

A FACILE SYNTHESIS OF 8-SUBSTITUTED-4-HYDROXY-2-METHYL- 6,7-METHYLENEDIOXY-1,2,3,4-TETRAHYDROISOQUINOLINES

Tariq R. Sobahi, Salem A. Basaif, Abdullah M. Asiri and Mohamed A. Hassan

Department of Chemistry, Faculty of Science, King Abdulaziz University,

Jeddah-21589, P.O.Box 80203, Saudi Arabia

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سب وجود التأثير المتلازم والمتناسق لمجموعتي السرايل أمينو و الألكوكسي المتجاورتين في مركب (3) *N*-methyl-*N*-(2,2-diethoxyethyl)piperonylamine ، الذي تم استخدامه كمادة أولية لتحضير عديد من مشتقات أيزوكينولين المستبدلة في الوضع 8- التي من المتوقع أن يكون لها نشاط بيولوجي فعال. يتم إحلال الليثيوم بسرعة وانتقائية مرتفعة في المركب 3 عند الموقع 2- بواسطة *n*-butyllithium في ثنائي إيثيل إيثر عند درجة صفر مئوية والذي يتفاعل بدوره مع الكهروفيولات المختلفة ومن ثم يتم الحلوقة في وسط حمضي ليعطي سلسلة من المركبات 8-substituted-4-hydroxy-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline

Owing to the concomitant coordinating effect of the adjacent benzylamino and alkoxy groups, *N*-methyl-*N*-(2,2-diethoxyethyl)piperonylamine (3), which was used as a starting material for the synthesis of different 8-substituted-4-hydroxy-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolines, is rapidly and exclusively lithiated at the position-2 with *n*-butyllithium in diethyl ether at 0°C. Successive reactions with electrophiles followed with cyclization in acidic medium give the corresponding 8-substituted-4-hydroxy-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolines

INTRODUCTION

The isoquinoline alkaloids are an important class of natural products including simple isoquinolines, like anhalamine produced by the cactus peyote, or benzoisoquinolines, such as morphine and codeine, present in the opiate poppies, whose powerful physiologic effects such as an anesthetics and analgesic effects are well-known. Probably due to this "bewitching" characteristics many chemists have attempted to synthesis these natural products as well as the synthesis of their analogues with the aim to modify their physiological activity [1-3].

It is well-known that different 8-substituted isoquinolines are rare due to their synthetic difficulties. In this general context we are engaged in the synthesis of 8-substituted-isoquinolines *via* lithiation of *N*-methyl-*N*-(2,2-diethoxyethyl)-piperonyl amine followed by ring closure in acid medium.

EXPERIMENTAL

Reagents: piperonal, bromoacetaldehyde diethyl acetal, dibenzyl disulfide, oxirane, paraformaldehyde and *n*-butyllithium (1.68M in hexane) were supplied by the Aldrich Chemical company, whilst *p*-toluenesulfonylazide was prepared by treatment of *p*-toluenesulfonyl-chloride with sodium azide.

Preparation of *N*-methylpiperonylamine (2).

Piperonal (1) (15g, 0.1mol) was added to 40% aqueous solution of methylamine, and the mixture stirred at room temperature for 1 hour. The crude reaction product was then extracted with ether (3x30ml). The combined ether extracts were washed with water (2x20ml), dried over MgSO₄, filtered and evaporated to yield the residue which was added to a solution of NaBH₄ (6.4g, 0.2mol) in anhydrous diethyl ether (50ml) while stirring under reflux for 1 hour. After cooling at 0°C, water (50ml) was cautiously added, the mixture filtered and the solid product was dissolved in chloroform (100ml) then washed

with water (3x50ml). The organic phase was separated and the aqueous phase extracted again with chloroform (3x50ml). The collected organic phases were dried over $MgSO_4$, filtered and evaporated to give **2** as colorless oil (13.2g, 83%); 1H NMR (200MHz, $CDCl_3$) δ 6.81 (1H, broad s, CH Ar), 6.75 (2H, broad s, 2CH Ar), 5.91 (2H, s, CH_2O), 3.63 (2H, s, CH_2N), 2.43 (3H, s, CH_3), 1.28 (1H, s, NH) ppm; MS (70 eV) m/z 44(45%), 77(38), 135(100), 164(49), 165(44 M^+); $C_9H_{11}NO_2$ (165), Calcd.: C, 65.45; H, 6.67; N, 8.48. Found: C, 65.37; H, 6.71; N, 8.40.

Preparation of *N*-methyl-*N*-(2,2-diethoxyethyl)-piperonylamine (**3**).

A mixture of *N*-methylpiperonylamine (**2**) (40g, 0.24mol), bromoacetaldehyde diethyl acetal (48g, 0.24mol) and potassium hydroxide (40g, 0.71mol) in water (20ml) was vigorously stirred for 2 hours at 100°C. After cooling to 20°C, diethyl ether (150ml) was added, the organic layer separated and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the residue was chromatographed on a silica gel column (200g, using diethyl ether as eluent) gave **3** as pale yellow oil (62g, 88%). This was purified to 99% by GLC. Further effort to improve the purity (e.g. by distillation) was unsuccessful; 1H NMR (200MHz, $CDCl_3$) δ 6.86 (1H, broad s, CH Ar), 6.73 (2H, broad s, 2CH Ar), 5.92 (2H, s, CH_2O), 4.62 (1H, t, $J=5.5$ Hz, CHCH₂), 3.81-3.32 (4H, m, 2CH₂), superimposed on 3.48 (2H, s, CH_2N), 2.56 (2H, d, $J=5.5$ Hz, CH_2CH), 2.27 (3H, s, CH_3), 1.20 (6H, t, $J=7.0$ Hz, 2CH₃) ppm; MS (70 eV) m/z 47(28%), 77(18), 103(8), 135(100), 178(15), 281(1 M^+); $C_{15}H_{23}NO_4$ (281), Calcd.: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.51; H, 8.47; N, 4.78.

General procedure for lithiation and electrophilic displacement of **3**: Formation of 2-substituted-*N*-methyl-*N*-(2,2-diethoxyethyl)piperonylamine **4-7**.

To a solution of **3** (7.0g, 25mmol) in anhydrous diethyl ether (120ml), at 0°C under nitrogen, *n*-butyllithium (17ml, 1.68M in hexane, 27mmol) was added dropwise by a syringe. The reaction mixture was stirred for 1 hour where a white precipitate was obtained. Electrophilic reagents (30mmol) such as dibenzyl disulfide, oxirane, paraformaldehyde and *p*-toluenesulfonylazide were added individually dropwise at

0°C. The reaction mixture was warmed to room temperature and stirred at this temperature for 1.5 hour. Water (25ml) was added, the organic layer separated, dried over anhydrous sodium sulfate and evaporated *in vacuo* to give the desired products **4-7**, respectively. Compounds **4** and **5** were not isolated since their crude products were directly treated with dilute HCl to give the corresponding isoquinolines **8** and **9**, respectively.

Compound 6: Colorless crystals from *n*-hexane, mp 51-52°C; 1H NMR (200MHz, $CDCl_3$) δ 6.67 (1H, d, $J=7.8$ Hz, CH Ar), 6.65 (1H, d, $J=7.8$ Hz, CH Ar), 6.33 (1H, broad s, OH), 5.98 (2H, s, CH_2O), 4.63 (1H, t, $J=5.5$ Hz, CHCH₂), 4.61 (2H, s, CH_2OH), 3.72-3.42 (4H, m, 2CH₂), superimposed on 3.57 (2H, s, CH_2N), 2.60 (2H, d, $J=5.5$ Hz, CH_2CH), 2.25 (3H, s, CH_3), 1.20 (6H, t, $J=7.0$ Hz, 2CH₃) ppm; $C_{16}H_{25}NO_5$ (311), Calcd.: C, 62.72; H, 8.09; N, 4.50. Found: C, 66.82; H, 7.93; N, 4.75.

Compound 7: Colorless crystals from *n*-hexane, mp 73-74°C; 1H NMR (200MHz, $CDCl_3$) δ 6.84 (1H, d, $J=6.9$ Hz, CH Ar), 6.60 (1H, d, $J=6.9$ Hz, CH Ar), 6.02 (2H, s, CH_2O), 4.68 (1H, t, $J=5.4$ Hz, CHCH₂), 3.88-3.35 (4H, m, 2CH₂), superimposed on 3.50 (2H, s, CH_2N), 2.63 (2H, d, $J=5.4$ Hz, CH_2CH), 2.35 (3H, s, CH_3), 1.22 (6H, t, $J=7.0$ Hz, 2CH₃) ppm; $C_{15}H_{22}N_4O_4$ (322), Calcd.: C, 55.90; H, 6.83; N, 17.39. Found: C, 55.78; H, 6.76; N, 17.42.

Reduction of *N*-methyl-*N*-(2,2-diethoxyethyl)-2-azido-3,4-methylenedioxybenzyl amine (**7**) to *N*-methyl-*N*-(2,2-diethoxyethyl)-2-amino-3,4-methylenedioxybenzyl amine (**11**).

To a suspension of lithium aluminium hydride (1.6g, 42mmol) in anhydrous diethyl ether (100ml), at room temperature under nitrogen, **7** (7.0, 22mmol) in diethyl ether (50ml) was added dropwise by a syringe. The reaction mixture was then heated under reflux for 1 hour. After cooling at 0°C, water (50ml) was cautiously added. The mixture was filtered and the solid washed with chloroform (50ml). The organic phase was separated and the aqueous phase extracted with chloroform (3x50ml). The collected organic phases were dried over anhydrous sodium sulfate and the solvent evaporated *in vacuo* to obtain **11** as pale yellow crystals, mp 63°C, (1.21g, 82%) and purified to 95% by GLC; 1H NMR (200MHz, $CDCl_3$) δ 6.48 (1H, d, $J=7.8$ Hz, CH Ar), 6.20 (1H, d, $J=7.8$ Hz, CH Ar), 5.89 (2H, s, CH_2O),

4.67 (1H, t, $J=5.6$ Hz, $CHCH_2$), 4.65 (2H, broad s, NH_2), 3.64 (2H, dq, $J=9.5, 7.1$ Hz, CH_2), 3.50 (2H, dq, $J=9.5, 7.1$ Hz, CH_2), superimposed on 3.50 (2H, s, CH_2N), 2.55 (2H, d, $J=5.6$ Hz, CH_2CH), 2.20 (3H, s, CH_3), 1.20 (6H, t, $J=7.0$ Hz, $2CH_3$) ppm; $C_{15}H_{24}N_2O_4$ (296), Calcd.: C, 60.81; H, 8.11; N, 9.46. Found: C, 60.67; H, 8.13; N, 9.35.

General procedure for cyclization of 4-6: Formation of 8-substituted-4-hydroxy-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolines 8-10.

The crude products of 4-6 were treated, individually, with 20% aqueous hydrochloric acid (150ml) and allowed to react at room temperature for 16 hrs with stirring. The resulting solution was treated with charcoal, filtered and basified with 40% aqueous sodium hydroxide, while keeping the temperature below 40°C. The aqueous solution was extracted with dichloromethane (3x100ml). The collected organic phase was dried over anhydrous sodium sulfate, filtered and the solvent was evaporated *in vacuo* to give the desired 8-substituted isoquinolines 8-10.

Compound 8: Pale yellow crystals from ethyl acetate, mp 194-195°C; 1H NMR (200MHz, $CDCl_3$) δ 7.10 (5H, m, 5CH Ar), 6.79 (1H, s, CH Ar), 5.96 (1H, d, $J=1.3$ Hz, OCH_2O), 5.94 (1H, d, $J=1.3$ Hz, OCH_2O), 4.37 (1H, broad s, $CHOH$), 3.94 (2H, s, $S-CH_2$), 3.88 (1H, broad s, OH), 3.58 (1H, d, $J=15.7$ Hz, CH_2N), 2.82 (1H, ddd, $J=11.7, 1.7, 0.9$ Hz, CH_2CH), 2.64 (1H, d, $J=15.7$ Hz, CH_2N), 2.31 (3H, s, CH_3), 2.26 (1H, dd, $J=11.7, 1.7$ Hz, CH_2CH) ppm; $C_{18}H_{19}NO_3S$ (329), Calcd.: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.47; H, 5.73; N, 4.37.

Compound 9: colorless crystals from ethanol, mp 182-183°C; 1H NMR (200MHz, $DMSO-d_6$) δ 6.80 (1H, s, CH Ar), 5.92 (1H, s, OCH_2O), 5.91 (1H, s, OCH_2O), 5.10 (1H, d, $J=7.0$ Hz, $CHOH$), 4.73 (1H, t, $J=5.4$ Hz, CH_2OH), 4.51 (1H, sym. m, $CHCH_2$), 3.50-3.30 (3H, m, $CH_2OH+CH_2CH_2N$), 3.29 (1H, d, $J=14.7$ Hz, CH_2CH_2N), 2.75 (1H, dd, $J=10.9, 5.0$ Hz, CH_2CH), 2.64 (2H, t, $J=7.4$ Hz, CH_2CH_2OH), 2.35 (3H, s, CH_3), 2.29 (1H, dd, $J=10.9, 7.3$ Hz, CH_2CH) ppm; $C_{13}H_{17}NO_4$ (251), Calcd.: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.31; H, 6.74; N, 5.79.

Compound 10: colorless crystals from ligroin: ethanol (1:1), mp 174-175°C; 1H NMR (200MHz, $DMSO-d_6$) δ 6.86 (1H, s, CH Ar), 5.95 (1H, s,

OCH_2O), 5.94 (1H, s, OCH_2O), 5.14 (1H, d, $J=6.5$ Hz, $CHOH$), 4.94 (1H, t, $J=5.0$ Hz, CH_2OH), 4.52 (1H, sym. m, $CHCH_2$), 4.39 (2H, d, $J=5.0$ Hz, CH_2OH), 3.62 (1H, d, $J=15.1$ Hz, CH_2N), 3.36 (1H, d, $J=15.1$ Hz, CH_2N), 2.78 (1H, dd, $J=10.8, 5.3$ Hz, CH_2CH), 2.34 (3H, s, CH_3), 2.28 (1H, dd, $J=10.8, 7.3$ Hz, CH_2CH) ppm; $C_{12}H_{15}NO_4$ (237), Calcd.: C, 60.56; H, 6.37; N, 5.90. Found: C, 60.71; H, 6.19; N, 6.02.

RESULTS AND DISCUSSION

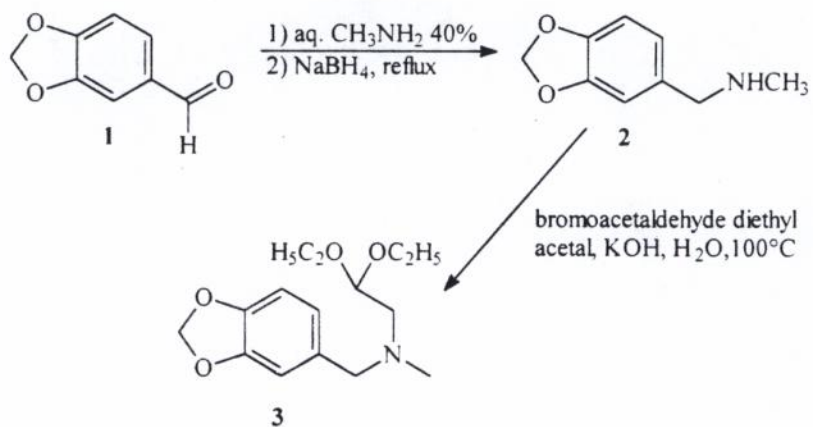
In order to synthesise different 8-substituted-4-hydroxy-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolines, *N*-methyl-*N*-(2,2-diethoxyethyl)piperonylamine (3) was used as a starting material. Preparation of *N*-methyl-*N*-(2,2-diethoxyethyl)piperonylamine (3) was achieved by treatment of *N*-methyl-piperonylamine (2), which was prepared by reacting 40% aqueous methylamine with piperonal (1) and successively adding of sodium borohydride, bromoacetaldehyde diethyl acetal and aqueous potassium hydroxide solution at 100°C to produce the desired product 3 in very good yield 88% (Scheme 1).

Owing to the concomitant coordinating effect of the adjacent benzylamino and alkoxy groups, *N*-methyl-*N*-(2,2-diethoxyethyl)piperonylamine (3) is rapidly and exclusively lithiated at the position-2 with *n*-butyllithium in diethyl ether at 0°C [4-6]. Successive reactions with different electrophiles such as dibenzyl disulfide, oxirane, paraformaldehyde and *p*-toluenesulfonylazide give the corresponding substituted products 4-7, respectively (Scheme 2) [7,8].

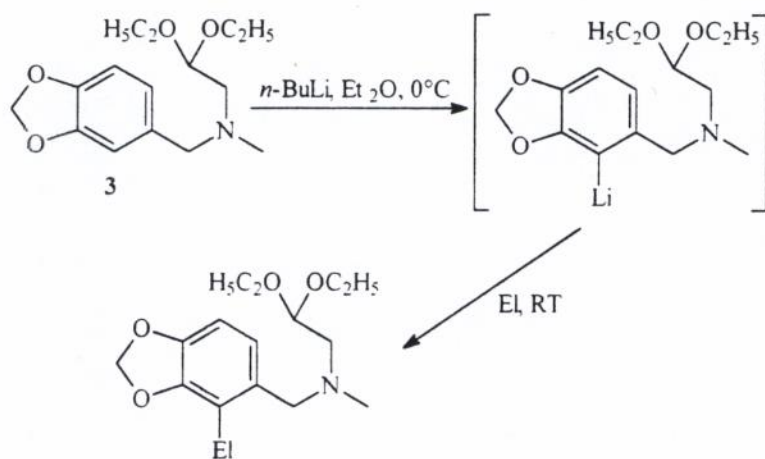
Acid-catalyzed cyclization of the products 4-6 give access to a series of 8-substituted-4-hydroxy-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolines 8-10, respectively, as shown in scheme 3 [9,10].

Reduction of the product *N*-methyl-*N*-(2,2-diethoxyethyl)-2-azido-3,4-methylenedioxybenzylamine (7) with lithium aluminium hydride in anhydrous diethyl ether under reflux, under nitrogen, produced *N*-methyl-*N*-(2,2-diethoxyethyl)-2-amino-3,4-methylenedioxybenzylamine (11) in excellent yield 95% (Scheme 4).

Unfortunately, cyclization of each azido- or amino-substituted products 7 and 11 respectively, gave a mixture of unidentified products.

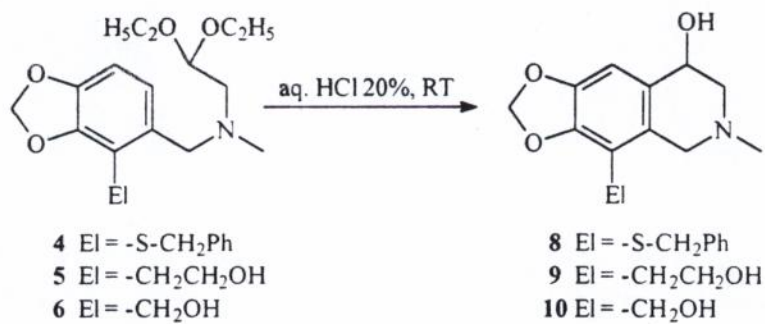


Scheme 1



- 4 El = $-\text{S}-\text{CH}_2\text{Ph}$
5 El = $-\text{CH}_2\text{CH}_2\text{OH}$
6 El = $-\text{CH}_2\text{OH}$
7 El = $-\text{N}_3$

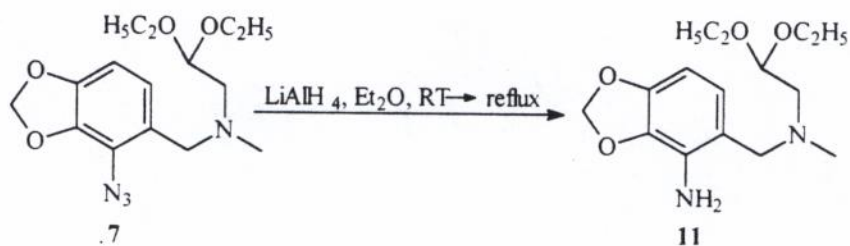
Scheme 2



- 4 El = $-\text{S}-\text{CH}_2\text{Ph}$
5 El = $-\text{CH}_2\text{CH}_2\text{OH}$
6 El = $-\text{CH}_2\text{OH}$

- 8 El = $-\text{S}-\text{CH}_2\text{Ph}$
9 El = $-\text{CH}_2\text{CH}_2\text{OH}$
10 El = $-\text{CH}_2\text{OH}$

Scheme 3



Scheme 4

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