Synthesis of Lysergic Acid Derivatives by Tandem Radical Cyclisation Reactions

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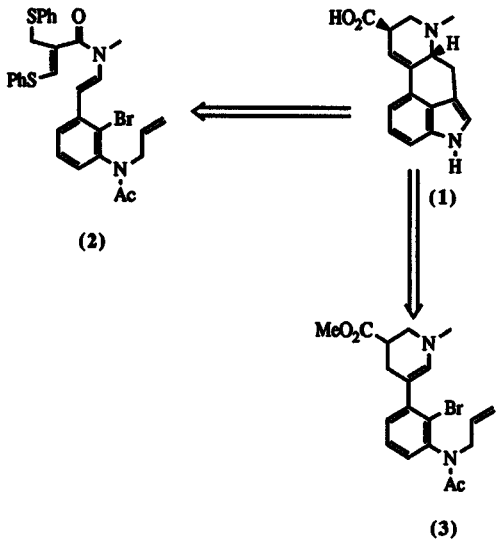
Received 1 March 1993

Abstract: A double radical cyclisation of a 2-bromoaniline derivative, initiated with tri-n-butyltin hydride, to construct the lysergic acid ring system is described; formation of a 6-membered D ring is controlled by an intramolecular thermal cyclisation prior to radical addition.

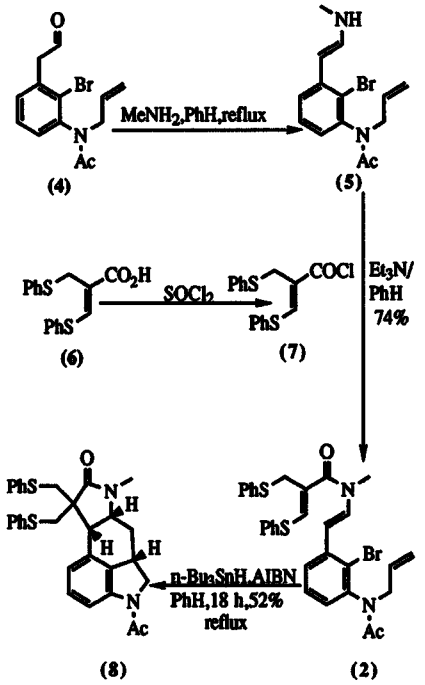
Lysergic acid **1** was first isolated from the hydrolytic solutions of ergot alkaloid peptides[1], and has become the centre of interest of both medicinal[2] and synthetic chemistry [3] due to remarkable pharmacological properties of its derivatives[4]. In our continuing study [5] towards the synthesis of lysergic acid **1** and its analogues via tandem radical cyclisation reactions[6], we investigated the use of enamide **2** and enamine **3** as starting materials for this conversion as detailed in Scheme 1.



Scheme 1

In our first approach a possible triple radical cyclisation of enamide **2** was undertaken. The first two cyclisations of the similar systems were established previously[5], and found to follow a 5-exo-trig, 6-endo-trig pathway. In the final step of the triple cyclisation, we hoped that the 6-endo ring closure would be encouraged by the geometry of the system brought about by the amide bond[7] and the possibility of ejecting a phenylsulphenyl radical[5,8], and also due to the electronic factors. Synthesis of enamide **2** was achieved in 74% yield by coupling enamine **5** with acid chloride **7** in the presence of tri-ethylamine. Enamine **5** was prepared from aldehyde **4**[5] by passing anhydrous methylamine through a boiling solution of **4** in benzene with the removal of water as it formed, and was treated immediately with the acid chloride **7**, which was prepared freshly from the corresponding carboxylic acid **6**[9] by the reaction of thionyl chloride.

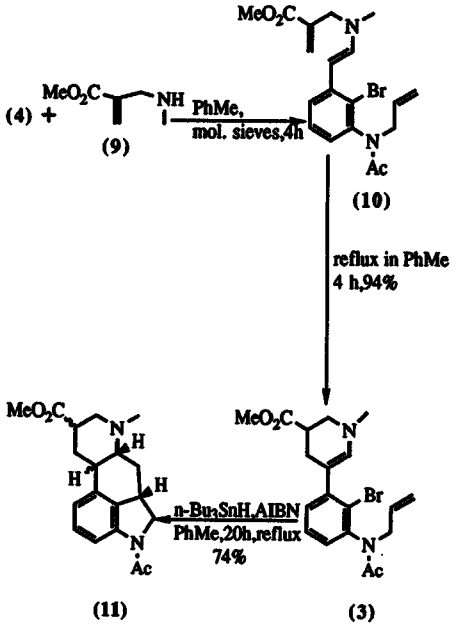
Addition of tri-*n*-butyltin hydride (1.1 mol. equiv.) in benzene containing azoisobutyronitrile (AIBN) (0.1 mol. equiv.) to a boiling solution of **2** in benzene gave the tetracyclic amine **8** in 52% yield, Scheme 2.



Scheme 2

Formation of the 5-membered ring was disappointing, showing that the kinetically favoured product **8** stabilized further by the sulphur atoms had overcome the factors favouring for 6-endo ring closure. Attempted ring expansion reaction of **8** by following literature procedures for similar systems[10] failed to give the desired 6-membered D ring system.

In our second approach, enamine **3** was chosen for our methodology since it already possessed the 6-membered D ring prior to radical



Scheme 3

cyclisation. This would offer an opportunity for the synthesis of tetrahydro lysergic acids **11** after a successful double radical cyclisation reaction. Preparation of the enamine **3** is straightforward; treatment of **4** with the amine **9** in the presence of molecular sieves (4Å) in dry toluene at room temperature afforded a mixture of cyclised **3**, and uncyclised **10**, enamines in 94% yield. Although cyclisation of **10** to **3** takes place slowly at room temperature , we found it more convenient to transform the crude mixture to **3** by refluxing in toluene immediately prior to radical cyclisation. Addition of a tri-*n*-butyltin hydride (1.1 mol. equiv.) solution containing AIBN (0.1 mol. equiv.) in toluene to a boiling solution of the enamine **3** afforded methyl 1-acetyl-2,3,9,10-tetrahydrolysergate **11** as a 3:1 (by NMR) mixture of two diastereoisomers [11] in 74% yield, Scheme 3.

With these results we are working on the total synthesis of 2,3-dihydro lysergic acid *via* a deprotection and indoline oxidation sequence of the amine **11**, and methods to establish the 9,10-double bond for the total synthesis of lysergic acid **1**.

Experimental Procedure

Anhydrous methylamine gas was bubbled through a solution of methyl α-bromoacrylate (1.2 mol. equiv., 0.085 g) in dry toluene (10 ml) for 20 min. at 0°C, during which a white solid formed. Excess methylamine was removed by passing nitrogen gas through the reaction solution for 4 hrs. at room temperature.Freshly prepared aldehyde (**4**, 0.402 mmol, 0.125 g) in dry toluene (5 ml) and Linde 13X molecular sieves (1.0 g) were added; and the resulting mixture was stirred at r.t. for 4 hrs. under a nitrogen atmosphere. The solution was filtered and the solvent removed *in vacuo* to give a mixture of cyclised **3**, and uncyclised **10**, enamines (0.154 g, 0.379 mmol) in 94% yield. Crude enamines were dissolved in dry toluene (25 ml, 0.0152M), and the mixture was deoxygenated by bubbling the nitrogen through for 0.5 h at room temperature. The reaction mixture was refluxed for 4 hrs, to ensure the cyclisation of **10** to the desired enamine **3** was complete. Then a solution of tri-*n*-butyltin hydride (1.1 mol. equiv., 0.110 ml) and azoisobutyronitrile (7 mg) in dry-degassed toluene (10 ml,0.040M) was added over 20 hrs to the boiling reaction mixture by using a syringe pump under a nitrogen atmosphere. The solvent was then removed *in vacuo* to give an oil which was purified by column chromatography (silica; 1.Petrol ether 2.ether:methanol 10:1) to give methyl 1-acetyl-2,3,9,10-tetrahydrolysergate **11**, (92 mg, 74%) as a foamy solid.

We thank the University of Ankara for a research grant to Y.O.

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11. υ_{max} (thin film) 1732s (ester), 1654s, 1637s (amide) cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.23-1.50(m, 2H), 2.50-3.20 (m, 6H), 3.26-3.33 (m, 1H), 3.50-3.70 (m, 2H), 4.14-4.24 (m, 1H), 6.78-6.92 (m, 1H), 7.11 (t, 1H), 7.80 (d, 1H), also singlets at: 2.19 (s, 3H, -NAc), 2.33 (s, 3H, -NMe) 3.66 (s, 3H, -COOMe) for the major isomer, and at 2.23 (s, -NAc) 2.36 (s, -NMe), 3.68 (s, -COOMe) for the minor isomer in a ratio of 3:1. M/z(EI) Found M^+, 328.1787, $C_{19}H_{24}N_2O_3$, requires 328.1788, 283 (3%), 243 (40%),131 (100%)