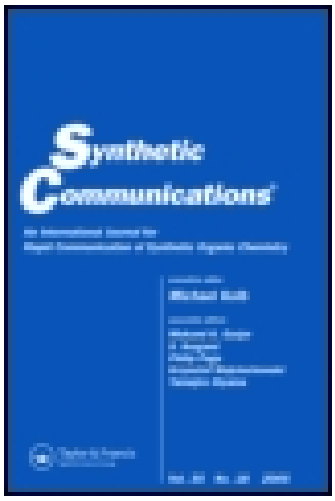

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Ceric Ammonium Nitrate (CAN) Catalyzed Efficient One-Pot Three Component Aza-Diels-Alder Reactions for a Facile Synthesis of Tetrahydropyranoquinoline Derivatives

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Ceric Ammonium Nitrate (CAN) catalyzed efficient one-pot three component aza-Diels-Alder reactions for a facile synthesis of tetrahydropyranoquinoline derivatives

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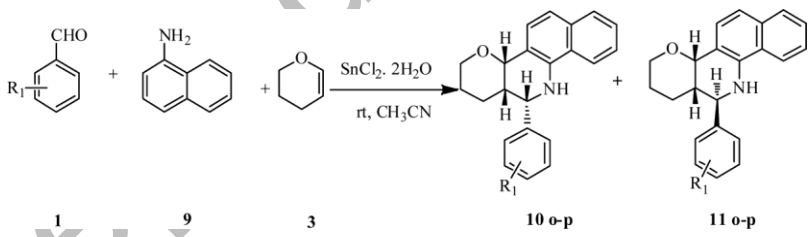
Abstract

A simple, efficient and cost-effective method for the synthesis of tetrahydropyranoquinoline derivatives by a one-pot condensation of aromatic aldehyde, aromatic amine and 3,4-dihydro-2*H*-pyran respectively in the presence of ceric ammonium nitrate (CAN) has been described.



KEYWORDS: Multicomponent reactions, tetrahydropyranoquinolines, 3,4-dihydro-2*H*-pyran

1. INTRODUCTION

In recent years, the multi-component reactions are highly important because of their wide range of applications in pharmaceutical chemistry for the rapid generation of structural

diversity in combinatorial libraries for drug discovery.[1-3] MCRs are extremely convergent, producing a remarkably high increase of molecular complexity in just one step. Recently Tetrahydroquinoline derivatives has attained considerable significance important class of natural products and exhibit biological activities in various fields, such as psychotropic, antiallergic, antiinflamatory and estronegic[4-7] and Pyrano tetrahydroquinolines are found in several alkaloids[8-10] such as Simulenoline **1**, huajiaosimuline **2**, zanthodioline **3**, flindersine **4**, veprisine **5** and oricine **6** (Figure 1). Due to their broad spectrum of biological interest chemists have developed methods for the synthesis of tetrahydroquinolines.[11-12]

Ceric (IV) ammonium nitrate (CAN) is a convenient and widely used reagent for affecting a wide array of synthetic transformations due to its many advantages such as solubility in organic solvents, low toxicity, high reactivity, and ease of handling. Although Ce (IV) derivatives are generally employed as one electron oxidants, the use of CAN as Lewis acid in C–C bond forming reaction has attracted great deal of attention.[13] In continuation of our ongoing research for the development of simple and efficient methods for the synthesis of various heterocyclic compounds[14-18] here, we present a simple, mild and efficient protocol for synthesis of tetrahydropyranoquinoline derivatives using CAN catalyst.

So far a very few methods have been reported[19-31] for the synthesis of tetrahydropyranoquinoline derivatives However, some of the methods employed for these synthesis have some limitations. To avoid these limitations we have searched for a new CAN catalyst, with high catalytic activity, easy availability, short reaction time and

simple work-up. CAN attraced our attention, since it has been used in many organic transformations.

2. RESULTS AND DISCUSSION

To the best of our knowledge, in literature there appears no report for the synthesis and screening of tetrahydropyranoquinoline derivatives using CAN. This fact has prompted us to investigate in depth the utility of CAN for the synthesis of tetrahydropyranoquinolines derivatives by a one-pot condensation of aryl aldehydes, substituted anilines, and 3,4-dihydro-2*H*-pyran in acetonitrile at room temperature (Scheme 1).

Initially, a pilot reaction was attempted using using benzaldehyde (2 mmol), aniline (2.2 mmol) and 3,4-dihydro-2*H*-pyran (2.6 mmol) in the presence of CAN (46 mg, 0.2 mmol) without any solvent. After 4 h, only 27 % of a mixture of the C-2 epimers (**4** and **5**) of a tetrahydroquinoline product was isolated as 1:1 ratio. This reaction (10 h) resulted in the isolation of the required product namely 5-Phenyl-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-c]quinolines (**4a**) and (**5a)** in low yield (45%). Increasing the amount of CAN to one mol equivalent did not improve the product yield to a considerable amount. Subsequently, we investigated on the use of different catalysts and solvents for the purpose. In chlorinated solvents such as dichloromethane and chloroform the reaction was very slow and resulted in lower product yield. Similar results were obtained in coordinating solvents such as THF, diethyl- and dimethyl ether and protic solvents such as MeOH or EtOH. After screening different solvents, CH_3CN came out as the solvent of

choice, which not only afforded the products in good yield, but also with higher reaction rates (90% yield in 0.5 h). It is also noticed that the condensation using CAN proceeds rapidly and is superior to the different reagents with respect to reaction time, temperature and yield. This claim is justified through the representative examples, illustrated in Scheme 1. All the reactions were characterized by ^{1}H NMR, IR and mass spectrometry.

In order to extend the scope of this catalytic transformation and find general applicability of this method, a reaction between aromatic aldehydes (**1**) and aniline (**2**) with 3,4-dihydro-2*H*-pyran (**3**) was verified. No observable *ortho*- and *para*- substituent effect was noted for various anilines used in the reaction (entry **4k**). This was one of the draw backs of the earlier methods. Aromatic aldehydes **1a-l**, aniline **2** and 3,4-dihydro-2*H*-pyran **3** in the presence of CAN undergo a fast 1:1:1 addition reaction at room temperature in acetonitrile (0.5-1 h) to produce substituted 5-Phenyl-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-c]quinolines (**4a**) and (**5a)** derivatives **4a-l** (Scheme 1). The results were excellent in terms of yields and product purity and compounds **4a-l, 5a-l** are stable solids whose structures are fully supported by IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry analysis.

In summary, we have developed an economically and environmentally friendly procedure for the synthesis of tetrahydropyranoquinoline derivatives with excellent yields and short reaction times which involve the use of inexpensive catalyst CAN under acetonitrile conditions. Furthermore, the present procedure is readily amenable to parallel synthesis and generation of combinatorial tetrahydropyranoquinoline libraries.

In order to extend the scope of this catalytic transformation, the general applicability of this method was verified by reacting with the number of substituted benzaldehydes, substituted anilines and different dienophiles. 2-Cyclohexenone (**6**) was utilized to obtain the corresponding phenanthridinone derivatives (**7 m-n)** and (**8 m-n)** (70:30) in 79.2% yield (Scheme 2).

Phenanthridine skeletons[32] are present in lycorine, chelidonine and haemanthamine alkaloids. CAN also catalyzed effectively the imino Diels-Alder reaction of in situ generated *N*-benzylidene-1-napthylamine (**9**) with 3, 4-dihydro-2*H*-pyran and 2,3-dihydrofuran to afford the phenanthridine derivatives (**10)** and (**11)** as a mixture of cis and trans isomers in good overall yields (65%) (Scheme 3). The pyran ring was cis-fused in the tetrahydroquinoline moiety and the stereochemistry of the products was established based on the coupling constants. The coupling constant of C5-H ($J_{4a,\,5}$ = 4.6-5.5 Hz) in **4** indicated the cis relationship between C-**4a** and C-5, whereas in **5** ($J_{4a,\,5}$ = 10.2-11.10 Hz) *trans* form. The simplicity, together with the use of inexpensive, non-toxic and environmentally benign nature of CAN catalyst in CH_3CN solvent is a remarkable feature of the procedure.

3. CONCLUSION

In summary, we have developed an economically and environmentally friendly procedure for the synthesis of tetrahydropyranoquinoline phenanthridinone, phenanthridine derivatives with excellent yields and short reaction times which involve the use of

inexpensive catalyst CAN under acetonitrile conditions. Furthermore, the present procedure is readily amenable to parallel synthesis and generation of combinatorial tetrahydropyranoquinoline libraries.

4. EXPERIMENTAL

4.1 Materials And Methods

All the commercial reagents and solvents were used without further purification unless otherwise stated. Melting points were recorded on a Buchi 535 melting point apparatus and are uncorrected. All the reactions were monitored by thin layer chromatography performed on precoated silica gel $60F_{254}$ plates (Merck). Compounds were visualized with UV light at 254 nm and 365 nm, I_2 and heating plates after dipping in 2% phosphomolybdic acid in 15% aq. H_2SO_4 soln. IR spectra were recorded on a Perkin-Elmer 683 or a 1310 FT-IR spectrometers with KBr pellets. NMR spectra were recorded on a Varian Unity-400 MHz and BRUKER AMX 300 spectrometers using TMS as an internal standard. ^{13}C NMR was recorded on a Varian Unity 100 MHz using $CDCl_3$ as internal standard. Mass spectra were recorded on a VG Micromass 7070H and a Finnigan Mat 1020B mass spectrometers operating at 70eV.

Typical experimental procedure for the preparation of compounds tetrahyroquinolines: Benzaldehye (1.1 mmol), Aniline (1.1 mmol), 3,4-dihydro-2*H*-pyran (1.3 mmol) and in acetonitrile (5 mL) were mixed in a flask and CAN (10 mol %) was added at room temperature. The resulting mixture was stirred at room temperature

for 30 min and completion of the reaction was monitored by TLC (ethyl acetate: hexane 4:6). The reaction mixture was extracted into $CHCl_3$and dried over Na_2SO_4 and solvent was evaporated and the crude residue obtained was purified by column chromatography [silica gel, ethyl acetate-hexane 10:90] to give pure tetrahydropyranoquinolines **4** and **5** in 97 % yield.

5-(3-Methoxy-phenyl)-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-c]quinoline (4 & 5b): ***Cis isomer* :** Thick syrup; *Rf* (20% EtOAc/n-hexane) 0.5.; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3374 (N-H), 3040, 2923, 2855, 1515, 1345, 1068, 759; ^{1}H NMR (300 MHz,$CDCl_3$), δ: 1.31-1.68 (m, 4H), 2.09-2.18 (m, 1H); 3.67 (m, 1H), 3.81 (s, 3H), 4.64 (d, *J* = 2.2 Hz, 1H), 5.27 (d, *J* = 5.2 Hz, 1H), 6.54 (d, *J* = 8.3 Hz, 1H), 6.78 (t, *J* = 11.3 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 3H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.37 (d, 1H); MS (ESI) m/z 296 $([M+H])^+$. Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74; O, 10.83. Found: C, 77.23; H, 7.17; N, 4.75.

Trans isomer : Mp 99-100 ^{o}C; *Rf* (20% EtOAc/n-hexane) 0.48.; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3374 (N-H), 3040, 2923, 2855, 1515, 1345, 1068, 759; ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.37-1.55 (m, 4H), 2.09-2.21 (m, 1H), 3.69 (dt, *J* = 3.0, 9.8 Hz, 1H), 3.79 (s, 3H), 4.09 (dd, *J* = 3.7, 11.3 Hz, 1H), 4.34 (d, *J* = 2.2 Hz, 1H), 4.67 (d, *J* = 10.5 Hz, 1H), 6.48 (d, *J* = 7.5 Hz, 1H), 6.65 (t, *J* = 8.3 Hz, 1H), 6.81 (dd, *J* = 3.7, 8.3 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 2H), 7.04 (dt, *J* = 1.51, 7.5 Hz, 1H), 7.16 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.24 (dd, *J* = 1.5, 7.5 Hz, 1H); MS (ESI) m/z 296 $([M+H])^+$. Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74; O, 10.83. Found: C, 77.25; H, 7.18; N, 4.74.

5-(2,4-Dichloro-phenyl)-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-c]quinoline (**4 & 5e**): ***Cis isomer***; Mp 133-136 ^{o}C; *Rf* (20% EtOAc/n-hexane) 0.5.; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3374 (N-H), 3040, 2923, 2855, 1515, 1345, 1068, 759; ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.39-1.57 (m, 4H), 2.18-2.38 (m, 1H), 3.42 (dt, *J* = 3.0, 11.3 Hz, 1H), 3.58 (dd, *J* = 3.7, 11.3 Hz, 1H), 5.01 (d, *J* = 2.2 Hz, 1H), 5.26 (d, *J* = 5.2 Hz, 1H), 6.55 (d, *J* = 6.8 Hz, 1H), 6.77 (t, *J* = 7.5 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 1H), 7.64 (m, 2H), 7.62 (d, *J* = 8.3 Hz, 2H); MS (ESI) m/z 334 $([M+H])^{+}$. Anal. Calcd. for $C_{18}H_{17}Cl_2NO$: C, 64.68; H, 5.13; Cl, 21.21; N, 4.19; O, 4.79. Found: C, 64.66; H, 5.14; N, 4.18.

Trans isomer *:* Thick syrup; *Rf* (20% EtOAc/n-hexane) 0.45.; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3374 (N-H), 3040, 2923, 2855, 1515, 1345, 1068, 759; ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.39-1.57 (m, 4H), 2.18-2.38 (m, 1H), 3.63 (dt, *J* = 3.0, 11.3 Hz, 1H), 3.92 (dd, *J* = 3.7, 11.3 Hz, 1H), 4.37 (d, *J* = 3.7 Hz, 1H), 5.09 (d, *J* = 8.3 Hz, 1H), 6.49 (d, *J* = 6.8 Hz, 1H), 6.69 (t, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 8.3 Hz, 1H), 7.24 (m, 3H), 7.39-7.45 (m, 2H); MS (ESI) m/z 334 $([M+H])^{+}$. Anal. Calcd. for $C_{18}H_{17}Cl_2NO$: C, 64.68; H, 5.13; Cl, 21.21; N, 4.19; O, 4.79. Found: C, 64.68; H, 5.12; N, 4.20

5-(4-Nitro-phenyl)-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinoline (**4 & 5q**): ***Cis isomer***; · Mp 163-165 ^{o}C; *Rf* (20% EtOAc/n-hexane) 0.5.; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3374 (N-H), 3040, 2923, 2855, 1515, 1345, 1068, 759 ; ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.17-1.59 (m, 4H), 2.16-2.24 (m, 1H), 3.41 (dt, *J* = 2.9, 9.5 Hz, 1H), 3.61 (dd, *J* = 3.2, 11.9 Hz, 1H), 3.81 (s, 1H), 4.68 (d, *J* = 2.2 Hz, 1H), 5.31 (d, *J* = 5.8 Hz, 1H), 6.61 (d, *J* = 8.1

Hz, 1H), 6.81 (t, *J* = 7.3 Hz, 1H), 7.07 (t, *J* = 7.3 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 8.26 (d, *J* = 8.8 Hz, 2H); MS (ESI) m/z 311 $([M+H])^+$. Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03; O, 15.47. Found: C, 69.64; H, 5.84; N, 9.00.

***Trans isomer* :** Mp 136-137 ^oC; *Rf* (20% EtOAc/n-hexane) 0.45.; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3377 (N-H), 3070, 2929, 2852, 1517, 1344, 1080, 750; ^1H NMR (300 MHz, $CDCl_3$), δ: 1.20-1.49 (m, 4H), 2.11-2.22 (m, 1H), 3.44 (dt, *J* = 2.9, 9.5 Hz, 1H), 3.77 (dd, *J* = 3.2, 1.9 Hz, 1H), 4.04 (s, 1H), 4.39 (d, *J* = 2.9 Hz, 1H), 4.85 (d, *J* = 10.2 Hz, 1H), 6.56 (d, *J* = 7.3 Hz, 1H), 6.74 (t, *J* = 7.3 Hz, 1H), 7.11 (t, *J* = 7.3 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 8.26 (d, *J* = 8.8 Hz, 2H); MS (ESI) m/z 311 $([M+H])^+$. Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03; O, 15.47. Found: C, 69.66; H, 5.84; N, 9.01.

5-(4-Bromo-phenyl)-9-isopropyl-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-]quinoline (4 & 5i): ***Cis isomer*** :Mp 101-104 ^oC; *Rf* (20% EtOAc/n-hexane) 0.5.; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3368 (N-H), 2936, 2860, 1493, 1067, 818; ^1H NMR (300 MHz, $CDCl_3$), δ: 1.21 (s, 3H), 1.25 (s, 3H), 1.42-1.59 (m, 2H), 2.02-2.13 (m, 1H), 2.74-2.88 (m, 1H), 3.32 (dt, *J* = 2.9, 10.9 Hz, 2H), 3.52 (dd, *J* = 3.6, 10.9 Hz, 2H), 4.92 (d, *J* = 2.18 Hz, 1H), 5.22 (d, *J* = 5.0 Hz, 1H), 6.45 (d, *J* = 8.0 Hz, 1H), 6.92 (dd, *J* = 2.1, 8.0 Hz, 1H), 7.22-7.30 (m, 3H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.69 (d, *J* = 8.7 Hz, 1H); MS (ESI) m/z 386 $([M+H])^+$. Anal. Calcd. for $C_{21}H_{24}BrNO$: C, 65.29; H, 6.26; Br, 20.68; N, 3.63; O, 4.14. Found: C, 65.26; H, 6.26; N, 3.61.

Trans isomer: Mp 94-95 ^{o}C; *Rf* (20% EtOAc/n-hexane) 0.45.; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3368 (N-H), 2936, 2860, 1493, 1067, 818; ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.94 (s, 3H), 1.23 (s, 3H), 1.39-1.54 (m, 2H), 2.02-2.13 (m, 1H), 2.72-2.82 (m, 1H), 3.62 (dt, *J* = 2.1, 11.65 Hz, 2H), 4.04 (dd, *J* = 2.1, 11.6 Hz, 2H), 4.30 (d, *J* = 2.1 Hz, 1H), 4.60 (d, *J* = 10.9 Hz, 1H), 6.45 (d, *J* = 8.0 Hz, 1H), 6.95 (dd, *J* = 2.1, 8.0 Hz, 1H), 7.01-7.02 (d, *J* = 2.18, 2H), 7.28 (d, *J* = 8.01 Hz, 2H), 7.48 (d, *J* = 8.7 Hz, 1H); MS (ESI) m/z 386 $([M+H])^{+}$. Anal. Calcd. for $C_{21}H_{24}BrNO$: C, 65.29; H, 6.26; Br, 20.68; N, 3.63; O, 4.14. Found: C, 65.28; H, 6.27; N, 3.65.

9-Fluoro-5-phenyl-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-c]quinoline (**4 & 5l**): ***Cis isomer*** : Mp 158-159 ^{o}C; *Rf* (20% EtOAc/n-hexane) 0.5.; ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.37-1.55 (m, 4H), 2.14 (m, 1H), 3.42 (dt, *J* = 3.02, 11.3Hz, 1H), 3.60 (dd, *J* = 3.02, 11.3 Hz, 1H), 3.70 (br s, 1H,), 4.63 (d, *J* = 3.0 Hz, 1H), 5.23 (d, *J* = 6.0 Hz 1H), 6.45-6.49 (d, *J* = 4.5 Hz, 1H), 6.78 (dt, *J* = 3.0, 8.3 Hz, 1H), 7.08-7.12 (dd, *J* = 3.0, 8.3 Hz, 1H), 7.24-7.39 (m, 5H); MS (ESI) m/z 284 $([M+H])^{+}$. Anal. Calcd. for $C_{18}H_{18}FNO$: C, 76.30; H, 6.40; F, 6.71; N, 4.94; O, 5.65. Found: C, 76.29; H, 6.40; N, 4.91.

***Trans isomer* :** Mp 82-84 ^{o}C; *Rf* (20% EtOAc/n-hexane) 0.48.; ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.31-1.50 (m, 2H), 1.57-1.68 (m, 1H), 1.75-1.87 (m, 1H); 2.07 (m, 1H), 3.71 (dt, *J* = 2.2, 11.3 Hz, 1H), 3.91 (br s, 1H), 4.08 (dd, *J* = 3.7, 10.5 Hz, 1H), 4.31 (d, *J* = 2.2 Hz, 1H), 4.64 (d, *J* =10.5 Hz, 1H), 6.39-6.44 (2d, *J* = 4.5 Hz, 1H), 6.81(dt, *J* = 3.0, 8.3 Hz, 1H), 6.88-6.92 (dd, *J* = 3.0, 9.0 Hz, 1H), 7.24-7.39 (m, 5H); MS (ESI) m/z 284

$([M+H])^+$. Anal. Calcd. for $C_{18}H_{18}FNO$: C, 76.30; H, 6.40; F, 6.71; N, 4.94; O, 5.65. Found: C, 76.29; H, 6.41; N, 4.95.

2-Fluoro-6-(4-fluoro-phenyl)-5,6a,7,8,9,10a-hexahydro-6*H*-phenanthridin-10-one (**4 & 5n**): ***Cis isomer*** : Mp 118-120 ^oC; *Rf* (20% EtOAc/n-hexane) 0.5.; ^1H NMR (300 MHz, $CDCl_3$), δ: 1.56-1.94 (m, 3H), 2.26-2.36 (m, 2H), 2.58-2.74 (m, 2H), 4.36-4.40 (m, 1H), 4.64 (d, J = 3.1 Hz, 1H), 6.40-6.46 (m, 2H), 6.72-6.81 (t, J = 7 .8 Hz, 1H), 7.32-7.34 (m, 4H); MS (ESI) m/z 314 $([M+H])^+$. Anal. Calcd. for $C_{19}H_{17}F_2NO$: C, 72.83; H, 5.47; F, 12.13; N, 4.47; O, 5.11. Found: C, 72.80; H, 5.46; N, 4.45.

Trans isomer : Mp 114-115 ^oC; *Rf* (20% EtOAc/n-hexane) 0.45.; ^1H NMR (300 MHz, $CDCl_3$), δ: 1.68-1.79 (m, 2H); 1.99-2.30 (m, 2H), 2.38-2.45 (m, 2H), 2.69-2.77 (m, 2H), 4.36-4.42 (m, 1H), 4.54 (d, J = 2.0 Hz, 1H), 6.50-6.55 (m, 2H), 6.79-6.81 (t, J = 8.3 Hz, 1H), 7.21-7.32 (m, 4H); MS (ESI) m/z 314 $([M+H])^+$. Anal. Calcd. for $C_{19}H_{17}F_2NO$: C, 72.83; H, 5.47; F, 12.13; N, 4.47; O, 5.11. Found: C, 72.85; H, 5.47; N, 4.45.

12-(2-Chloro-phenyl)-2,3,4a,11,12,12a-hexahydro-1*H*-4-oxa-11-aza-chrysene (Table 2, entry r): ***Cis isomer*** : m.p. 152-154 ^oC; *Rf* (20% EtOAc/n-hexane) 0.5.; ^1H NMR (300 MHz, $CDCl_3$), δ: 1.21-1.59 (m, 3H), 2.48 (m, 1H), 3.29-3.36 (m, 1H), 3.52-3.61 (m, 1H), 4.29-4.30 (m, 1H), 5.18 (d, J = 2.6 Hz, 1H), 5.45 (d, J = 6.4, Hz 1H), 7.17-7.35 (m, 2H), 7.37-7.45 (m, 5H), 7.48-7.54 (m, 2H), 7.93 (d, J = 2.07 Hz, 1H); MS (ESI) m/z 350 $([M+H])^+$. Anal. Calcd. for $C_{22}H_{20}ClNO$: C, 75.53; H, 5.76; Cl, 10.13; N, 4.00; O, 4.57. Found: C, 75.53; H, 5.74; N, 4.01.

Trans isomer : Thick syrup; *Rf* (20% EtOAc/n-hexane) 0.48.; ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.20-1.65 (m, 3H), 2.29 (m, 1H), 3.36-3.55 (m, 1H), 3.63-3.64 (m, 1H), 4.19-4.60 (m, 1H), 4.61 (d, J = 3.6 Hz, 1H), 5.31 (d, J = 10.9 Hz, 1H), 6.67-7.46 (m, 6H), 7.62-7.78 (m, 4H); MS(ESI) m/z 350 $([M+H])^+$. Anal. Calcd. for $C_{22}H_{20}ClNO$: C, 75.53; H, 5.76; Cl, 10.13; N, 4.00; O, 4.57. Found: C, 75.55; H, 5.75; N, 4.04.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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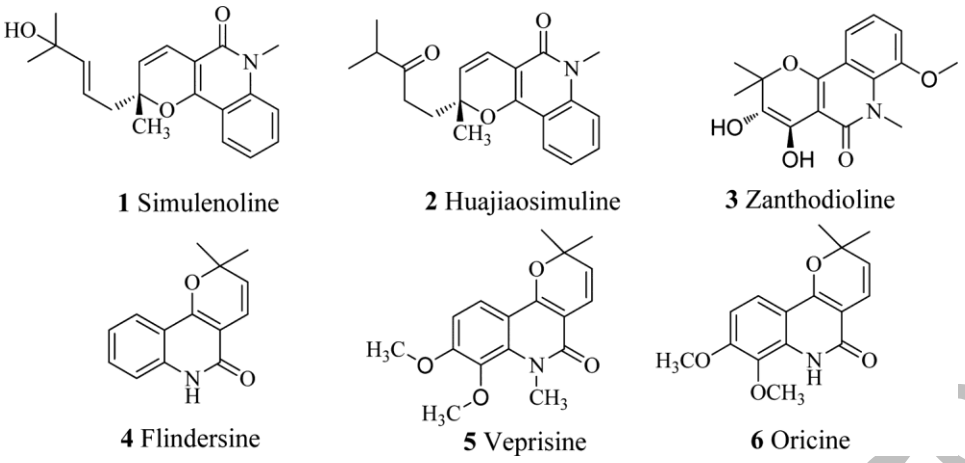
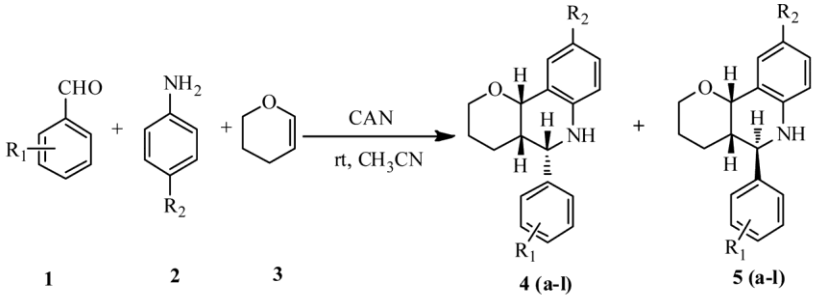
Figure 1.

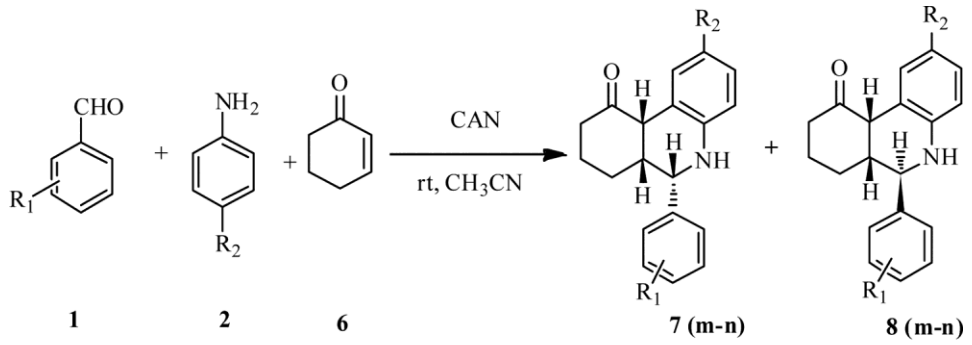


Scheme 1.



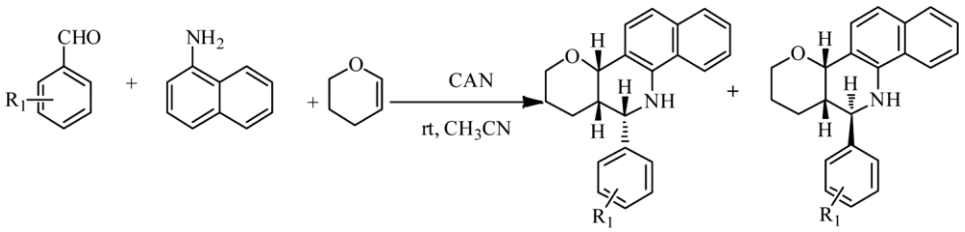
4&5a) R_1 & R_2 = H; **4&5b**) R_1 = 3-OMe, R_2 = H; **4&5c**) R_1 = 4-OMe, R_2 = H; **4&5d**) R_1 = 4-Cl, R_2 = H; **4&5e**) R_1 = 4-OMe, R_2 = H; **4&5f**) R_1 = 4-NO_2, R_2 = H; **4&5g**) R_1 = 4-F, R_2 = H; **4&5h**) R_1 = 4-Me, R_2 = H; **4&5i**) R_1 = 4-Br, R_2 = $(CH_3)_2$-CH-;**4&5j**) R_1 = H, R_2 = 4-Br; **4&5k**) R_1 = H, R_2 = 4-Cl; **4&5l**) R_1 = H, R_2 = 4-F;

Scheme 2.



7&8m) R_1 & R_2 = H; **7&8n**) R_1 = 4-F, R_2 = 4-F.

Scheme 3.



1 **9** **3** **10 o-p** **11 o-p**

10&11o) R_1 = H, R_2 = 1-Naphthyl; **10&11p**) R_1 = 2-Cl, R_2 = 1-Naphthyl.