Pergamon

Tetrahedron Vol. 50, No. 27, pp. 8099-8102, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4020/94 $7.00+0.00

0040-4020(94)00422-6

A ß,ß,ß-Trialkoxyethyllithium Stable towards Fragmentation: a Carboxyl Protected Acetic Acid Dianion Equivalent

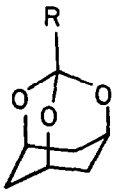
Sosale Chandrasekhar* and Chandra Deo Roy

Department of Organic Chemistry, Indian Institute of Science,

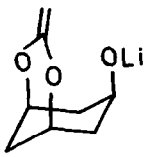
Bangalore 560 012, India

Abstract: The novel alkyllithium **1b** is not only intriguingly stable towards fragmentation, but also a synthetically useful reagent, complementing current carboxylic ester enolate methodology. Its design is based on interesting mechanistic principles, and harnesses the known stability of the 2,4,10-trioxaadamantane framework.

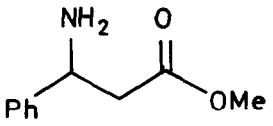
Cyclic acetals and orthoesters are much more stable than their acyclic analogs to hydrolysis. This is thought to be because of a proximity effect, the oxocarbonium ion intermediates in the cyclic cases recyclising very much faster than hydrating.[1] We report here an application of these mechanistic facts in the design of a novel compound which is also a synthetically useful reagent.



1



2



3

1a-h, R: **a** H, **b** CH_2Li, **c** CH_2Br, **d** Me, **e** $PhCH(OH)CH_2$-, **f** $PhCOCH_2$-, **g** $PhC(=NOH)CH_2$-, **h** $PhCH(NH_2)CH_2$-

During mechanistic studies on the origin of the stability of 2,4,10-trioxatricyclo[3.3.1.$1^{3,7}$]decane (**1a**),[2] it occurred to us that trioxatricyclodecylmethyllithium **1b** could be unusually stable to elimination: because of the above proximity effect, the equilibrium between **1b** and its ring-opened isomer **2** should lie well in favor of **1b** which, in fact, is a 'carboxyl-masked α-lithio acetic acid'.

Halogen-metal exchange with *n*-BuLi on bromide **1c**[2b] (0.2M in THF/0-5 °C/N_2/1 h) did indeed generate **1b** as shown by its electrophilic reactions. Quenching of **1b** with water produced methyltrioxatricyclodecane **1d**[2c], whilst reaction with benzaldehyde produced expected alcohol **1e**, both in excellent yields. **1e** could be smoothly oxidised by pyridinium chlorochromate (CH_2Cl_2, 25 °C) to ketone **1f**, which could be converted to oxime **1g**. Hydride reduction of the oxime produced an excellent yield of **1h**, from which the carboxyl group could be easily retrieved to get methyl ß-amino-ß-phenylpropanoate (**3**). These transformations are, of course, impossible without the protective trioxatricyclodecyl group,[2,3] and thus demonstrate the synthetic utility of **1b**. Also, **1b** offers an alternative to the use of acetic acid dianion,[4] but with the advantage of carboxyl protection.

Preliminary studies indicate that **1b** is rather unreactive towards alkylation, failing to react with MeI, *n*-$C_5H_{11}I$ and BnBr (THF/0-5 °C/2 h; rt/18 h): a lowering of nucleophilicity by the three electron-withdrawing oxygens, and the *neo*-pentyl like steric environment, are possible explanations. Further work is planned to extend the scope of the above studies.

EXPERIMENTAL

Instruments used: Perkin Elmer 781 & 684, and Hitachi 270-50 (IR); JEOL FX-90Q and Varian T-60 (NMR); JEOL MS-DX 303 (GC-MS); Carlo Erba 1160 (elemental analysis). NMR was recorded on $CDCl_3$ solutions in the 0-10δ range, and acidic protons were often not clearly discernible. IR was recorded for nujol mulls or thin films. Melting and boiling points are uncorrected. Bromide **1c** was prepared as reported [2b]. *n*-BuLi was purchased from Aldrich Chemical Co. Other compounds and reagents were of standard commercial grade. Reaction mixture solutions were dried on Na_2SO_4 or $MgSO_4$ unless stated otherwise. 'H_{eq}' and 'H_{ax}' mean equatorial and axial protons respectively.

Lithiation of Bromide 1c.

1c (0.117 g, 0.50 mmol) in dry THF (2 mL) at 0-5 °C under dry N_2 was treated with *n*-BuLi (0.5 mL, 1.6 M in hexane, 0.8 mmol) with stirring which was continued for 1 h. The formation of **1b** was indicated by reactions of this mixture with electrophiles as detailed below. (**1b** was prepared on the above scale for these studies).

Reaction with Water.

Quenching of **1b** with water (0.1 mL), concentration *in vacuo*, extraction with Et_2O (3X25 mL), drying and evaporation, and column chromatography of the resulting crude yielded pure **1d** (0.056 g, 0.36 mmol, 72%). Mp 125 °C (from hexane; lit. [2c] 126 °C). IR, NMR and HRMS in accord with structure.

Reaction with Benzaldehyde.

1b was treated with PhCHO (0.106 g, 1.0 mmol) in THF (1 mL), with stirring which was continued for 3 h at 0-5 °C and 14-18 h at 25 °C. After concentration *in vacuo* and treatment with H_2O (5 mL), the mixture was extracted with CH_2Cl_2 (100 mL), and the extracts dried and distilled. The residue was chromatographed on neutral Al_2O_3 (eluent: EtOAc-hexane), and recrystallised (hexane-$CHCl_3$), to obtain pure **1e** (0.105 g, 0.40 mmol, 80%).

Alcohol 1e. Mp 145-146 °C. IR (cm^{-1}) 3490. ^1H NMR δ 7.50-7.20 (5 H, m, Ar *H*), 5.10 (1 H, dd, *J* 7.2, 5.4 Hz, HO-C*H*), 4.45 (3 H, br. s, C-O-C*H*), 2.85 (4 H, 'd', *J* 14 Hz, CH_{eq} and O*H*, D_2O exchangable), 2.05 (2 H, m, HO-C-CH_2), 1.75 (3 H, d, *J* 14 Hz, CH_{ax}). MS, *m/e* 262 (M^+), 245 (-OH), 165, 156. HRMS, $C_{15}H_{18}O_4$ requires *m/e* 262.1200, found 262.1205. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.91. Found: C, 69.05; H, 6.94.

Oxidation of Alcohol **1e**.

1e (0.524 g, 2.0 mmol) in dry CH_2Cl_2 was stirred with pyridinium chlorochromate (0.860 g, 4.0 mmol), at 25 °C for 24 h. The mixture was filtered through Al_2O_3 eluting well with CH_2Cl_2. Evaporation of the filtrate, and chromatography (Al_2O_3) of the residue gave pure **1f** (0.492 g, 1.9 mmol, 95%), recrystallised from hexane-$CHCl_3$.

Ketone **1f**. Mp 105-106 °C. IR (cm^{-1}) 1683. ^1H NMR δ 8.20-8.00 (2 H, m, Ar*H*), 7.60-7.40 (3 H, m, Ar*H*), 4.40 (3 H, br. s, C-O-C*H*), 3.30 (2 H, s, -CO-CH_2), 2.60 (3 H, d, *J* 14 Hz, CH_{eq}), 1.68 (3 H, d, *J* 14 Hz, CH_{ax}). MS, *m/e* 260 (M^+), 165, 147, 105. Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.21; H, 6.19. Found: C, 68.87; H, 6.19.

Preparation of Oxime **1g**.

A solution of **1f** (0.130 g, 0.50 mmol), $NH_2OH.HCl$ (0.104 g, 1.5 mmol) and pyridine (0.1 mL) was refluxed in EtOH (2.5 mL) for 1 h, and concentrated *in vacuo*; the cooled residue was stirred in H_2O (5 mL). The resulting crystals were collected, washed with ice-cold H_2O (3 X 15 mL) and recrystallised (hexane-$CHCl_3$), to obtain pure **1g** (0.108 g, 0.39 mmol, 78%).

Oxime **1g**. Mp 169-171. IR (cm^{-1}) 3232. ^1H NMR δ 7.80-7.20 (5 H, m, Ar*H*), 4.40 (3 H, br. s, C-O-C*H*), 3.30 (2 H, s, HON=CCH_2), 2.60 (3 H, d, *J* 14 Hz, CH_{eq}), 1.68 (3 H, d, *J* 14 Hz, CH_{ax}). MS, *m/e* 275 (M^+), 258 (-OH). HRMS, $C_{15}H_{17}NO_4$ requires *m/e* 275.1158, found 275.1148. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.40; H, 6.28; N, 4.74.

Reduction of Oxime **1g**.

$LiAlH_4$ (0.053 g, 1.4 mmol) in dry THF (4 mL) was treated with the oxime (0.095 g, 0.35 mmol) in dry THF (4 mL). The mixture was stirred at 80-85°C for 8 h, then concentrated and treated with H_2O. Extraction with Et_2O (4 X 25 mL), drying of the extracts (K_2CO_3) and evaporation yielded a residue. Chromatography (Al_2O_3/hexane-EtOAc) gave pure **1h** (0.069 g, 0.26 mmol, 74%, viscous liquid).

Amine **1h**. IR (cm^{-1}) 3358. ^1H NMR δ 7.50-7.00 (5 H, m, Ar*H*), 4.40 (3 H, br. s, C-O-C*H*), 3.55 (1 H, m, N-C*H*), 2.80 (2 H, br. s, NH_2), 2.50 (3 H, d, *J* 14 Hz, CH_{eq}), 1.95 (2 H, m, N-C-CH_2), 1.60 (3 H, d, *J* 14 Hz, CH_{ax}). MS, *m/e* 261 (M^+), 245 (-NH_2), 164, 156, 106. HRMS, $C_{15}H_{19}NO_3$ requires *m/e* 261.1365, found 261.1367.

Preparation of Methyl 3-Amino-3-phenylpropanoate (3).

1h (0.10 g, 0.38 mmol) in 5N HCl (2 mL) was stirred at 25 °C for 24 h. The mixture was concentrated *in vacuo* and the resulting residue refluxed in absolute MeOH for 7-9 h. After neutralisation (solid $NaHCO_3$) and concentration *in vacuo*, H_2O was added and the resulting mixture (pH 8-9) extracted with CH_2Cl_2 (3 X 25 mL). Drying (K_2CO_3), evaporation of extracts and chromatography (Al_2O_3) gave pure **3** (0.05 g, 0.28 mmol, 74%, viscous liquid).[5]

Amino ester **3**. IR (cm^{-1}) 3364, 1731. ^1H NMR δ 7.40-7.20 (5 H, m, Ar*H*), 4.40 (1 H, m, NC*H*), 3.68 (3 H, s, OMe), 2.64 (2 H, d, *J* 7 Hz, accidentally equivalent -CO-CH_2), 2.00 (2 H, br. s, NH_2). MS, *m/e* 179 (M^+), 106. HRMS, $C_{10}H_{13}NO_2$ requires *m/e* 179.0946, found 179.0952.

ACKNOWLEDGMENT

We thank CSIR and DST for generous financial support.

REFERENCES

(1) (a) Kirby, A. J.; Martin, R. J. *J. Chem. Soc. Perkin Trans. II.***1983**, 1627-1632.
(b) Bouab, O.; Lamaty, G.; Moreau, C.; Pomares, O.; Deslongchamps, P.; Ruest, L. *Can. J. Chem.* **1980**, *58*, 567-573.

(2) (a) DeWolfe, R. H. *Carboxylic Orthoacid Derivatives*; Academic Press: New York, 1970; p 22.
(b) Stetter, H.; Steinacker, K. H. *Chem. Ber.* **1954**, *87*, 205-209.
(c) Stetter, H.; Steinacker, K. H. *Chem. Ber.* **1953**, *86*, 790-793.

(3) (a) Bohlmann, F.; Sucrow, W. *Chem. Ber.* **1964**, *97*, 1839-1856.
(b) Voss, G.; Gerlach, H. *Helv. Chim. Acta.* **1983**, *66*, 2294-2307.
(c) Kunz, H.; Waldmann, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds., Pergamon Press: Oxford, 1991; Vol. 6, pp 673-675.

(4) (a) Petragnani, N.; Yonashiro, M. *Synthesis* **1982**, 521-578.
(b) Pfeffer, P. E.; Silbert, L. S.; Chirinko, Jr., J. M. *J. Org. Chem.* **1972**, *37*, 451-458.

(5) Pietsch, H. *Tetrahedron Lett.* **1972**, *27*, 2789-2792.

(*Received in UK* 18 *February* 1994; *revised* 10 *May* 1994; *accepted* 13 *May* 1994)