistry above all in carbon-carbon bond formation processes by reaction with electrophilic reagents[1]. Among these type of intermediates the corresponding geminal dilithium compounds [2] are very rare and unstable species. For instance, the preparation of dilithiomethane[3,4], the simplest *gem*-dilithioalkane, has been carried out (a) by pyrolysis of methyllithium[5] or (b) by mercury-lithium transmetallation[6]. The direct replacement of halogen (bromine[7] or chlorine[8]) with lithium, the most useful method for the synthesis of organolithium compounds, is not applicable, in general, to the synthesis of *gem*-dilithiated molecules due to the α-elimination of lithium halide after the first step giving a carbene, being this process faster than the second lithiation[7-9]. On the other hand, we have recently discovered[10] that the use of a catalytic amount of an arene in lithiation processes with lithium powder allows the preparation of very reactive functionalised organolithium intermediates[11] under very mild reaction conditions. This procedure works nicely not only for chlorine-lithium exchange[12] but also in other lithiation processes[13]. The recent report of Klumpp *et al.*[14] on reduction of geminal dihalocyclopropanes with lithium 4,4-di-*tert*-butylbiphenyl prompted us to communicate in this paper our findings on the arene-catalysed dilithiation of dichloromethane and other *gem*-dichloro derivatives in a Barbier-type reaction.

The reaction of dichloromethane **1** with an excess of lithium powder (1:7 molar ratio) and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (5 mol %) in the presence of a carbonyl compound **2** (1:2 molar ratio) in tetrahydrofuran at -40°C led, after hydrolysis, to the corresponding 1,3-diols **3** (Scheme 1 and Table 1). In the case of using an aldehyde as the carbonylic component the corresponding diastereoisomeric mixture was separated by flash chromatography and each diastereoisomer analysed by 300 MHz ^1H NMR in order to assign the corresponding stereochemistry (Table 1, entries 1-3). All reactions gave a small amount (<15%) of the corresponding pinacoline-type compounds **4**, except in the case of using isopentanal in which a 31% of pinacol was isolated; separation of compounds **3** and **4** was carried out by careful flash chromatography. When cyclopentanone or cyclohexanone were used as carbonyl substrates 1-methylcycloalkanes **5d,e** were detected by GLC in 15 and 25% yield, respectively (Table 1, entries 4 and 5).



Scheme 1. ***Reagents and conditions*:** i, Li powder (1:7 molar ratio), 4,4'-di-*tert*-butylbiphenyl cat. (5 mol %), THF, -40°C; ii, H_2O.



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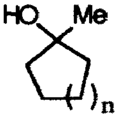


5d : n=1
5e : n=2

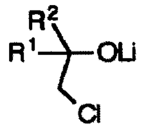
Table 1. Preparation of 1,3-Diols **3**

	Carbonyl compound		Product 3[a]			
Entry	R^1	R^2	no.	yield (%)[b]	*anti/syn* ratio[c] [m.p.(°C)][d]	$\delta_H[\delta_C](OCCH_2CO)$[e] *anti/syn*
1	H	Pr^i	**3a**	52	5 [79-80]/2 [oil]	1.60[36.35]/1.41,1.59 [35.85]
2	H	Bu^i	**3b**	35	3 [111-112]/2 [oil]	1.58[43.3]/1.43, 1.46[44.0]
3	H	Bu^t	**3c**	61	3 [149-151]/2 [98-101]	1.42[32.6]/1.27, 1.72[30.95]
4	$-(CH_2)_4-$		**3d**	27 (15)[f]	[80-82]	1.94[48.8]
5	$-(CH_2)_5-$		**3e**	25 (25)[f]	[100-101]	1.65[49.95]

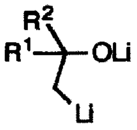
[a] All isolated compounds **3** were >95% pure (GLC and 300 MHz ^1H NMR) and were fully characterised by spectroscopic methods (IR, ^1H and ^{13}C NMR, and MS). [b] Isolated yield of pure compounds after flash chromatography (silica gel, hexane/ethyl acetate). [c] Diastereoisomers ratio deduced after isolation of each component by flash chromatography; the stereochemistry was deduced from 300 MHz ^1H NMR data. [d] From chloroform. [e] In deuteriochloroform. [f] GLC yield of the corresponding 1-methylcycloalkanol **5d,e**.

From a mechanistic point of view we think that after the first lithiation a carbenoide of the type **I** is obtained[15], which in the presence of the carbonyl compound **2** undergoes mainly a rapid condensation (instead of the corresponding α-elimination reaction) to give a chlorohydrine salt of the type **II**[16]. The further lithiation of the intermediate **II** affords a very reactive β-alkoxide organolithium species **III**[17], which in the presence of the electrophile yields the dialkoxide **IV** and, after hydrolysis, the obtained products **3**. The transformation **III**→**IV** is a crucial step due to the great instability of intermediate **III**: in absence of the electrophile it decomposes even at -78°C to give either proton abstraction[18] (yielding compounds of the type **5**) or β-elimination of lithium oxide (giving an olefin)[19]. The extreme instability of the species **I** and **III** can explain the modest yields in the obtained 1,3-diols **3** (Table 1).

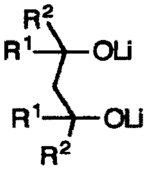
I



II

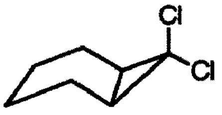


III

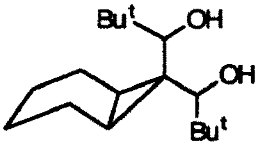


IV

In order to extend the methodology here described we tried preliminary the same process using other *gem*-dichloro derivatives. Thus, using the starting material **6**[20] and pivalaldehyde, a mixture of compounds **7** (25%; *ca.* 2:1 diastereoisomer mixture) and **8** (37%; *ca.* 3:1 diastereoisomer mixture) was obtained in 62% global yield. As expected, substitution on the carbanionic center makes it more unstable.



6



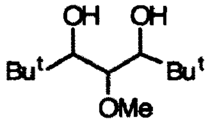
7

8

Finally we applied the same reaction to commercially available methyl dichloromethyl ether **9**, which reacted with pivalaldehyde under the same reaction conditions as above the expected mixture of diastereoisomers **10** (10:3:1 ratio) was isolated in 41% yield.

$MeOCHCl_2$

9



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From the results described in this communication we conclude that dichloromethane can be used as a source of the synthon CH_2^{2-} in a Barbier-type reaction with carbonyl compounds. This methodology can be applied to other *gem*-dichloro derivatives; studies are in due course in order to stablish the scope of this methodology.

In a *typical reaction* to a blue suspension of lithium powder (*ca.* 100 mg, 14 mmol) and 4,4'-di-*tert*-butylbiphenyl (26 mg, 0.1 mmol, 5 mol %) in THF (5 ml) was slowly added a solution of dichloromethane (2 mmol) and the corresponding carbonyl compound (4 mmol) in THF (5 ml) during *ca.* 45 min at -40°C. After the addition the corresponding mixture was stirred for 10 additional min at the same temperature. Then it was hydrolysed with water (4 ml), neutralised with 2 N hydrochloric acid and extracted with diethyl ether (2x10 ml). The organic layer was dried with anhydrous Na_2SO_4 and evaporated (15 Torr). The resulting residue was purified by flash chromatography (silica gel, hexane/ethyl acetate) to give the expected products **3**[21].

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