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Note

Novel method for the preparation of tricyclic [6:6:5] systems by reductive cyclisation with LAH†

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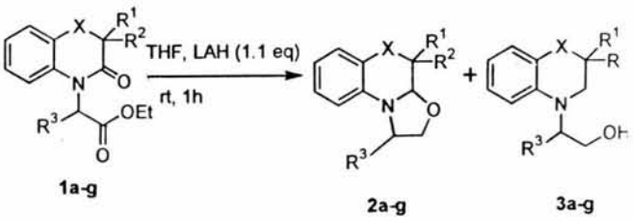
Several tricyclic [6:6:5] and [6:7:5] systems **2a-f** have been synthesized from the corresponding amido esters **1a-f**. The possible mechanistic pathways have been suggested for the LAH reduction of **1a-f** and are based on the products distribution.

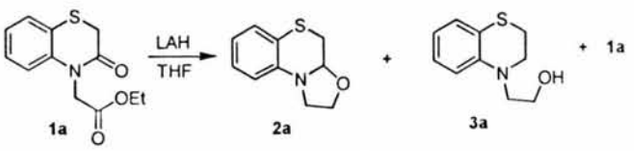
Metal hydride reduction of aldehydes, ketones, carbamates and esters by lithium aluminium hydride (LAH) is a well-documented process.[1-4] Reports are also available for the reduction of ketoximes to amines[5] and aziridines.[6,7] LAH was also used for the reduction of isoxazolines to give γ-aminoalcohols[8] and in a few cases it was employed for the reduction of allenic alcohol[9] and intramolecular cyclization reactions.[10] Though LAH was widely used for several organic transformations, to the best of our knowledge there is no report for its use for intramolecular reductive cyclisation of amide esters to give oxazole derivatives. We report herein a novel method for the preparation of various tricyclic [6:6:5] systems by reductive cyclisation of amide esters by LAH.

The amide ester derivatives **1a-g** were prepared by a known protocol.[11] LAH (1.1 eq) reduction of ethyl 2-(3-oxo-3,4-dihydro-2*H*-[1,4]benzthiazine-4-yl)-acetate **1a** in THF at room temperature for 1 hr gave 1,2,3a,4-tetrahydro[1,3]oxazolo[2,3-*c*]benzthiazine **2a** (**Scheme I**) in excellent yield (80%). Formation of the expected alcohol derivative 2-(benzthiazine-4-yl)ethanol **3a** was not observed even as a minor product. The spectroscopic data confirmed the structure of the tricyclic product as **2a**.

We wanted to explore the mechanistic pathways



Scheme I



Scheme II

through which the reductive cyclisation might be proceeding. Thus, we carried out the reactions of **1a** with LAH (**Scheme II**) in different molar ratios as can be seen in **Table I**.

From the result, it is clear that even with 0.5 eq. of LAH, 40% (ratio was determined by HPLC) of the tricyclic product **2a** was formed along with the unreacted starting material (60%). No amino alcohol **3a** was detected. When 1 eq. of LAH was used, the yield of tricyclic adduct increased to 96%, reducing the amount of the unreacted starting material to nearly 4 %. (**Table I**).

When 2 to 6 % molar equivalents of LAH was used, 3-28 % of amino alcohol **3a** was formed as indicated by HPLC analysis along with 97-72% of the tricyclic adduct **2a**. With increasing amount of LAH,

Table I—Lithium aluminium hydride reduction of ethyl 2-(3-oxo-3,4-dihydro-2*H*-[1,4]benzthiazine-4-yl) acetate **1a**

Sl. No.	LAH[a] (eq)	Ratio of products[b] (%)		
		1a	2a	3a
1	0.5	60	40	0
2	1	4	96	0
3	1.1	0	100	0
4	2	0	97	3
5	4	0	91	9
6	6	0	72	28

[a]All reactions were carried out in dry THF under inert atmosphere at room temperature (*ca*, 25°C) for 0.45 hr; [b]Product ratios were determined by HPLC; column: Inertsil ODS; mobile phase : 0.01 M KH_2PO_4 and CH_3CN (30:70); λ_{max}. 235 nm; retention time : **1a**, 5.29 min.; **2a**, 4.37 min.; **3a**, 8.2 min.

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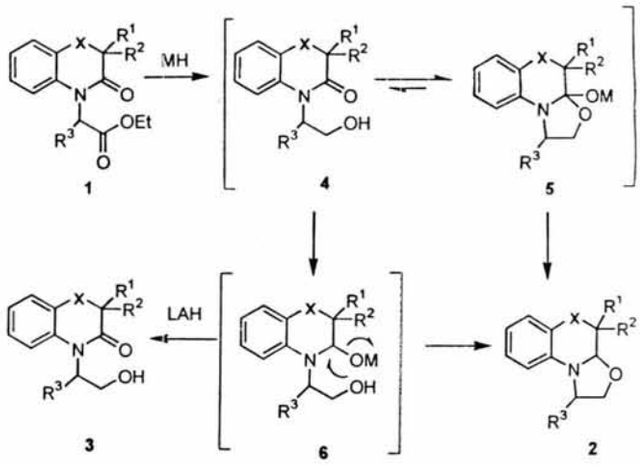
the ratio of **2a:3a** changed from 97:3 to 72:28. Isolation of products in experiments using 2-6 equivalents of LAH suggests that the total yield of the products is decreasing, perhaps due to the formation of some undesired side product. This suggests that the tricyclic adduct **2a** may be an intermediate which is getting further reduced to the amino alcohol **3a**; however, when **2a** was treated with 4-6 equivalents of LAH under similar conditions, no amino alcohol was formed. Hence, formation of the amino alcohol **3a** *via* **2a** is ruled out. Thus, both the products, namely amino alcohol **3a** and the tricyclic compound **2a** must be arising through independent pathways as shown in **Scheme III**.

Formation of the tricyclic compound **2** can be rationalized through the initial reduction of **1** to amino alcohol **4** which may instantaneously cyclise to the cyclic compound **5**. In contrast, compound **4** may react with excess of LAH to form the diol **6** which may get reduced further with LAH to give the amino alcohol **3** or cyclise to afford **2**. In the presence of excess of LAH, therefore, the yield of **2** decreases as the yield of alcohol **3** increases. In order to substantiate this mechanism as well as to develop a new method to synthesize the hitherto unknown tricyclic compound **2**, we carried out LAH reduction of several amido esters **1b-1g**. The results are shown in **Table II**. All the reactions were carried out in inert atmosphere using LAH (1.1 eq.) in THF.

In cases where the resultant tricyclic products are **2b-2e**, no side products were observed. In contrast, reduction of **1f** under identical conditions resulted in the formation of a seven membered cyclic adduct **2f** (40%) along with the amino alcohol **3f** (48%). Surprisingly, reduction of the amido ester **1g** did not give the cyclic product **2g** at all. Instead, the corresponding amino alcohol **3g** was isolated in a quantitative yield. With the present knowledge of understanding, it is rather difficult to rationalize



Scheme III

complete switch of reaction pathways from [6:6:5] system to [6:7:5] system. However, one can perhaps imagine a poor thermodynamic stability of ring closure to form **5** from **4**, which is possibly a reversible process. Under such condition, pathway leading to **3** may predominate. However, the present reaction offers a tool to prepare several heterocycles of [6:6:5] type tricyclic system with remarkable ease and excellent yield, and are of synthetic utility.

Experimental Section

IR spectra (Neat) were recorded on a Perkin-Elmer FTIR 1600 spectrophotometer, ^{1}H and ^{13}C NMR spectra were recorded on Varian Gemini 200 MHz spectrometer using TMS as internal standard. HPLC was carried out on a Waters equipment. Mass spectra were run on HP 5989A mass spectrometer. Reactions were monitored by TLC on silica gel 60 (E. Merck) of 0.25 mm thickness. Column chromatography was carried on Merck silica gel (70-230 mesh). Room temperature mentioned varied between 25 and 30°C. Lithium aluminium hydride was obtained from

Table II—Preparation of tricyclic[6:6:5] and [6:7:5] derivatives

Sl. No.	Substrate	R^1	R^2	R^3	X	Yield[a] (%)	
						2	3
1	**1a**	H	H	H	S	80	-
2	**1b**	H	H	H	O	76	-
3	**1c**	H	H	H	CH_2	56	-
4	**1d**	H	H	Ph	S	60	-
5	**1e**	H	Cl	H	S	70[b]	-
6	**1f**	H	H	H	$(CH_2)_2$	40	48
7	**1g**	Cl	Cl	H	$(CH_2)_2$	-	89

[a]Isolated yields after column chromatography [b]**2e** = **2a**

Aldrich and was used directly. Solvents were purified and dried according to standard procedures.

Reaction of 1a-g with lithium aluminium hydride : General procedure. To a solution of amide ester **1a-g** (2 mmoles) in dry THF (10 mL) at 0 °C, lithium aluminium hydride (LAH, 2.2 mmoles) was added in several portions over a period of 20 min. and stirred for 1 hr at room temperature. The reaction mixture was quenched with aqueous Na_2SO_4 solution. The reaction mixture was filtered and the filtrate concentrated. The crude product was purified by column chromatography using ethyl acetate and pet. ether (5:95) to give the required product **2a-g**.

1,2,3a,4-tetrahydro[1,3]oxazolo[2,3-*c*] benzthiazine 2a : Yield 80%, light yellow syrup, liquid; IR (Neat) : 3058, 2866, 1588, 1489, 1347, 989, 747 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): 7.14 (t, J = 7 Hz, 1H), 7.03 (d, J = 7 Hz, 1H), 6.66 (t, J = 7 Hz, 1H), 6.52 (d, J = 8 Hz, 1H), 5.04 (dd, J = 3 and 9 Hz, 1H), 4.3 (m, 1H), 4.1 (q, J = 7 Hz, 1H), 3.5 (m, 2H), 3.1 (dd, J = 2.3 and 10 Hz, 1H), 2.65 (dd, J = 9 and 11 Hz, 1H); ^{13}C NMR (DEPT) : δ 27.67 (CH_2), 46.34 (CH_2), 65.26 (CH_2), 86.0 (CH), 112.07 (CH),115.18 (C), 117.06 (CH), 126.29 (CH), 127.05 (CH), 141.3 (C) ; MS (relative intensity) : m/z 193 (M^+, 100%), 178 (5), 164 (10), 162 (30), 150 (60).

1,2,3a,4- Tetrahydro[1,3]oxazolo[2,3-*c*]benzoxazine 2b : Yield 76%, light yellow syrupy liquid; IR (Neat) : 2878, 1607, 1501, 1467, 1213, 1046, 746 cm^{-1}; ^1H NMR. ($CDCl_3$, 200 MHz) : δ 6.9 (m, 2H), 6.72 (m, 2H), 4.88 (dd, J = 3 and 10 Hz, 1H), 4.4 (dd, J = 2.9 and 13 Hz, 1H), 3.8-4.2 (m, 2H), 3.4-3.7 (m, 4H); MS (relative intensity) : m/z 177 (M^+, 100 %), 146 (75), 134 (20), 118 (60).

1,2,4,5-Tetrahydro 3a *H*-[1,3]oxazolo[3,2-*a*]quinoline 2c : Yield 56% pale yellow thick liquid; IR (Neat) : 2925, 2853, 1605, 1502, 1461, 1159, 757, 589 cm^{-1}, ^1H NMR ($CDCl_3$, 200 MHz) : δ 7.99 (d, J = 7 Hz, 1H), 7.56 (m, 1H), 7.1 (m, 1H), 6.5 (m, 1H), 4.8 (dd, J = 4 and 9 Hz, 1H), 4.2 (m, 1H), 4.0 (m, 1H), 3.4 (m, 2H), 2.8 (m, 2H), 2.3 (m, 1H), 2.1 (m, 2H), 1.56 (m, 4H); MS (relative intensity) : m/z 174 (M^+, 30%), 149 (70), 135 (40), 125 (75), 111 (50), 97 (100).

1-Phenyl-1,2,3a,4-tetrahydro[1,3]oxazolo-[2,3-*c*]benzthiazine 2d. Yield 60% light yellow syrupy liquid; IR(Neat) : 3026, 2929, 2867, 1586, 1484, 1308, 1040, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) : 7.1-7.3 (m, 6H), 6.8 (t, J = 8 Hz, 1H), 6.62 (t, J = 7 Hz, 1H), 6.34 (d, J = 9 Hz, 1H) 5.42 - 5.49 (dd, J = 4 and 14 Hz, 1H), 3.12-3.20 (dd, J = 4 and 16 Hz, 1H), 2.62 (dd, J = 9 and 12 Hz, 1H); MS (relative intensity) : m/z 269 (M^+, 100%), 226 (40), 222 (10), 208 (20), 194 (30), 149 (30), 136 (50).

1,2,3a,4,5,6-hexahydro[1,3] oxazolo[3,2-*a*]-benzazepine 2f.. Yield 70%, pale yellow thick liquid; IR (Neat) : 2934, 1598, 1493, 1088, 768 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) : δ 7.25-6.85 (m, 4H), 4.29 (dd, J = 2.2 and 10 Hz, 1H), 4.1 (dd, J = 2 and 10 Hz, 2H), 3.6 (m, 1H), 3.4 (m, 1H), 2.85 (m, 1H), 2.7 (m, 1H), 2.2 (m, 1H), 1.9 (m, 1H), 1.7 (m, 1H); MS (relative intensity) : m/z 189 (M^+, 75%), 160 (50), 130 (100), 118 (40).

2-(2,3,4,5- tetrahydro-1*H*-benzazepine-1-yl)-ethanol 3f. Yield 48 %, pale yellow thick liquid; IR (Neat) : 3417, 2925, 1596, 1494, 1450, 1055, 761 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) : δ 7.15 (m, 2H), 6.9 (m, 2H), 3.8 (m, 2H), 3.3 (m, 2H), 2.9 (m, 2H), 2.8 (m, 2H), 1.8 (m, 2H), 1.6 (m, 2H); MS (relative intensity) : m/z 191 (M^+, 10 %), 160 (100), 145 (10), 130 (20), 118, (91).

2-(3,3- dichloro-2,3,4,5-tetrahydro-1*H*-benzazepine-1-yl)ethanol 3g. Yield 89 % pale yellow thick liquid; IR (Neat) : 3420, 2931, 1606, 1493, 1305, 1050, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) : δ 7.2 (m, 3H), 6.7 (m, 2H), 4.3 (m, 2H), 3.5-3.9 (m, 6H), 2.6 (m, 2H); MS (relative intensity) : m/z 259 (M^+, 10%), 207 (20), 176 (100), 161, 146, 130.

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11 The starting materials **1a-g** were prepared following the procedure described by : Pachter S J & Kloetzel M C, *J Am Chem Soc*, 74, **1982**, 1321; all the compounds gave satisfactory spectral data.