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Naphthalene-Catalysed Reductive Opening of Aziridines with Lithium: A Direct Preparation of *N*-Lithio-2-lithioalkylamines

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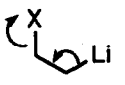
Abstract: **The reductive opening of *N*-phenylaziridine (1) with an excess of lithium powder in the presence of a catalytic amount (5 molar %) of naphthalene at -78°C leads to the corresponding *N*-lithio-2-lithioethylamine (2), which by reaction with different electrophiles (water, deuterium oxide, dimethyl disulphide, pivalaldehyde or cyclohexanone) affords the expected products 3. The same process aplied to *N*-cyclohexylaziridine fails. The reaction also works with the chiral aziridine 4 yielding the chiral deuteriated amine 5, through the corresponding chiral dianionic intermediate.**

β-Functionalized organolithium compounds[1] of the type **I** (X=Hal, OR, NR_2, ...) are very unstable species, which undergo spontaneously β-elimination to yield olefins[2], even at very low temperatures. In the last decade we have studied the preparation and synthetic applications of species of the type **II**, in which the existence of a negative charge on the heteroatom inhibits the β-elimination process at low temperature, so carbanions of this type have found synthetic use for the preparation of polifunctionalized compounds[1]. Two different methods have been employed for the preparation of the corresponding d^2-reagents[3] of the type **III**: (a) mercury-lithium transmetallation from the adequate aminomercurials **IV**[4]; (b) chlorine-lithium exchange from the corresponding β-chloroamides **V** with lithium naphthalenide[5], in both cases at -78°C and previous *N*-deprotonation with an alkyllithium reagent (Scheme 1). However, the method b fails using β-chloroamines **VI** as starting materials, because after the first deprotonation the formation of the corresponding aziridine **VII** takes place even at -78°C and this system does not suffer reductive opening by means of the lithio-arene[6]. By contrast, the low temperature lithio-arene reductive opening of epoxides have been used for the preparation of intermediates of the type **II** with X=O[7]. On the other hand, we have recently reported that the use of lithium powder and a catalytic amount of an arene -naphthalene being the most generally used[8]- is more powerful and effective than the corresponding lithio-arene in different lithiation reactions, above all at low temperature[9]. In the present paper we describe for the first time the naphthalene-catalysed reductive opening of aziridines using lithium powder as lithiating agent.



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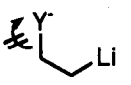

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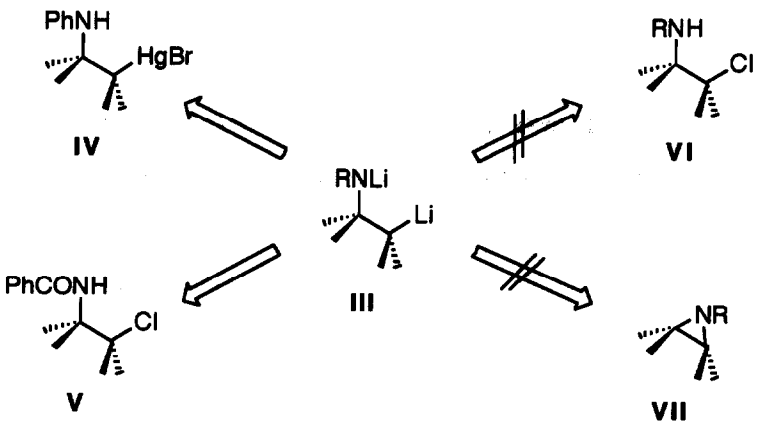
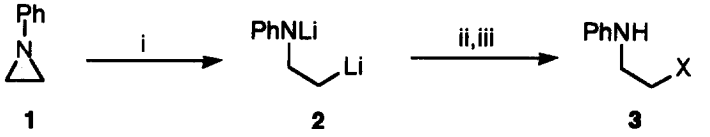


Scheme 1.

The reaction of *N*-phenylaziridine **1**[10] with an excess of lithium powder and a catalytic amount of naphthalene (5 mol %) in THF at -78°C led to a solution of the dianion **2**, which by treatment with different electrophiles such as water, deuterium oxide, dimethyl disulphide, pivalaldehyde or cyclohexanone afforded, after hydrolysis, the expected products **3** (Scheme 2 and Table 1). The lithiation step has to be carried out at low temperature in order to avoid decomposition of the dianion **2** by proton abstraction from the reaction media[4]: when the temperature during the lithiation was allowed to rise to room temperature the only reaction product isolated was **3a**.



Scheme 2. *Reagents and conditions*: i, Li powder (5 eq), $C_{10}H_8$ cat. (0.05 eq), THF, -78°C, 6 h; ii, E^+=H_2O, D_2O, Me_2S_2, Bu^tCHO, $(CH_2)_5CO$ (1.1 eq), -78 to 20°C, 3 h; iii, H_2O.

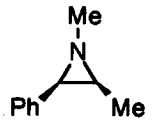
Alternatively the aziridine **1** can be generated *in situ* starting from the corresponding *N*-(2-chloroethyl)aniline[11]; thus, treatment of this material with *n*-butyllithium at -78°C in THF for 30 min led to the formation of the compound **1**[6] (>90% from GLC analysis), which after catalytic lithiation as above and final deuteriolysis yielded the expected product **3b** in 85% isolated yield (>95% deuterium from mass spectrometry).

Table 1. Naphthalene-catalysed opening of *N*-phenylaziridine **1** and reaction with electrophiles E+. Isolation of Compounds **3**

Entry	Electrophile E+	Product 3[a] no.	X	yield (%)[b]	R_f or m.p. (°C)[c]	lit.
1	H_2O	**3a**	H	93	0.30[d]	14
2	D_2O	**3b**[e]	D	89	0.30[d]	4a
3	Me_2S_2	**3c**	MeS	75	0.42[f]	4c
4	Bu^tCHO	**3d**	Bu^tCHOH	71	70-71	-
5	$(CH_2)_5CO$	**3e**	$(CH_2)_5COH$	66	128-129	-

[a] All products **3** were fully characterized [IR, ^1H and ^{13}C NMR, mass spectra and microanalysis (for **3d** and **3e**)]. [b] Isolated yield after column chromatography (silica gel) based on the starting aziridine **1**. [c] From pentane-dichloromethane. [d] Silica gel, hexane/ethyl acetate: 20/1. [e] >95% Deuterium from mass spectrometry. [f] Silica gel, hexane/ethyl acetate: 10/1.

We tried also the reductive opening of a *N*-alkylaziridine, but in this case the reaction failed. Thus, the naphthalene-catalysed lithiation of *N*-cyclohexylaziridine as it was above described (-78°C, 5 h) afforded, after hydrolysis, the starting material; even at room temperature the same result was obtained after 10 h. However, when a phenyl group is present in the aziridine ring the reductive opening takes place with *N*-alkylaziridines. We studied this reaction with the aziridine **4**[12] in order to prepare, at the same time, chiral dianions of the type **III** (Scheme 1). The catalytic lithiation of this starting material under the above described reaction conditions afforded, after deuteriolysis, the expected product **5**, arising from the corresponding most stable benzylic intermediate, in 77% isolated yield. Only one diastereoisomer of compound **5** is visible in ^{13}C NMR spectrum, but at this moment we do not know the actual stereochemistry at the C-2. Experiments are in due course in order to study not only the stereochemistry of the reaction but also its possible application to the synthesis of enantiomerically pure compounds (EPC-synthesis[13]) through the corresponding chiral dianions of the type **III**.



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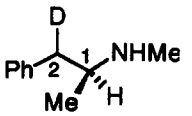

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In a *general procedure*, to a cooled (-78°C) green suspension of lithium powder (0.125 g, 18.0 mmol) and naphthalene (0.023 g, 0.18 mmol) in THF (10 ml) was added the corresponding aziridine (1.8 mmol) under argon and the mixture was stirred for 6 h at the same temperature. Then, the corresponding electrophile (2.0

mmol; 0.5 ml in the case of water or deuterium oxide) was added and the temperature was allowed to rise to 20°C during *ca.* 3 h. The resulting mixture was hydrolyzed with water, acidified with 3 M hydrochloric acid and extracted with dichloromethane. The aqueous layer was then basified with 2.5 M sodium hydroxide and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and evaporated (15 Torr). The resulting residue was purified by column chromatography (silica gel; hexane/ethyl acetate) and/or recrystallized (Table 1) to yield pure products **3** or **5**.

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References and Notes

1. For a recent review on functionalized organolithium compounds, see: Nájera, C.; Yus, M. *Trends in Organic Chemistry* **1991**, *2*, 155-181.
2. See, for instance: Barluenga, J.; Yus, M.; Concellón, J. M.; Bernad, P. *J. Org. Chem.* **1981**, *46*, 2721-2726, and references cited therein.
3. Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239-258.
4. (a) Barluenga, J.; Fañanás, F. J.; Yus, M.; Asensio, G. *Tetrahedron Lett.* **1978**, 2015-2016. (b) Barluenga, J.; Fañanás, F. J.; Yus, M. *J. Org. Chem.* **1979**, *44*, 4798-4801. (c) Barluenga, J.; Villamaña, J.; Fañanás, F. J.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1982**, 355-356. (d) Barluenga, J.; Fañanás, F. J.; Villamaña, J.; Yus, M. *J. Org. Chem.* **1982**, *47*, 1560-1564. (e) Barluenga, J.; Fañanás, F. J.; Villamaña, J.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2685-2692.
5. (a) Barluenga, J.; Foubelo, F.; Fañanás, J.; Yus, M. *Tetrahedron Lett.* **1988**, *29*, 2859-2860. (b) Barluenga, J.; Foubelo, F.; Fañanás, F. J.; Yus, M. *Tetrahedron* **1989**, *45*, 2183-2192.
6. Foubelo, F. Ph. D. Thesis, University of Oviedo, 1989.
7. (a) Bartmann, E. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 653-654. (b) Barluenga, J.; Fernández-Simón, J. L.; Concellón, J. M.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1987**, 915-916. (c) Cohen, T.; Jeong, I.-H.; Mudryk, B.; Bhupathy, M.; Awad, M. I. *J. Org. Chem.* **1990**, *55*, 1528-1536.
8. Yus, M.; Ramón, D. J. *J. Chem. Soc., Chem. Commun.* **1991**, 398-400.
9. (a) Yus, M.; Ramón, D. J. *J. Org. Chem.* **1992**, *57*, 750-751. (b) Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **1992**, *33*, 2217-2220. (c) Ramón, D. J.; Yus, M. *Tetrahedron* **1992**, *48*, 3585-3588. (d) Guijarro, D.; Mancheño, B.; Yus, M. *Tetrahedron* **1992**, *48*, 4593-4600. (e) Guijarro, D.; Mancheño, B.; Yus, M. *Tetrahedron Lett.* **1992**, *33*, 5597-5600. (f) Guijarro, A.; Ramón, D. J.; Yus, M. *Tetrahedron*, in press. (g) Guijarro, D.; Mancheño, B.; Yus, M. *Tetrahedron*, in press.
10. Rudesill, J. T.; Severson, R. F.; Pomonis, J. G. *J. Org. Chem.* **1971**, *36*, 3071-3076.
11. This compound was obtained by chlorination of 2-anilinoethanol with thionyl chloride: Raiziss, G. W.; Clemence, L. W. *J. Am. Chem. Soc.* **1941**, *63*, 3124-3126.
12. De Kimpe, N.; Verhe, R.; De Buyck, L.; Schamp, N. *J. Org. Chem.* **1980**, *45*, 5319-5325.
13. (a) Seebach, D.; Hungerbühler, E. In *Modern Synthetic Methods 1980*, Scheffold, R. Ed; Salle + Sauerländer-Verlag: Arau, 1980; pp. 91-171. (b) Seebach, D. Imwinkelried, R.; Weber, T. In *Modern Synthetic Methods 1986*, Scheffold, R. Ed.; Springer Verlag: Berlin, 1986; pp. 125-259.
14. *The Aldrich Catalogue Handbook of Chemicals*; Aldrich Chemie GmbH & Co. KG: Steinheim, 1992-1993.

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