Pergamon

Tetrahedron Letters, Vol. 38, No. 4, pp. 687-690, 1997
Copyright © 1997 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02393-3

Lithiated Benzyllithiums from Chlorobenzyl Chlorides by a DTBB-Catalysed Lithiation

Cecilia Gómez, Fernando F. Huerta and Miguel Yus*

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Apdo. 99, E-03080-Alicante, Spain

Abstract: The reaction of 2-, 3- or 4-chlorobenzyl chlorides (**1a-c**) with an excess of lithium and a catalytic amount of DTBB (7 mol%) in the presence of different electrophiles [Pr^{i}CHO, Bu^{t}CHO, Et$_2$CO, (CH$_2$)$_5$CO, PhCOMe, Me$_3$SiCl] in THF at -50°C leads after hydrolysis with water, to the expected dioles or disilylated compounds **2aa-2cf**. © 1997, Elsevier Science Ltd. All rights reserved.

The preparation of benzyllithium from the corresponding benzylic halides and lithium does not present synthetic interest because the main process is the formation of the corresponding Wurtz coupling product, that is 1,2-diphenylethane.[1] Some alternatives to overcome this problem are: (a) direct deprotonation of toluene, which needs the use of a co-reactant such as an alkoxide or an amine leading to the corresponding "mixed" carbanions or the organolithium-amine complex, respectively;[1,2] (b) mercury-lithium transmetallation;[3] (c) lithiation of benzyl mesylates.[4] Another possibility of using halides would be a Barbier-type process,[5] carrying out the lithiation reaction in the presence of the electrophile but large quantities of 1,2-diphenylethane are found among the reaction products in all cases,[6a] except when an excess of lithium-naphthalenide is used as the lithiation reagent with benzyl bromide as the substrate.[6b-d] On the other hand, in the last few years we have developed a methodology, which consists in the use of an arene [usually naphthalene or 4,4'-di-*terc*-butylbiphenyl (DTBB)] as catalyst in the lithiation process.[7] Applying this procedure, in a two-step reaction (lithiation followed by reaction with the electrophile) or under Barbier-type reaction conditions (lithiation in the presence of the electrophile), new ways for organolithium compounds starting from non-halogenated materials[8] or heterocyclic substrates,[9] as well as highly reactive functionalised organolithium compounds[10,11] or polylithium systems[12] have been developed in our laboratory. In this paper we apply the above mentioned methodology to the DTBB-catalysed lithiation of chlorobenzyl chlorides under Barbier-type reaction conditions.

As a preliminary study we considered the reaction of benzyl chloride with an excess of lithium in the presence of a catalytic amount of DTBB (7 mol%) in THF at -50°C: After 1h at the same temperature the starting material was consumed but, after hydrolysis with water, 1,2-diphenylethane was the only reaction product isolated in high yield (46%; theoretical 50%). However, when the same process was carried out in the presence of cyclohexanone during the lithiation step, the expected condensation product, 1-benzylcyclohexanol was isolated in 76% yield.[13]

The reaction of chlorobenzyl chlorides **1** with different electrophiles [Pr^iCHO, Bu^tCHO, Et_2CO, $(CH_2)_5CO$, PhCOMe, Me_3SiCl] under the above described reaction conditions (Barbier-type) gave the expected diols or disilylated compounds **2** (Scheme 1 and Table 1). So, comparising reactions with the starting material **1a** and isobutyraldehyde or cyclohexanone were carried out in the absence of the arene catalyst under ther same reaction conditions, the yields obtained being substantially lower (Table 1, entries 1 and 4, respectively, and footnote c). A final remark concerns the stereochemistry of products **2** when prochiral carbonyl compounds were used as eletrophiles: in these cases a *ca.* 1:1 diastereoisomers mixture was obtained (GLC and/or NMR; Table 1, footnote d)

In the case of the starting material **1** the two-step reaction failed. Thus, the DTBB-catalysed lithiation of compound **1a** under the above reactions conditions followed by reaction with cyclohexanone yielded almost quantitatively 1,2-diphenylethane, resulting from the corresponding Wurtz coupling process followed by chlorine/hydrogen exchange during the final hydrolysis in the presence of an excess of lithium.[14]

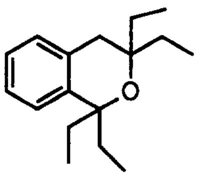
1a: 1,2-
1b: 1,3-
1c: 1,4-

2aa : E = Pr^iCHOH
2ab : E = Bu^tCHOH
2ac : E = Et_2COH
2ad : E = $(CH_2)_5COH$
2ae : E = PhC(OH)Me
2af : E = Me_3Si
2bb : E = Bu^tCHOH
2bc : E = $(CH_2)_5COH$
2bf : E = Me_3Si
2cb : E = Bu^tCHOH
2cc : E = $(CH_2)_5COH$
2cf : E = Me_3Si

Scheme 1. *Reagents and conditions:* i, Li/DTBB cat. (7 mol %), E^+= Pr^iCHO, Bu^tCHO, Et_2CO, $(CH_2)_5CO$, PhCOMe, Me_3SiCl, THF, 50°C; ii, H_2O, -50 to 20°C.

To demonstrate the utility of 1,5- diols **2a** derived from the starting material **1a**, compound **2ac** was submitted to cyclisation under acidic conditions. Treatment of this material with concentrated hydrochloric acid in diethyl ether at room temperature overnight yielded the expected pure heterocycle **3ac** in almost quantitative crude yield.

In conclusion, we have reported here the *in situ* generation of lithiated benzyllithium which can be trapped carriying the reaction in the presence of an electrophile, permiting diols or disilylated compounds **2** to be prepared in one-step.



3ac

Table 1. Preparation of Compounds 2

Entry	Starting material	Electrophile E^+	Product[a] No.	Product[a] Yield (%)[b]
1	**1a**	$\mathrm{Pr^iCHO}$	**2aa**	38 (15)[c]
2	**1a**	$\mathrm{Bu^tCHO}$	**2ab**	57[d]
3	**1a**	$\mathrm{Et_2CO}$	**2ac**	83
4	**1a**	$\mathrm{(CH_2)_5CO}$	**2ad**	64 (43)[c]
5	**1a**	PhCOMe	**2ae**	48[d]
6	**1a**	$\mathrm{Me_3SiCl}$	**2af**	53
7	**1b**	$\mathrm{Bu^tCHO}$	**2bb**	40[d]
8	**1b**	$\mathrm{(CH_2)_5CO}$	**2bc**	60
9	**1b**	$\mathrm{Me_3SiCl}$	**2bf**	78
10	**1c**	$\mathrm{Bu^tCHO}$	**2cb**	58[d]
11	**1c**	$\mathrm{(CH_2)_5CO}$	**2cc**	74
12	**1c**	$\mathrm{Me_3SiCl}$	**2cf**	83

[a] All products **2** were >95% pure (GLC) and were fully characterised spectroscopically (^{1}H, ^{13}C-NMR, and MS). [b] Isolated yield after recrystallisation or column chromatography (silica gel, hexane/ethyl acetate) based on the starting material **1**. [c] Isolated yield for the non-catalysed reaction. [d] A *ca.* 1:1 diastereomers mixture (GLC and/or NMR) was obtained.

Typical procedure. To a green suspension of lithium (200 mg) and DTBB (80 mg) in THF (5 ml) cooled at -50°C was slowly added (*ca.* 1 h) a mixture of the starting dichlorinated material **1** and the corresponding electrophile (4 mmol) in THF (5 ml). After 10 min stirring at this temperature the reaction mixture was hydrolysed with water (5 ml) and extracted with ethyl acetate (3x10 ml). The organic layer was dried over anhydrous $\mathrm{Na_2SO_4}$ and the solvents were removed *in vacuo* (18 Torr). The residue obtained was then purified by column chromatography (silica gel, hexane/ethyl acetate) or recrystallised (hexane/ethyl acetate) to yield pure products **2**.

ACKNOWLEDGEMENTS

This work was supported by the DGITYC (PB94-1514). F. F. H. thanks ASAC PHARMACEUTICAL INTERNATIONAL for a grant.

REFERENCES AND NOTES

1. See, for instance: Wakefield, B. J. *Organolithium Methods*; Academic Press: London, 1988.
2. Akiyama, S.; Hooz, J. *Tetrahedron Lett.* **1973**, 4115-4118.
3. Schlenk, W.; Holtz, J. *Ber. Dtsch. Chem. Ger.* **1917**, *50*, 262-274; *Chem. Abstr.* **1917**, *11*, 2796.
4. Guijarro, D.; Mancheño, B.; Yus, M. *Tetrahedron* **1992**, *48*, 4593-4600.
5. For a monograph see: Blomberg, C. *The Barbier Reaction and Related One-step Process*; Springer-Verlag: Berlin, 1993.
6. (a) Reference 5, p. 79. (b) Reference 5, p. 83. (c) Alternatively benzyl methyl ether can be used as starting material to generate benzyllithium under Barbier-type reaction conditions: reference 5, p. 79. (d) For a recent paper on the use of 2-bromobenzyl bromide for benzyl coupling by bromine/lithium exchange, see: Warren, S.; Wyatt, P.; McPartlin, M.; Woodroffe, T. *Tetrahedron Lett.* **1996**, *37*, 5609-5612.
7. (a) For the first account on this reaction, see: Yus, M.; Ramón, D. J. *J. Chem. Soc., Chem. Commun.* **1991**, 398-400. (b) For a recent review, see: Yus, M., *Chem. Soc. Rev.* **1996**, 155-161.
8. For the last paper on this topic from our laboratory, see: Bachki, A.; Foubelo, F.; Yus, M., *Tetrahedron: Asymmetry* **1996**, *7*, 2997-3008.
9. For the last paper on this topic from our laboratory, see: Almena, J.; Foubelo, F.; Yus, M., *Tetrahedron* **1996**, *52*, 8545-8564.
10. For a review, see: Najera, C.; Yus, M. *Trends Org. Chem.* **1991**, *2*, 155-181.
11. For the last paper on this topic from our laboratory, see: Ramón, D. J.; Yus, M., *Tetrahedron* **1996**, *52*, 13739-13750.
12. For the last paper on this topic from our laboratory, see: Guijarro, A.; Yus, M., *Tetrahedron* **1996**, *52*, 1797-1810.
13. As a comparison, surprisingly the same process carried out in absence of the arene catalyst also works giving the expected product in even better yields (>90%). One possible explanation for this apparently strange behaviour could be that the starting material (benzyl chloride), the reaction product (1-benzylcyclohexanol) or other aromatic species generated during the reaction (benzyllithium, 1,2-diphenylethane, ...) could act as electron carrier catalysts. One proof of that would be that during the non-catalysed reaction, after an induction time of *ca.* 20 min, a slight red-brown colour is developed, which is, in general, typical whenfor radical-anion species are generatedin this type of processes. We thank the referee for calling our attention on a justification for the non-catalysed reaction.
14. Under these reaction conditions (-50°C) the nuclear chlorine/lithium exchange works very slowly so, for short reaction times (*ca.* 20 min), no aromatic lithiation was observed. For the two-step process we never found reaction products in which the electrophile is attached to the aromatic ring.

(*Received in UK* 18 *November* 1996; *revised* 3 *December* 1996; *accepted* 6 *December* 1996)