



# A new method for benzylic deprotonative lithiation: synthesis of 1- and 1,3-disubstituted (aza)phthalans

Yves Fort,\* Philippe Gros and Alain L. Rodriguez

*Synthèse Organique et Réactivité, UMR CNRS-UHP 7565, Université Henri Poincaré-Nancy I, BP 239, 54506 Vandoeuvre-Lès-Nancy, France*

Received 15 March 2002; revised 6 April 2002; accepted 8 April 2002

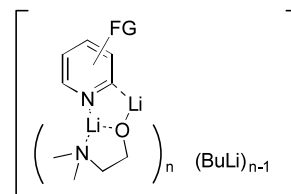
**Abstract**—The *n*-BuLi–Me<sub>2</sub>N(CH<sub>2</sub>)<sub>2</sub>OLi (noted *n*-BuLi–LiDMAE) superbase promotes the direct and regioselective  $\alpha$ -lithiation of (aza)phthalan derivatives. © 2002 Published by Elsevier Science Ltd.

In the course of our studies on the metallation of heterocycles, our laboratory has recently reported the usefulness of *n*-BuLi–Me<sub>2</sub>N(CH<sub>2</sub>)<sub>2</sub>OLi (noted *n*-BuLi–LiDMAE) for the metallation of pyridine derivatives in apolar solvents.<sup>1</sup> The aminoalkoxide increases by aggregation the basicity of *n*-BuLi over its nucleophilicity. The superbase formed then prevents the classical nucleophilic addition of *n*-BuLi onto the heteroaromatic ring. Furthermore, an unprecedented regioselective lithiation at C- $\alpha$  of the pyridine ring is obtained, avoiding the use of the classical halogen–metal exchange on corresponding brominated derivatives. This selectivity was explained by the formation of aggregates between *n*-BuLi–LiDMAE and substrates via lithium complexation by the pyridine nitrogen atom. The aminoalkoxide subsequently ensures stabilisation of the lithiated intermediates formed (Scheme 1).

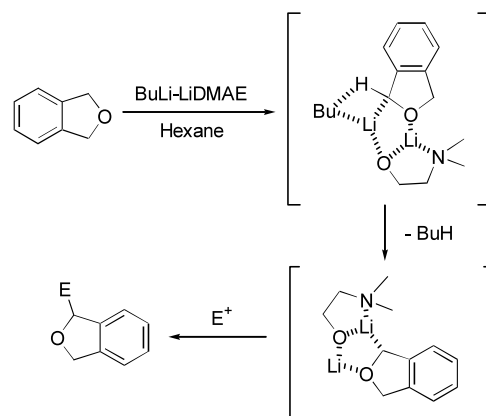
In connection with these studies, we wished to extend the usefulness of *n*-BuLi–LiDMAE for the direct metallation at the benzylic position of phthalan derivatives, important oxygenated heterocycles because of their pharmacological and spectroscopic properties.<sup>2–5</sup> The presence of two lithium cations in the *n*-BuLi–LiDMAE superbase should promote at first the complexation of the phthalan oxygen. The aggregates formed might then deliver *n*-BuLi near the benzylic proton of the substrate and finally ensure stabilisation of the benzylic lithiated species (Scheme 2).

To the best of our knowledge,  $\alpha$ -lithiation of phthalans has only been reported by Davies and co-workers, with

*t*-BuLi in THF, at  $-78^\circ\text{C}$  to ensure stabilisation of the lithiated species, with complete lithiation in 6 h.<sup>6a</sup> With other basic systems (*n*-BuLi–*t*-BuOK, Li–naphthalene, Li–4,4'-di-*tert*-butyl-biphenyl), ring cleavage was observed, presumably as a consequence of the weakness of the C–O bond.<sup>7–9</sup> The  $\alpha$ -lithiation of phthalan derivatives has also been described with tricarbonyl( $\eta^6$ -arene)chromium complexes derived from substituted dihydro-isobenzofurans.<sup>10</sup> Unfortunately, with lithium



Scheme 1.



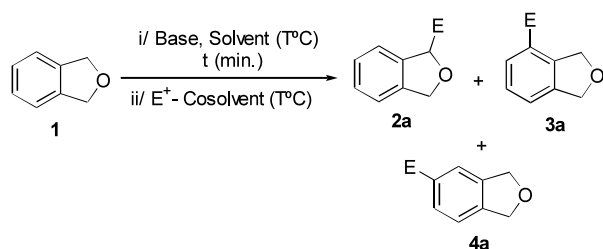
Scheme 2.

\* Corresponding author. E-mail: [yves.fort@sor.uhp-nancy.fr](mailto:yves.fort@sor.uhp-nancy.fr)

amide bases or *n*-BuLi, the lithiation is poorly selective and proceeds also partially on the aromatic nucleus. In this paper, we describe the direct and regioselective benzylic lithiation of substituted phthalans and azaphthalans mediated by the *n*-BuLi–LiDMAE superbase.

As a preliminary study (Scheme 3, Table 1), we attempted to metallate phthalan **1** with *n*-BuLi. In hexane, whatever the conditions, no reaction occurred and the starting material was recovered quantitatively (entries 3 and 4). In contrast, the lithiation in THF at a temperature above  $-78^{\circ}\text{C}$  (entries 1 and 2) led only to an intractable mixture, presumably as a consequence of the nucleophilic addition of *n*-BuLi onto phthalan followed by a ring cleavage.

Thus, we turned to the metallation with the *n*-BuLi–LiDMAE superbase. As a general trend (entries 5–9), the usefulness of *n*-BuLi–LiDMAE was clear since **2a** was always obtained as a single product. Such clean lithiation probably results from both a strong complexation of the lithium aggregates and an acidification of the benzylic position by the oxygen atom. This was clearly demonstrated by the absence of reaction observed with indan whatever the conditions used. This regioselectivity obtained with *n*-BuLi–LiDMAE finally contrasts with the deprotonation of tricarbonyl( $\eta^6$ -arene)chromium complex of **1** where a mixture of **2a**, **3a** and **4a** was observed with *n*-BuLi.<sup>10</sup> As expected, we also found that the course of the reaction with the *n*-BuLi–LiDMAE reagent was sensitive to experimental conditions: (i) an excess of 3 equiv. of base<sup>11</sup> was necessary to metallate phthalan **1** efficiently at  $-15^{\circ}\text{C}$  in



Scheme 3.

20 min (entries 7–9); (ii) no cosolvent was necessary with electrophile nevertheless THF favoured the trapping of lithiated intermediates (entries 5 and 7).

To examine the synthetic value of the reaction for the preparation of substituted phthalans, we studied the condensation with various representative electrophiles (Table 2).<sup>12</sup> The versatility of our process was clearly demonstrated to introduce various functionalities efficiently at the benzylic positions. The derivatives **2e–2f** and **2i** bearing reactive moieties were obtained in moderate to good yields (52–71%). Nevertheless, the instability of the 3-lithio-1-substituted-dihydrobenzofurans implied to perform metallation at  $-40^{\circ}\text{C}$  (entries 8–10), within a short reaction time (30 min).

We finally investigated the preparation of functionalised azaphthalans with the *n*-BuLi–LiDMAE reagent (entries 11–12). We found that the *n*-BuLi–LiDMAE superbase also induced regioselective metallation at benzylic position. This result contrasts with the usual C-6 lithiation of pyridine ring.<sup>1</sup> Thus, the O–Li interaction may be assumed to be stronger than the N–Li one. The consequence is a delivery of the butyl base near the benzylic position rather than in the proximity of the H-6 pyridinic proton. However, compare to phthalans, an inversion of the diastereoselectivity was observed presumably as a consequence of the formation of aggregates between LiDMAE, the benzylic lithiated species and the pyridine nitrogen atom. To the best of our knowledge, *n*-BuLi–LiDMAE is the first basic system for this unprecedented functionalisation of azaphthalan derivatives.

In summary, we have described a convenient way to introduce reactive moieties at the benzylic position of phthalans and azaphthalans via lithiation with the *n*-BuLi–LiDMAE reagent. This regioselective process avoids the activation of the benzylic position of phthalan compounds by the tricarbonyl( $\eta^6$ -arene)chromium complexes as well as the use of the *t*-BuLi under careful temperature control. Work is now in progress to elaborate an enantioselective version by using the association of *n*-BuLi with chiral vicinal aminoalkoxides.

Table 1. Lithiation of phthalan **1** mediated by several basic systems

Entry	Base (equiv.)	Solvent (T, $^{\circ}\text{C}$ , t min)	Cosolvent (T, $^{\circ}\text{C}$ )	<b>2a</b> <sup>0%</sup> <sup>a</sup>	<b>3a</b> + <b>4a</b> <sup>0%</sup>
1 <sup>c</sup>	<i>n</i> -BuLi (1.1)	THF ( $-78$ , 60)	<sup>b</sup> ( $-78$ )	–	–
2 <sup>d</sup>	<i>n</i> -BuLi (1.1)	THF ( $-40$ , 60)	<sup>b</sup> ( $-40$ )	–	–
3 <sup>c</sup>	<i>n</i> -BuLi (1.1)	Hexane ( $-78$ , 60)	<sup>b</sup> ( $-78$ )	–	–
4 <sup>c</sup>	<i>n</i> -BuLi (3)	Hexane ( $-15$ , 60)	<sup>b</sup> ( $-15$ )	–	–
5	BuLi–LiDMAE (3)	Hexane ( $-15$ , 20)	<sup>b</sup> ( $-15$ )	60	–
6	BuLi–LiDMAE (3)	Hexane ( $-15$ , 20)	<sup>b</sup> ( $-78$ )	61	–
7	BuLi–LiDMAE (3)	Hexane ( $-15$ , 20)	THF ( $-78$ )	78	–
8	BuLi–LiDMAE (2)	Hexane ( $-15$ , 20)	THF ( $-78$ )	59	–
9	BuLi–LiDMAE (4)	Hexane ( $-15$ , 20)	THF ( $-78$ )	76	–

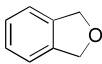
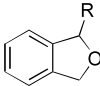
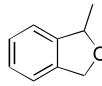
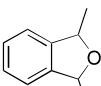
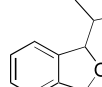
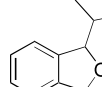
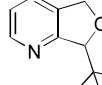
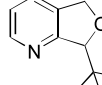
<sup>a</sup> Yields of isolated product, with MeOD as electrophile. Deuterium incorporation >95% (determined by <sup>1</sup>H NMR).

<sup>b</sup> MeOD was introduced neat.

<sup>c</sup> The starting material was recovered quantitatively.

<sup>d</sup> Partial decomposition of **1**.

**Table 2.** Preparation of functionalised (aza)phthalan derivatives

Entry	Substrat	Electrophile	Product	Yield % (cis/trans) <sup>a</sup>	
					
	<b>1</b>		R :		
1		MeOD	D	<b>2a</b>	78 <sup>b</sup>
2		MeSSMe	SMe	<b>2b</b>	81
3		Me <sub>2</sub> SO <sub>4</sub>	Me	<b>2c</b>	74
4		<i>i</i> -Pr-I	<i>i</i> -Pr	<b>2d</b>	62
5		Me <sub>3</sub> SnCl	Me <sub>3</sub> Sn	<b>2e</b>	71
6		PhCHO	PhCHOH	<b>2f</b>	69
7		(+/-)-camphor	bornyl	<b>2g</b>	52 <sup>c</sup>
8 <sup>d</sup>		Me <sub>2</sub> SO <sub>4</sub>		<b>2h</b>	66 (66/33)
	<b>2b</b>				
9 <sup>d</sup>		Bu <sub>3</sub> SnCl	Bu <sub>3</sub> Sn	<b>2i</b>	61 (60/40)
10 <sup>d</sup>		Me <sub>2</sub> SO <sub>4</sub>	Me	<b>2j</b>	75 (70/30)
	<b>2d</b>		R :		
11 <sup>e</sup>		MeOD	D	<b>2k</b>	71 <sup>b</sup> (n.d.) <sup>f</sup>
12 <sup>e</sup>		MeSSMe	MeS	<b>2l</b>	81 (35/65)
	<b>5</b>		R :		

Reactions were performed with BuLi-LiDMAE (3 equiv), in hexane at -15°C in 20 minutes. THF as cosolvent. <sup>(a)</sup> Yields of isolated products. All compounds were fully characterized by NMR (<sup>1</sup>H, <sup>13</sup>C), IR and MS (a purity as high as 98% was determined by GC-MS). Cis/trans ratio determined by <sup>1</sup>H NMR. The configuration was determined by the measurement of J<sub>trans</sub> and J<sub>cis</sub> (Ref. 3). <sup>(b)</sup> Deuterium incorporation >98% (determined by <sup>1</sup>H NMR). <sup>(c)</sup> Complex mixture of diastereomers. <sup>(d)</sup> Metallation was performed in hexane at -40°C in 30 minutes. THF as cosolvent. <sup>(e)</sup> Metallation was performed in hexane at -78°C in 1 hour, without cosolvent. <sup>(f)</sup> Not determined.

## References

- (a) Gros, P.; Fort, Y.; Quéguiner, G.; Caubère, P. *Tetrahedron Lett.* **1995**, *36*, 4791; (b) Gros, P.; Fort, Y.; Caubère, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, *20*, 3071; (c) Gros, P.; Fort, Y.; Caubère, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, *24*, 3597; (d) Gros, P.; Fort, Y.; Caubère, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, *10*, 1685; (e) Gros, P.; Ben Younès-Millot, C.; Fort, Y. *Tetrahedron Lett.* **2000**, *41*, 303; (f) Mathieu, J.; Gros, P.; Fort, Y. *J. Chem. Soc., Chem. Commun.* **2000**, 951; (g) Mathieu, J.; Gros, P.; Fort, Y. *Tetrahedron Lett.* **2000**, *41*, 1879; (h) Choppin, S.; Gros, P.; Fort, Y. *Org. Lett.* **2000**, *2*, 803; (i) Gros, P.; Choppin, S.; Mathieu, J.; Fort, Y. *J. Org. Chem.* **2002**, *67*, 234; (j) Cuperly, D.; Gros, P.; Fort, Y. *J. Org. Chem.* **2002**, *67*, 238.
- (a) Fraser, R. R.; Renaud, R. N. *Can. J. Chem.* **1971**, *49*, 755; (b) Ram, S.; Saxena, A. K.; Jain, P. C.; Patnaik, G. K. *Ind. J. Chem.* **1984**, *23B*, 1261.
- Barfield, M.; Spear, R. J.; Sternhell, S. *J. Am. Chem. Soc.* **1975**, *97*, 5160.
- Brown, D. S.; Elliot, M. C.; Moody, C. J.; Mowlem, T. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1137.
- (a) King, T. J.; Imre, S.; Öztunc, A.; Thomson, R. H. *Tetrahedron Lett.* **1979**, *20*, 1453; (b) Howard, B. M.; Schulte, G. R.; Fenical, W.; Solheim, B.; Clardy, J. *Tetrahedron* **1980**, *36*, 1747.

6. (a) Coote, S. J.; Davies, S. G. *J. Organomet. Chem.* **1989**, *379*, 81. For an enantioselective version with chiral bis(oxazoline), see: (b) Tomooka, K.; Wang, L.-F.; Okazaki, F.; Nakai, T. *Tetrahedron Lett.* **2000**, *41*, 6121.
7. Baston, E.; Maggi, R.; Friedrich, K.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, 3985.
8. Azzena, U.; Demartis, S.; Fiori, M. G.; Melloni, G.; Pisano, L. *Tetrahedron Lett.* **1995**, *36*, 8123.
9. (a) Najera, C.; Yus, M. *Trends Org. Chem.* **1991**, *2*, 155; (b) Najera, C.; Yus, M. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 67; (c) Guijirro, D.; Yus, M. *Recent Res. Dev. Org. Chem.* **1998**, *2*, 713; (d) Yus, M.; Foubelo, M. *Rev. Heteroat. Chem.* **1997**, *17*, 73; (e) Foubelo, M.; Yus, M. *Trends Org. Chem.* **1998**, *7*, 1.
10. Ewin, R. A.; Simpkins, N. S. *Synlett* **1996**, 317.
11. The superbases *n*-BuLi–LiDMAE was prepared from *n*-BuLi (2 equiv.) and DMAE (1 equiv.) leading to a 1:1 *n*-BuLi:LiDMAE ratio which was previously found to give the best results.
12. Typical procedure: A solution of 2-(dimethylamino)-ethanol (534 mg, 6 mmol) in hexane (6 mL) was cooled at  $-15^{\circ}\text{C}$  and *n*-BuLi (7.5 mL, 12 mmol) was added dropwise under a nitrogen atmosphere. After 30 min at this temperature, a solution of phthalan **1** (240 mg, 2 mmol) in hexane (1 mL) was added. After 20 min of stirring at  $-15^{\circ}\text{C}$ , the orange solution was cooled at  $-78^{\circ}\text{C}$ , and THF (8 mL) was added dropwise. The dark-red solution was treated with the appropriate electrophile (10 mmol) in THF (1 mL). The temperature was then allowed to rise to  $0^{\circ}\text{C}$ . Hydrolysis was performed at this temperature with  $\text{H}_2\text{O}$  (5 mL). The aqueous phase was extracted with dichloromethane (10 mL). After drying ( $\text{MgSO}_4$ ), filtration and evaporation of solvents, the crude product was purified by chromatography on silica gel using hexane–AcOEt as eluent. A purity as high as 98% was determined by GC–MS for all products. All compounds were fully characterised by NMR ( $^1\text{H}$ ,  $^{13}\text{C}$ ), IR and MS. *cis/trans* Ratio determined by  $^1\text{H}$  NMR and the configurations were determined by the measurement of  $J_{trans}$  and  $J_{cis}$ .<sup>6</sup> Selected data for *cis*-**2h**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400.1 MHz): 7.35–7.28 (m, 2H), 7.21–7.16 (m, 2H), 5.26 (q,  $J=6.0$  Hz, 2H), 1.59 (d,  $J=6.0$  Hz, 6H). Data for *trans*-**2h** (in agreement with Ref. 6a):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400.1 MHz): 7.35–7.28 (m, 2H), 7.21–7.16 (m, 2H), 5.43 (q,  $J=6.0$  Hz, 2H), 1.48 (d,  $J=6.0$  Hz, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz): 144.1, 127.8, 121.3, 79.1, 22.7. MS (EI)  $m/z$  (rel. int.): 148 (13,  $\text{M}^{+\bullet}$ ), 133 (100), 115 (11), 105 (42), 103 (14), 91 (9), 77 (21), 51 (9).