Reaction of Oxime Dianions with Aldimines; A Useful Route to 2-Hydroxylaminoazetidines

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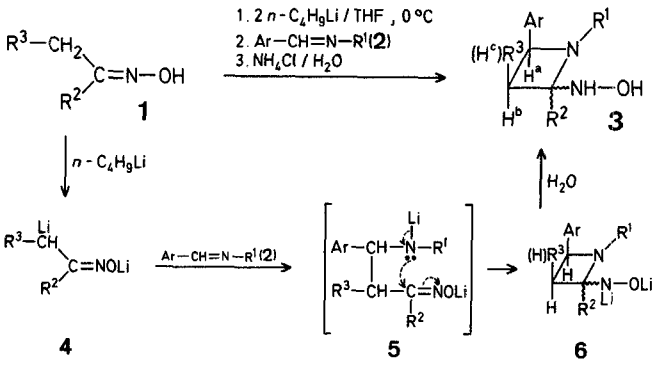
Dianions generated from oximes are useful intermediates in organic synthesis. These dianions react with electrophiles such as carboxylic esters[1-5], carbon dioxide[6], aldehydes and ketones[7,8,9], alkyl halides[8,10], acid chlorides[11], nitriles[12], amides[13], and epoxides[14]. However, the action of the dilithiooximes on imines has, to our knowledge, hitherto not been investigated. We show here that this reaction can be applied to the synthesis of substituted azetidines of considerable biological interest[15-18].

Treatment of acetophenone oxime (**1**, $R^2=C_6H_5$, $R^3=H$) with 2 equivalents of butyllithium in tetrahydrofuran at 0°C followed by the addition of benzylidenaniline (**2**, $Ar=R^1=C_6H_5$) leads to the formation of 2-hydroxylamino-1,2,4-triphenylazetidine (**3a**) in 71% yield. Formation of the expected β-aminooxime derived from the open-chain intermediate **5** could in no case be observed. Several experiments to avoid the cyclization of the presumable intermediate **5** failed. The structure of product **3a** was verified by microanalysis as well as by I.R., ^{1}H-N.M.R. (250 MHz), and ^{13}C-N.M.R. spectrometry and the reaction then utilized for the synthesis of a variety of substituted products **3**. The reaction is assumed to proceed via the intermediates **4**, **5**, and **6**.



This new method has the advantage of giving 2-hydroxylaminoazetidines in generally good yields from readily available starting materials.

Substituted 2-Hydroxylaminoazetidines (3); General Procedure:
To a stirred solution of the oxime **1** (0.05 mol) of an enolizable ketone in tetrahydrofuran (150 ml) under a nitrogen atmosphere is added, over a 15 min period, a solution of butyllithium (0.11 mol) in hexane at 0°C. Stirring is continued for 1 h whereupon the aldimine **2** (0.05 mol) is added. The mixture is refluxed for 1 h and then saturated ammonium chloride solution (100 ml) is added and the mixture is extracted with ether (2 × 100 ml). The organic phase is dried with magnesium sulfate and the solvent evaporated to leave the azetidine **3** as a powder.

Received: December 20, 1982
(Revised form: May 20, 1983)

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Table. 2-Hydroxylaminoazetidines (**3**) prepared

3	Ar	R^1	R^2	R^3	Yield[a] [%]	Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
a	C_6H_5	C_6H_5	C_6H_5	H[c]	71	$C_{21}H_{20}NO_2$ (316.4)	2.97-3.04 (dd, 1 H, H[c]); 3.57-3.66 (dd, 1 H, H[b]); 4.60-4.66 (dd, 1 H, H[a]); 6.35-7.6 (m, 15 H, $3C_6H_5$); 9.5 (br. s, 2 H, NHOH)
b	4-H_3CO—C_6H_4—	C_6H_5	C_6H_5	H[c]	75	$C_{22}H_{22}N_2O_2$ (346.4)	2.75-3.25 (dd, 1 H, H[c]); 3.35-3.65 (dd, 1 H, H[b]); 3.75 (s, 3 H, OCH_3); 4.45-4.82 (dd, 1 H, H[a]); 6.35-7.8 (m, 14 H, $2C_6H_5+C_6H_4$)
c	C_6H_5	CH_3	C_6H_5	H[c]	80	$C_{16}H_{18}NO_2$ (254.3)	2.30 (s, 3 H, N—CH_3); 2.80-3.75 (m, 2 H, H[b]+H[c]); 3.77-4.11 (m, 1 H, H[a]); 5.40-6.20 (br. s, 2 H, NHOH); 7.1-7.8 (m, 10 H, $2C_6H_5$)
d	C_6H_5	C_6H_5	CH_3	H[c]	70	$C_{16}H_{18}N_2O$ (254.3)	1.78 (s, 3 H, N—CH_3); 2.20-2.75 (dd, 1 H, H[c]); 3.05-3.45 (dd, 1 H, H[b]); 4.45-4.95 (dd, 1 H, H[a]); 6.38-7.75 (m, 10 H, $2C_6H_5$)
e	4-H_3CO—C_6H_4—	C_6H_5	CH_3	H[c]	74	$C_{17}H_{20}N_2O_2$ (284.3)	1.78 (s, 3 H, 2-CH_3); 2.25-2.65 (dd, 1 H, H[c]); 3.05-3.50 (dd, 1 H, H[b]); 3.75 (s, 3 H, OCH_3); 4.45-4.85 (dd, 1 H, H[a]); 6.4-7.6 (m, 9 H, $C_6H_4+C_6H_5$)
f	C_6H_5	CH_3	CH_3	H[c]	67	$C_{11}H_{16}N_2O$ (192.3)	1.62 (s, 3 H, 2-CH_3); 2.25 (s, 3 H, N—CH_3); 2.25-2.65 (m, 1 H, H[c]); 2.90-3.30 (dd, 1 H, H[b]); 3.75-4.12 (dd, 1 H, H[a]); 5.10-6.10 (br. s, 2 H, NHOH); 7.1-7.75 (m, 5 H, C_6H_5)
g	C_6H_5	C_6H_5	C_6H_5	C_2H_5	67	$C_{23}H_{24}N_2O$ (344.4)	0.65-1.00 (t, 3 H, CH_2—CH_3); 1.12-1.75 (m, 2 H, CH_2—CH_3); 3.6-4.0 (m, 3 H, NHOH+H[b]); 4.30-4.60 (d, 1 H, H[a]); 6.4-7.6 (m, 15 H, $3C_6H_5$)
h	4-H_3CO—C_6H_4—	C_6H_5	C_6H_5	C_2H_5	81	$C_{24}H_{26}N_2O_2$ (374.5)	(in acetone-d_6): 0.75 (t, 3 H, CH_2—CH_3); 1.25-1.36 (m, 2 H, CH_2—CH_3); 3.62-3.9 (m, 4 H, OCH_3+H[b]); 4.56-4.90 (br. s, 2 H, NHOH); 5.38-5.41 (d, 1 H, H[a]); 6.42-7.52 (m, 14 H, $2C_6H_5+C_6H_4$)
i	C_6H_5	C_6H_5	—$(CH_2)_4$—		62	$C_{19}H_{22}N_2O$ (294.4)	1.1-2.75 [m, 8 H, $(CH_2)_4$]; 3.6-4.05 (m, 1 H, H[b]); 4.30-4.75 (d, 1 H, H[a]); 6.25-7.75 (m, 10 H, $2C_6H_5$)
j	4-H_3CO—C_6H_4—	C_6H_5	—$(CH_2)_4$—		82	$C_{20}H_{24}N_2O_2$ (324.4)	1.1-2.6 [m, 8 H, $(CH_2)_4$]; 3.6-3.95 (m, 4 H, OCH_3+H[b]); 4.30-4.60 (d, 1 H, H[a]); 6.35-7.6 (m, 9 H, $C_6H_4+C_6H_5$)
k	C_6H_5	CH_3	—$(CH_2)_4$—		55	$C_{14}H_{20}N_2O$ (232.3)	1.1-2.75 [m, 11 H, $(CH_2)_4$+N—CH_3]; 3.55-3.95 (m, 1 H, H[b]); 4.25-4.60 (d, 1 H, H[a]); 5.25-6.45 (br. s, 2 H, NHOH); 6.85-7.9 (m, 5 H, C_6H_5)

[a] Melting points are not given since the products **3** are mixtures of isomers. The microanalyses were in satisfactory agreement with the calculated values: C, ±0.25; H, ±0.30; N, ±0.30.

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