

Synthesis and Characterization of Some New Diazahomoadamantan Derivatives

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الخلاصة

لقد تم تحضير بعض مشتقات أريل - 3 ، 6 - ثنائي أزا هومو أدامنتان الجديدة ، الحاملة لمجموعة معوضة في الهيكل الأروماتي أو الأليفاتي . إن تكثيف المركب ميتا نيترو بنزائل مثيل كيتون ورباعي مثيلين ثنائي أثيلين رباعي أمين (الاسم التجاري - تيوتروبين) مع حامض الخليك أدى الى تحضير المركب الأولي 1- ميتا نيترو فنيل - 3 ، 6 - ثنائي أزا هومو أدامنتان - 9 - أون (1) وبمنتوج جيد اعتماداً على تفاعل ماناخ . إن تفاعل المركب الأولي (1) مع مختلف الكواشف الكيميائية مثل بورون رباعي هيدريد الصوديوم وحامض الخليك اللامائي ، ونظام الاختزال المعدني المؤلف من (ألنسيوم - كلوريد النيكل المائي) ، وهيدروكسيل أمين هيدروكلوريد ، تحت ظروف مناسبة ، أعطى المركبات المقابلة الجديدة . لقد تم تشخيص هذه المركبات الجديدة بواسطة التقنيات الفيزيائية مثل التحليل الكمي الدقيق للعناصر ، وطيف الأشعة تحت الحمراء ، وطيف الرنين النووي المغناطيسي للبروتون ، إضافة الى تعيين درجة الانصهار .

ABSTRACT

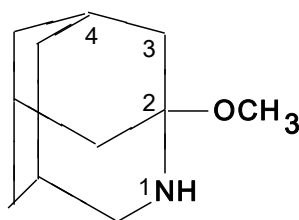
Some new aryl-3,6-diazahomoadamantan derivatives , (where the substituents are on the aromatic or on the aliphatic skeleton) are prepared . Condensation of m-nitrobenzylmethylketone , tetramethylenediethylenetetramine (teotropine) and acetic acid gave the starting material of 1-(m-nitrophenyl)-3,6-diazahomoadamantan-9-one 1 in a good yield according to the Mannich's reaction . Reaction of compound 1 or it's derivatives with various chemical agents like { NaBH_4 , $(\text{CH}_3\text{CO})_2\text{O}$, $\text{Al-NiCl}_2.6\text{H}_2\text{O}$ and $\text{NH}_2\text{OH.HCl}$ } under appropriate conditions gave the new corresponding derivatives . These new compounds were characterized by various physical techniques like : microanalysis , FTIR spectra , ¹HNMR spectra and melting point .

INTRODUCTION

The synthesis and application of monoaza , diaza and triazamacrocyclic

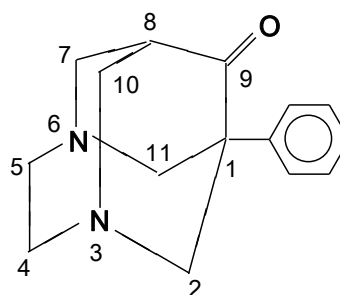
compounds such as 2-methoxyazaadamantan (A-structure) , 1-phenyl-3,6-diazahomoadamantan-9-one (B-structure) and Tris(ethylene) triamine (C-structure) have an enormous interest and diversity in recent years [1 – 5] . Metal complexes of these compounds have found application as oxidation catalysts and as hydrolase enzyme mimics capable of the non-oxidative cleavage of RNA and DNA [6] . According to the Mannich's reaction , condensation of benzyl methylketone with tetramethylenediethylenetetramine in acetic acid gave 1-phenyl-3,6-diazahomoadamantan-9-one (B structure) in a selective yield [7 – 8] . The nitration process for aryl-3,6-diazahomoadamantan with acidic mixture of ($\text{H}_2\text{SO}_4 / \text{HNO}_3$, in

a molar ratio of (1 : 1) guide to obtain nitro group in the para-position of aromatic skeleton [9] . When (B structure) have been treated with NaBH_4 as a reducing agent , carbonyl group can be converted into hydroxyl group in a good yield [9] . In the recent years , reagent based on aluminium find wide application in organic synthesis because of their ready availability , easy handling and low cost [11] . The system metallic of aluminium – nickel chloride hexahydrate in THF chemoselectively reduces the double bond of a , β – unsaturated ketones without effecting other reducible functional group like carbonyl and ester groups [11] .



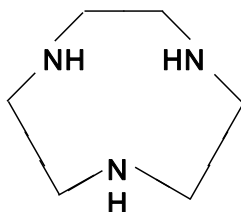
A structure

2-methoxyazaadamantan-9-one



B structure

1-phenyl-3,6-



C structure

Tris(ethylene)triamine

MATERIALS AND METHODS

Chemicals and instruments

Reagents and solvents were of standard grade and used without further purification . Crude tetramethylenediethylenetetramine (teotropine) was purified by recrystallization from isopropanol . Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected . FTIR spectra were recorded on a Perkin – Elmer 1720X FTIR spectrometer , KBr disc . Microanalysis were obtained using a Carlo Erba 1106 elemental analyzer . ^1H NMR spectra were obtained using a Bruker WM – 250 spectrometer in $\text{DMSO} - d_6$ using TMS as an internal standard . The analyses were achieved in (Institute of Organic Chemistry , Lenine Street , Moscow – Russia) .

Typical procedure

Synthesis of 1-(m-Nitrophenyl)-3,6-diazahomoadamantan-9-one 1

It was prepared according to the published procedure [9] as follows :

A mixture of m-nitrobenzylmethylketone (40 mmole , 7.16 gm) , tetramethylenediethylenetetramine (teotropine) (40 mmole , 6.72 gm) and acetic acid (120 mmole , 6.8 ml , 7.2 gm) in 40 ml of isopropanol were stirred for 1.5 hr at room temperature . The mixture was filtered off and added 20 ml of cold isopropanol . The volume's solution was reduced to 25 ml . The residue was kept for 12 hrs at (- 10 °C) , then filtered off . The crude product was recrystallized from toluene to obtain yellowish brown material (24 mmole , 6.9 gm , 60%) . $C_{15}H_{17}N_3O_3$ (M.wt = 287) , microanalysis (Found ; C , 62.5 ; H , 5.7 ; N , 14.3 , Calc. ; C , 62.7 ; H , 5.9 ; N , 14.6) , m.p = 128 – 130 °C . FTIR spectra , wave number (cm^{-1}) , KBr disc , stretching vibration of functional groups were : NO_2 (1345 , 1516) ; CO (1710) . 1H NMR spectra (Chem. Shift , ppm) in DMSO – d_6 solvent : N- CH_2 - CH_2 -N (s , 3.05 , 4H) , N- CH_2 -C (d , 3.19 – 3.48 , 8H , $J_{AB} = 13.5$ Hz) ; CH (s , 2.59 , 1H) ; C_6H_4 (m , 7.5-8.1 , 4H) .

Synthesis of 1-(m-nitrophenyl)-3,6-diazahomoadamantan-9-ol 2

It was prepared according to the published procedure [10] as follows :

A solution of sodium borohydride (15 mmole , 0.6 gm) in 15 ml ethanol was added dropwise to a solution of 1-(m-nitrophenyl)-3,6-diazahomoadamantan-9-one 1 (10 mmole , 5.2 gm) in 35 ml ethanol during 0.5 hr at room temperature . The mixture was stirred for 4.5 hrs at room temperature , also . 15 ml of distilled water was added , then extracted with toluene (2 x 20 ml) . The organic layer was dried over anhydrous $MgSO_4$ and filtered off . The solvent was evaporated under a reduced pressure . The crude product was recrystallized from hexane to obtain a pale yellow material (12.8 mmole , 3.71 gm , 71%) . $C_{15}H_{19}N_3O_3$ (M.wt = 289) , microanalysis (Found ; C , 62.6 ; H , 6.4 ; N , 14.2 , Calc. ; C , 62.2 ; H , 6.5 ; N , 14.5) , m.p = 107 – 109 °C . FTIR spectra , wave number (cm^{-1}) , KBr disc , stretching vibration of functional groups were : NO_2 (1425 , 1560) ; OH (3460) . 1H NMR spectra (Chem. Shift , ppm) in DMSO – d_6 solvent : N- CH_2 - CH_2 -N (s , 3.07 , 4H) , N- CH_2 -C (d , 3.15 – 3.48 , 8H , $J_{AB} = 13.5$ Hz) ; CH (s , 2.00 , 1H) ; C_6H_4 (m , 7.6-8.2 , 4H) ; OH (s , 4.49 , 1H) ; \underline{CH} -OH (s , 2.6 , 1H) .

Synthesis of 9-Oxoacetyl-1-(m-nitrophenyl)-3,6-diazahomoadamantan 3

A mixture of 1-(m-nitrophenyl)-3,6-diazahomoadamantan-9-ol 2 (2.45 mmole , 0.7 gm) and 7.5 ml of acetic anhydride in 4 ml hexane were stirred and refluxed for 1.5 hr. The solvent was evaporated under a reduced pressure . A solution of 5% NaOH was added to neutralize the solution . The product was extracted with toluene (2 x 10 ml) . The organic layer was dried over anhydrous MgSO₄ and filtered off. The solvent was evaporated under a reduced pressure . The product was purified by recrystallization from ethanol to obtain a yellowish - paige material (1.97 mmole , 0.65 gm , 82% yield) . C₁₇H₂₀N₃O₄ (M.wt = 330) , microanalysis (Found ; C , 61.4 ; H , 5.8 ; N , 19.2 , Calc. ; C , 61.8 ; H , 6.1 ; N , 19.4) , m.p = 196 – 198 °C .

Synthesis of 9-Oxoacetyl-1-(m-aminophenyl)-3,6-diazahomoadamantan 4

To a mixed solid mixture of aluminium powder (10 mmole , 0.58 gm) , nickel chloride hexahydrate (15 mmole , 3.56 gm) is added a solution of 9-oxoacetyl-1-(m-nitrophenyl)-3,6-diazahomoadamantan 3 (0.9 mmole , 0.3 gm) in freshly distilled 25 ml of THF at room temperature . A vigorous exothermic reaction takes place immediately which subsides for 15 minutes . The reaction mixture showed disappearance of the starting material , then diluted with 25 ml of THF and filtered off . Evaporation of the filtrate gave the crude product . Recrystallization from chloform – ethanol (1 : 1) gave a white material (0.67 mmole , 0.2 gm , 74% yield) . C₁₇H₂₂N₃O₂ (M.wt = 300) , microanalysis (Found ; C , 68.3 ; H , 7.1 ; N , 13.7 , Calc. ; C , 68 ; H , 7.3 ; N , 14) , m.p = 144 – 146 °C .

Synthesis of 9-Oxoacetyl-1-(m-acetamidophenyl)-3,6-diazahomoadamantan 5

The dry 9-oxoacetyl-1-(m-aminophenyl)-3,6-diazahomoadamantan 4 (2.5 mmole , 0.75 gm) in a beaker , 8 ml of acetic acid anhydride was added to cover the solid completely .

The beaker was covered and set aside at room temperature . The mixture became warm spontaneously during 5 minutes and allowed to proceed for 5 hrs . 10 ml of methylene chloride was added . The solid product was collected by filtration , washed with 3 ml of methylene chloride and dried at room temperature . Recrystallization from ethanol gave a white material (1.75 mmole , 0.6 gm , 71% yield) . C₁₉H₂₅N₃O₃ (M.wt = 343) , microanalysis (Found ; C , 66.9 ; H , 7.7 ; N , 12.8 , Calc. ; C , 66.4 ; H , 7.3 ; N , 12.2) , m.p = 204 – 206 °C .

Synthesis of 9-Oximo-1-(m-nitrophenyl)-3,6-diazahomoadamantan 6

A solution of hydroxylaminehydrochloride (10 mmole , 0.7 gm) in 5 ml of distilled water was added to a solution of 1-(m-nitrophenyl)-3,6-diazahomoadamantan-9-one 1 (5 mmole , 1.43 gm) in 5 ml of distilled water at room temperature . The mixture stirred and heated at 60 – 70 °C for 1 hr. A solution of Na₂CO₃ (10 mmole , 1.1 gm) in 5 ml of distilled water was added . The mixture was heated for 30 minutes at 60 – 70 °C again , then filtered off . The crude product was recrystallized from toluene to give a yellowish - white material (3.24 mmole , 0.98 gm , 65% yield) . C₁₅H₁₈N₄O₃ (M.wt = 302) , microanalysis (Found ; C , 60.3 ; H , 8.5 ; N , 22.3 , Calc. ; C , 59.6 ; H , 8.1 ; N , 21.8) , m.p = 218 – 220 °C .

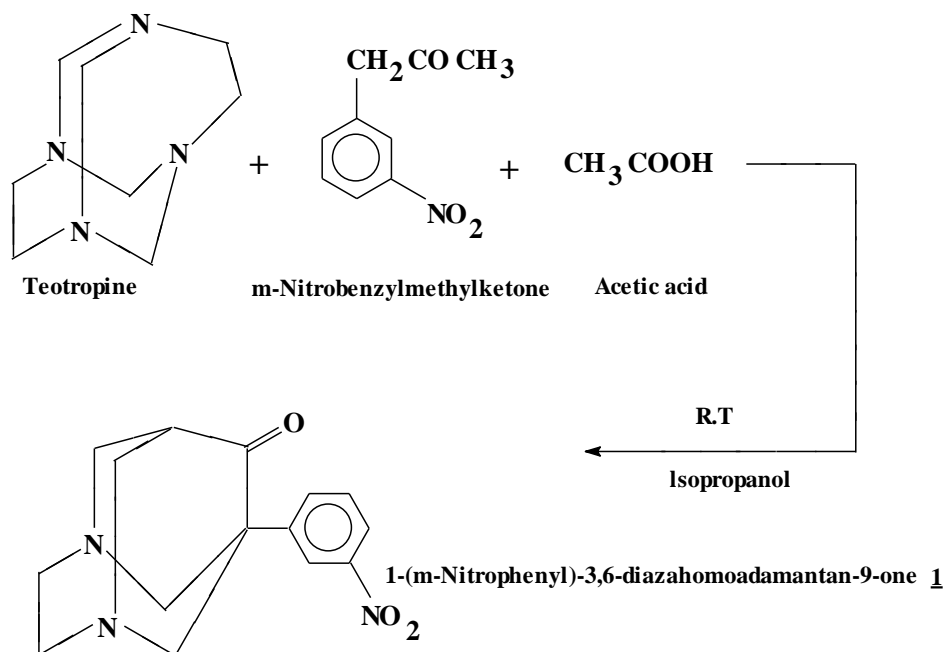
Synthesis of 9-Amino-1-(m-aminophenyl)-3,6-diazahomoadamantan 7

Analogous to the procedure of 9-oxoacetyl-1-(m-aminophenyl)-3,6-diazahomoadamantan 4 . Aluminium powder (15 mmole , 0.88 gm) , NiCl₂.6H₂O (22.5 mmole , 5.34 gm) and 9-oximo-1-(m-nitrophenyl)-3,6-diazahomoadamantan 6 (0.9 mmole , 0.27 gm) . Recrystallization from hexane gave a white material (0.66 mmole , 0.17 gm , 76 % yield) . C₁₅H₂₁N₄ (M.wt = 257) , microanalysis (Found ; C , 69.7; H , 8.5 ; N , 22.3 , Calc. ; C , 70 ; H , 8.1 ; N , 21.8) , m.p = 173 – 175 °C .

RESULTS AND DISCUSSION

A survey of diazahomoadamantan chemistry in recent years showed their importance in organic chemistry due to among other reasons their microbial effects , their roles as accelerators in rubber's industry and their thermal stability [4 , 9 – 10] . The present investigation describes the synthesis of some new aryldiazahomoadamantan derivatives (scheme 2 and scheme 3) , which were containing a substituted groups in the meta – position of the aromatic skeleton and a functional group in a position of carbon no. (C₉) of the aliphatic skeleton . The synthetic strategy is based on the Mannich's reaction in the present work . Kuznetsov and Co – Workers have prepared para – isomer of 1-(p-nitrophenyl)-3,6 – diazahomoadamantan-9-one derivatives in good yields and explained the synthesis , mechanism , characterization and stereochemistry [4 , 7 – 8] . In previous work , we prepared meta – isomer of 1-(m-nitrophenyl)-3,6 – diazahomoadamantan-9-one 1 and 1-(m-nitrophenyl)-3,6 – diazahomoadamantan-9-ol 2 in selective yields [9 – 10] . The condensation of m-nitrobenzylmethylketone , tetramethylenediethylenetetramine (trade's nomenclature – teotropine) and acetic acid in isopropanol are capable of producing the major

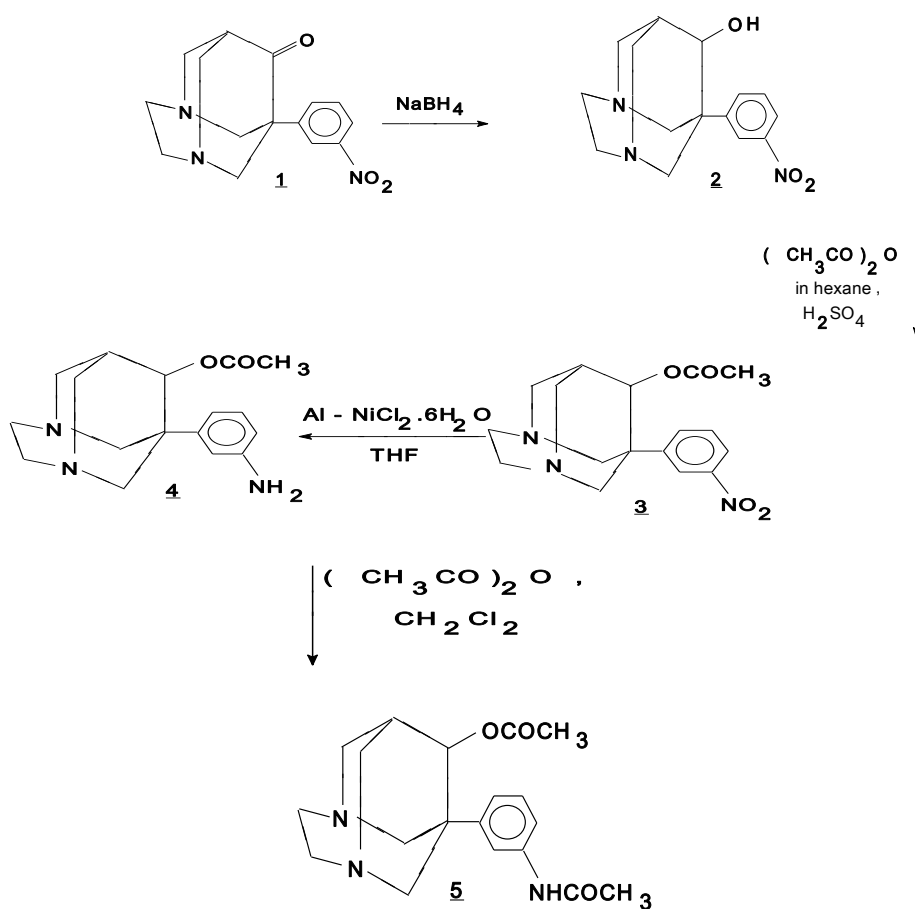
product 1-(m-nitrophenyl)-3,6-diazahomoadamantan-9-one 1 (65% yield , in a molar ratio of 1:1:3) . It is known that the reduction of compound 1 with NaBH_4 converts carbonyl group into hydroxyl group to get 1-(m-nitrophenyl)-3,6-diazahomoadamantan-9-ol 2 (81% yield , in a molar ratio of 1:1) . Based on the encouraging results , we carried out the acetylation of hydroxyl group when compound 2 reacted with excess of acetic anhydride to obtain 9-oxoacetyl-1-(m-nitrophenyl)-3,6-diazahomoadamantan 3 (82% yield) . We wish to report that the metallic system of ($\text{Al-NiCl}_2 \cdot 6\text{H}_2\text{O}$ / substrate in THF , in a molar ratio of 10:15:0.9) is very efficiently



Scheme-1: The reaction of synthesis the starting material of 1-(m-nitrophenyl)-3,6-diazahomoadamantan-9-one 1 [9]

reduces nitro group of compound 3 into amino group to give 9-oxoacetyl-1-(m-aminophenyl)-3,6-diazahomoadamantan 4 (74% yield) in a neutral condition, a short time reaction and a simple procedure . Anhydrous NiCl_2 does not react with aluminium powder even after long exposure . Addition of few drops of H_2O to this system initiates a vigorous exothermic reaction with evolution of H_2 and formation of a black precipitate which probably is NiO . The hydrogen might be produced by aluminium with HCl generated from hydrolysis of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$. Thus , the reduction of nitro group is probably due to electron transfer from NiO to the substrate . In compound 4 , amino group can be acetylated when sufficient acetic acid anhydride was covered the solid material completely in CH_2Cl_2 solvent to obtain 9-oxoacetyl-1-(m-acetamidophenyl)-3,6-diazahomoadamantan 5 (71%

yield) . The 9-oximo-1-(m-nitrophenyl)-3,6-diazahomoadamantan 6 can be obtained from the reaction between compound 1 and $\text{NH}_2\text{OH}\cdot\text{HCl}$ with Na_2CO_3 (65% yield , in a molar ratio of 1:2.5:2.5) . The metallic system of (Al-NiCl₂.6H₂O / substrate in THF and a molar ratio of 15:22.5:0.9) reduces oximo group and nitro group (compound 6) together into two various positions in aliphatic and aromatic skeletons to obtain 9-amino-1-(m-aminophenyl)-3,6-diazahomoadamantan 7 (76% yield) , (scheme 3) . FTIR spectra of all compounds showed bands of the stretching vibrations due to (C = O , NO₂ , NH₂ , NH , OH and C = N) groups in regions 1710 – 1735 cm⁻¹ , 1350 – 1530 cm⁻¹ , 3310 – 3430 cm⁻¹ , 3420 cm⁻¹ , 3450 cm⁻¹ and 1630 cm⁻¹ respectively , (table 1) . In the ¹HNMR spectra , the expected ratio of aliphatic to aromatic protons were observed . The protons of (NCH₂C) group for diazahomoadamantan derivatives have proved (AB – system) , due to doublet - doublet signals at range (2.8 – 3.5 ppm , ²J_{AB} = 13.5 Hz) . The protons of (NCH₂CH₂N) group appeared as a singlet around (3.1 – 3.6 ppm) . Some representative ¹HNMR data for the new compounds are gathered in (table 1) . The microanalysis for these new compounds agreed well with the calculated values.

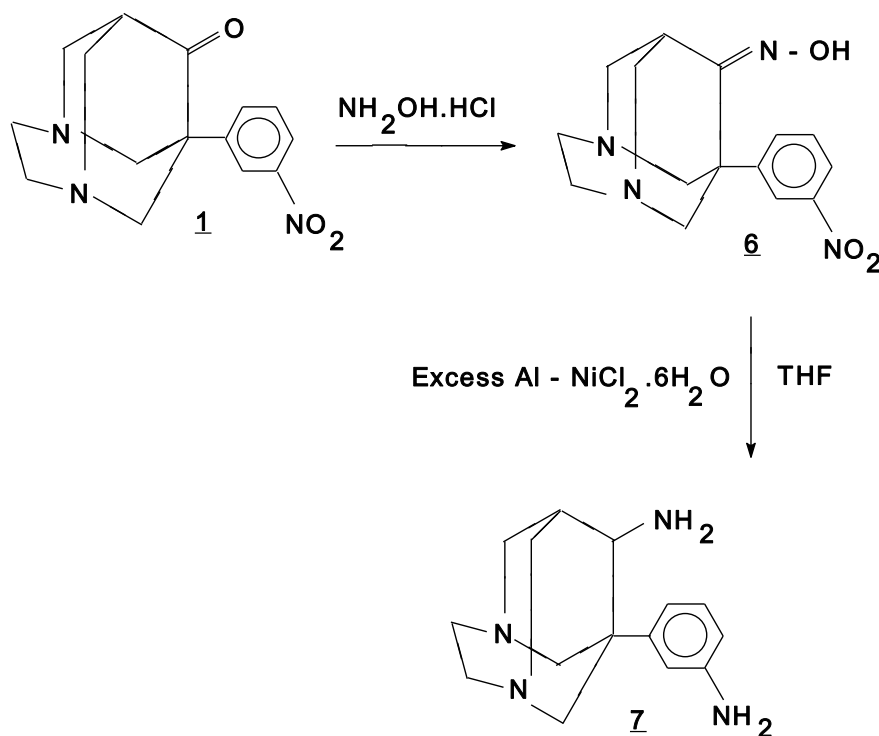


Scheme-2: The reactions of aryldiazahomoadamantan derivatives

Table -1: The ^1H NMR and FTIR data for the new compounds

Comp. No.	^1H NMR spectra (Chem. Shift , ppm) in DMSO – d_6 solvent , singlet signal at 2.5 ppm				FTIR spectra , wave number in (cm^{-1})
	N- CH_2 - CH_2 -N (S)	N- CH_2 -C (D) $^2J_{\text{AB}} = 13.5$ Hz	C-H (S)	C_6H_4 (M) , OCOCH_3 (S) , NCOCH_3 (S) , C = N – OH (Sb) , NH_2 aliph. (S) , NH_2 aromat. (Sb)	
3	3.6	3.3 – 3.5	2.6	$\text{C}_6\text{H}_4 = 7.6 – 8.1$, $\text{COCH}_3 = 1.6$	C=O (1735) , NO_2 (1350 , 1520)
4	3.5	3.2 – 3.3	2.6	$\text{C}_6\text{H}_4 = 7.5 – 8.1$, $\text{NH}_2 = 3.7$, $\text{COCH}_3 = 1.3$	C=O (1730) , NH_2 (3420 , 3320)
5	3.5	3.1 – 3.4	2.6	$\text{C}_6\text{H}_4 = 7.6 – 8.1$, $\text{NH} = 3.7$, $\text{OCOCH}_3 = 2.6$, $\text{NCOCH}_3 = 1.3$	OC=O (1730) , NC=O (1710) , NH (3420)
6	3.5	3.4 – 3.5	2.6	$\text{C}_6\text{H}_4 = 7.6 – 8.2$, C=N-OH = 9.5	OH (3450 , 3110) , C=N (1630) , NO_2 (1355 , 1530)
7	3.1	2.8 – 3.2	2.6	$\text{C}_6\text{H}_4 = 6.6 – 7.8$, NH_2 aliph. = 3.5 , NH_2 aromat. = 1.2	NH_2 (3430 , 3310 , 3200)

S = singlet , D = doublet , M = multiplet , Sb = broad singlet , $^2J_{\text{AB}} = \text{AB}$ system .



Scheme 3:-The new oximo and diaminodiazahomoadamantan derivatives

The present investigation furnished effective routes for synthesis of five new aryldiazahomoadamantan derivatives in selective yields by using $(\text{CH}_3\text{CO})_2\text{O}$, $\text{Al-NiCl}_2.6\text{H}_2\text{O}$ and $\text{NH}_2\text{OH.HCl}$ as reagents . Synthesis, optimization and characterization of aryldiazahomoadamantan derivatives with the base of Mannich's reaction for the starting material only are described herein . The reactions are operationally simple and use the effective metallic system is the first with aryldiazahomoadamantan derivatives to fulfill the reduction of nitro and oximo groups into amino group . The $^1\text{HNMR}$, FTIR spectra and microanalysis were done successfully to determine the structures of these new compounds .

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