Pergamon

Tetrahedron Letters 43 (2002) 3463–3465

TETRAHEDRON LETTERS

Improved addition of phenyllithium to hindered ketones by the use of non-polar media

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Received 10 January 2002; accepted 26 March 2002

Abstract—The use of a non-polar medium at room temperature is an efficient, cheap and easy way to improve the low reactivity of six hindered ketones towards phenyllithium.

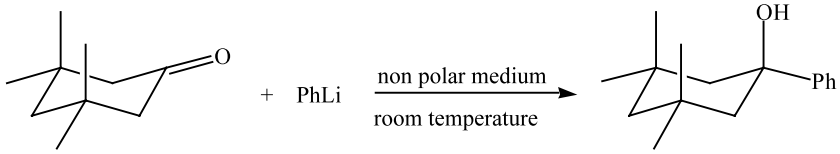
We have recently shown that the addition of aryllithium derivatives to a hindered 11-keto-steroid could be easily achieved by using a non-polar medium (toluene or a toluene–diethyl ether mixture).[1] Such a solvent seems to favor addition versus enolisation when working on a hindered and enolisable ketone as this steroid. However, the results described in the literature concerning the addition of phenyllithium (PhLi) to this peculiar kind of ketones show that this addition is usually performed in ethers (diethyl ether or THF) with moderated yields. Even if these yields could be increased with phenylmagnesium bromide[2–5] with or without activation by cerium chloride[2,6–8] no mention was found of the use of a solvent effect to solve this problem.

The ketones used for this study are (−)-fenchone **1**, (−)-menthone **2**, (+)-camphor **3**, 3,3,5-trimethylcyclohexanone **4**, 3,3,5,5-tetramethylcyclohexanone **5** and 2,4-dimethylpentan-3-one **6**. Ketones **2** and **3** are quite hindered and enolisable, **1** is non-enolisable, **4** and **5** present one or two axial methyls similar to those of some androstanes and could be used as models for a subsequent work. The carbonyl compounds **1**–**5** can give 2 epimers. The reaction is described for the ketone **5** as an example (Scheme 1) and the results are gathered in Table 1.

The conditions described for addition of PhLi in diethylether or THF generally provide modest yields. However, in all cases the yield of the addition was improved by using PhMgBr in the presence of cerium chloride (addition to fenchone,[8] menthone[2] and camphor[2]). It should be noted that cerium chloride may modify the stereochemistry of the addition[8] (addition of PhMgBr to fenchone).

It thus appeared that a non-polar solvent (such as toluene or toluene/diethyl ether), at room temperature, provides high to quantitative addition of PhLi to ketones **1**, **2** and **6**. The conditions chosen were those which allowed the best yields.

Good yields were also obtained with the ketones **4** and **5** (Table 1, entry 4 and 5) but ketone **3** gave only a lower result (Table 1, entry 3). In this case we observed the reversibility of the addition. However, the addition occurs, in all cases, in a stereospecific manner; the alcohol obtained is the product of addition to the less-hindered side. It is thus not only possible but even



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Scheme 1.

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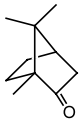
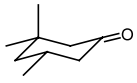
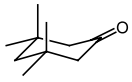
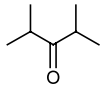
0040-4039/02/$ - see front matter
PII: S0040-4039(02)00597-X

Table 1. Addition of PhLi to hindered ketones: literature and experimental results

Entry	Ketone	Literature results		Yield (%)	Ref.	Experimental results[a]		Yield (%)[b]
		Solvent	Isomer percentage (%)			Solvent	Isomer percentage (%)	
1	 **1**	Et_2O	OH-*endo* (100)	35–64	9,10	Toluene	OH-*endo* (100)	96
2	 **2**	Et_2O	OH-*ax* (100)	31	10	Toluene	OH-*ax* (100)	83
3	 **3**	Et_2O	OH-*exo* (100)	58	11	Toluene/Et_2O 6:4	OH-*exo* (100)	45
4	 **4**	–	–	–	–	Toluene	OH-*ax* (100)	71
5	 **5**	–	–	–	–	Toluene/Et_2O 6 :4	OH-*ax* (100)	63
6	 **6**	–	–	–	–	Toluene	–	90

[a] All examples except entry 3 were carried out as follows: the ketone was dissolved in the selected non-polar solvent under argon. Commercial PhLi was then added slowly by syringe and the mixture stirred at rt for 2–4 h. For entry 3, PhLi was added at –20°C, and the mixture stirred at –20°C for 2 h then allowed to warm to rt. The configuration of the adducts was established by ^{13}C NMR according to literature methods.
[b] As an isolated product after purification by column chromatography.

advantageous to use a non-polar medium for the addition of PhLi to hindered ketones.

The good reactivity of aryl organolithium compounds with hindered ketones in non-polar media and at room temperature is probably attributable, amongst other things, to changes in the mechanism and in the way the organolithium compounds associate.[1]

In conclusion, good levels of selective addition of phenyllithium onto various hindered ketones can be obtained in non-polar media at room temperature. This method is thus inexpensive, safe and easy. An in-depth study is underway to take advantage of the considerable potential of this new and surprisingly simple and efficient approach.

Moreover, the adducts resulting from the addition of organolithium compounds to some of the ketones presented here (fenchone, menthone and camphor) are often used as chiral inducers[3,12] and the synthesis of derivatives of this type, by a simple and stereospecific method such as the one reported here, offers a significant advantage.

Acknowledgements

The authors wish to thank B. McGlinchey for her assistance in translating the manuscript.

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