Tetrahedron Letters, Vol.29, No.23, pp 2859-2860, 1988 Printed in Great Britain

<u>N-LITHIO-N-(2-LITHIOETHYL)BENZAMIDE</u>: DIRECT PREPARATION OF A

2-LITHIOETHYLAMINE EQUIVALENT

José Barluenga,* Francisco Foubelo, Francisco J. Fañanás, and Miguel Yus

Departamento de Química Organometálica, Facultad de Química, Universidad de Oviedo, 33071 Oviedo, Spain

<u>Summary</u>: The successive reaction of 2-chloroethylbenzamide with <u>n</u>-butyl-lithium and lithium naphthalenide at -78°C leads to <u>N</u>-lithio-<u>N</u>-(2-lithioethyl)benzamide, which reacts with different electrophiles (H_2O , D_2O , Me_2S_2 , CO_2 , <u>i</u>-PrCHO, PhCHO, Me_2CO , Ph_2CO) to afford the expected 2-functionalized benzamides.

 β -Functionalized organolithium derivatives of the type 1 are very difficult to be prepared due to their tendency to undergo a β -elimination reaction yielding olefins,¹ even at very low temperatures. In the last decade new methodologies have been reported, which permit the preparation of the more stable dianionic intermediates of the type 2; they are based either in a) a mercury/lithium transmetallation from β -functionalized organomercury compounds,² or b) a direct lithiation of the corresponding chlorohydrins³ or epoxides.⁴ Since the second procedure fails for the nitrogen-containing species (2 with Z=NR), they can only be prepared by the mercury route. In our hands only the intermediate 3, which actually is an ylide, has been prepared by a direct method: double lithiation of the adequate precursor with <u>n</u>-buty1-lithium.⁵ We now describe at the first time a new way to prepare directly an aminated intermediate of the type 2, which is an useful synthon for the unit $H_2NCH_2CH_2^{-}$.



The successive treatment of 2-chloroethylbenzamide **4** with <u>n</u>-butyl-lithium and lithium naphthalenide at -78° C led to the β -substituted organolithium intermediate **5**. The <u>in situ</u> treatment of this dianion with different electrophilic reagents (water, deuterium oxide, dimethyl disulphide, carbon dioxide, oxygen, isobutyraldehyde, benzaldehyde, acetone, and benzophenone) yielded the expected β -substituted ethylbenzamides **6** (Scheme and Table).



Scheme. <u>Reagents and conditions</u>: i, <u>n</u>-BuLi, -78°C; ii, $\text{Li}^{+}\text{C}_{10}\text{H}_{8}^{-}$, -78°C; iii, Electrophile = H₂O, D₂O, Me₂S₂, CO₂, O₂, <u>i</u>-PrCHO, PhCHO, Me₂CO, Ph₂CO, -78 to 20°C; iv, H₂O.

with electrophiles; preparation of compounds b				
				B.p./ ^O C (mmHg) or
Product ^a	Electrophile	х	% Yield ^b	m.p./ ^o C (solvent)
6a	н ₂ 0	Н	91	112-114 (0.1) ^c
6b	D ₂ O	D	88	112-114 (0.1)
6c	Me ₂ S ₂	MeS	86	118-120 (0.001)
6d	co	содн	64	oil ^d
6e	02	OH	65	148-150 (0.1) ^e
6 f	<u>i</u> -PrCHO	<u>i</u> -PrCHOH	72	106-108 (hexane-CHCl ₃)
6g	PhCHO	PhCHOH	. 72	oil ^f
6h	Me ₂ CO	Me,COH	74	oil ^g
61	Ph ₂ CO	Ph_COH	71	145-147 (hexane-CHCl ₂)

^a All compounds **6** gave satisfactory spectral data (IR, ¹H and ¹³C NMR, and mass spectra). ^b Isolated yield based on starting material **4**. ^c Lit., ⁶ b.p. 298-300°C (760 mmHg). ^d \underline{R}_{f} 0.54 [silica gel, THF-hexane (3:2)]. ^e Lit., ⁷ m.p. <u>ca</u>. 58°C. ^f \underline{R}_{f} 0.60 [silica gel, THF-hexane (3:2)]. ^g \underline{R}_{f} 0.50 [silica gel, THF-hexane (3:2)].

In a <u>typical reaction</u>, to a solution of <u>N</u>-(2-chloroethyl)benzamide (0.98 g, 5 mmol) in tetrahydrofuran (25 ml) was added an ethereal solution of <u>n</u>-butyl-lithium (5 mmol) at -78°C under argon and stirring was continued for 20 min at the same temperature. To the resulting mixture was added a solution of lithium naphthalenide in tetrahydrofuran (11 mmol) and it was stirred for 5 h at -78°C. The corresponding electrophile (5 mmol)⁸ was then added and the mixture was stirred overnight allowing the temperature to rise to 20° C. The resulting mixture was hydrolysed with water and extracted with ether. The organic layer was dried (Na₂SO₄) and evaporated (15 mmHg). Naphthalene was removed <u>in vacuo</u> (0.01 mmHg; 60° C bath temperature) and the resulting residue was purified by distillation or recrystallization (see Table).

References and Notes

- 1 J. Barluenga, J. L. Fernández-Simón, J. M. Concellón, and M. Yus, <u>J. Chem. Soc., Chem. Com-</u> <u>mun</u>., **1986**, 1665.
- 2 J. Barluenga, F. J. Fañanás, J. Villamaña, and M. Yus, <u>J. Chem. Soc., Perkin Trans. 1</u>, **1984**, 2685.
- 3 J. Barluenga, J. Flórez, and M. Yus, <u>J. Chem. Soc., Chem. Commun</u>., **1982**, 1153.
- 4 E. Bartmann, Angew. Chem., Int. Ed. Engl., 1986, 25, 653.
- 5 R. J. Linderman and A. I. Meyers, Tetrahedron Lett., 1983, 3043.
- 6 Beilstein Handbuch der Organischen Chemie, <u>9</u>, 202.
- 7 Beilstein Handbuch der Organischen Chemie, $\overline{9}$, 205.
- 8 When H₂O, D₂O, or solid CO₂ was used as an electrophile a large excess (ca. 100 mmol) was added.² In the oxidation dry oxygen precooled at -78° C was bubbled for 2 h at -78° C.