Ceric Ammonium Nitrate: An Efficient Catalyst for One-Pot Synthesis of 2,2,4-Trimethyl-1,2-dihydroquinolines

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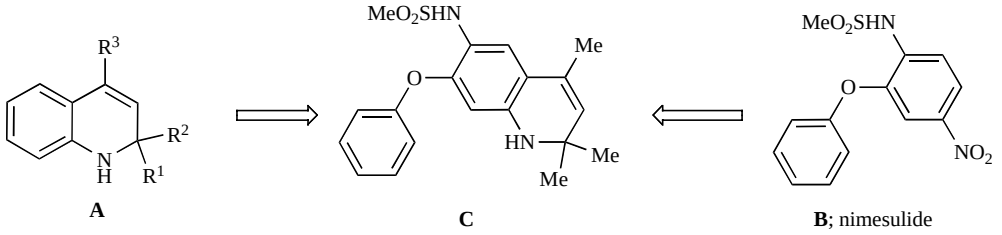
Abstract: Ceric ammonium nitrate (CAN) catalyzed the one-pot synthesis of 2,2,4-trimethyl-1,2-dihydroquinoline derivatives from substituted anilines and acetone *via* a modified Skraup reaction. The methodology was used to synthesize a novel dihydroquinoline-based compound derived from an anti-inflammatory agent nimesulide.

Keywords: CAN, catalysis, aniline, dihydroquinoline.

2,2,4 Substituted 1,2-dihydroquinolines **A** (Fig. **1**) have been found to be integral part of many bioactive molecules [1, 2]. They are also key synthetic precursors for a number of pharmacologically important compounds possessing antibacterial [3], antidiabetic [4] and anti-inflammatory [5] activities. Nimesulide (**B**, Fig. **1**) on the other hand is a well known anti-inflammatory drug available for patient's use to treat pain [6]. We hypothesized that combination of structural features of both **A** and **B** in a single molecule would provide a novel dihydroquinoline **C** (Fig. **1**) of potential pharmacological interest and therefore we planned to synthesize compound **C**.



A **C** **B**; nimesulide

Fig. (1). 2,2,4 Substituted 1,2-dihydroquinoline.

While a variety of methods [7-14] has been reported for the synthesis of compound **A** the most commonly used method however has been a modified Skraup [15] cyclization [16] due to its simplicity and easy availability of starting materials. This method involves the reaction of an aniline with acetone (or the desired ketone), in the presence of a volatile catalyst e.g. iodine at 170-175 °C (or 145 °C under pressure for 2–3 days). Other volatile catalysts, such as hydrogen chloride [17-20] and bromine [17] have also been used near the boiling point of aniline (184 °C) or lower temperatures at around 100 °C. Boron trifluoride has been used as a salt of aniline [21] or ether adduct [12]. Hydrogen chloride [22] and aluminum trichloride [23] were occasionally used in an autoclave. The use of nonvolatile homogeneous acids, such as p-aminobenzenesulfonic acid [17], benzenesulfonic acid [19], and *p*-toluenesulfonic acid [18-20] has also been reported. Recently, the use of lanthanide catalysts and microwave technology has been reported [24]. The methodology however, involved the use of expensive catalysts such as $Sc(OTf)_3$. Moreover, the use of microwave is challenging in large scale synthesis. More recently, synthesis *via* $Bi(OTf)_3$ catalyzed condensation of 2,2-dimethoxypropane with aromatic amines has been reported [25]. In our endeavor to develop a mild, inexpensive and microwave free scalable method to prepare compound **C** we now report ceric ammonium nitrate (CAN) catalyzed one-pot synthesis of 2,2,4-trimethyl-1,2-dihydroquinolines (**2**) from substituted anilines (**1**) and acetone *via* the modified Skraup reaction (Scheme **1**).

Our interest in the use of CAN stems from the fact that it catalyzed the reaction of anilines with vinyl ethers to afford 4-alkoxy-2-methyl-1,2,3,4-tetrahydroquinolines [26]. In the beginning of our study we carried out the reaction of aniline (**1a**) with acetone in the presence or absence of CAN. The results of this study are summarized in Table **1**. Initially, the reaction was carried out using 0.50 equiv of CAN when the product **2a** was isolated in 77% yield (entry 1, Table **1**). Encouraged by this observation we then planned to optimize the reaction conditions. Accordingly, a series of reactions were carried out changing the equiv of CAN used, reaction

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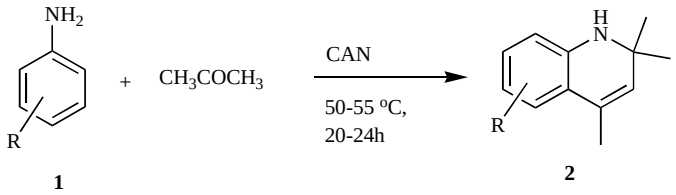
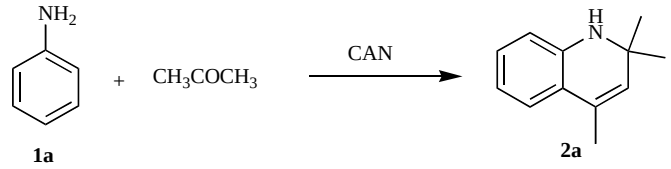


1 **2**

Scheme 1. CAN-mediated synthesis of 2,2,4-trimethyl-1,2-dihydroquinolines.

Table 1. The Effect of Reaction Conditions on the Reaction of Aniline and Acetone[a]



1a **2a**

Entry	equiv of CAN used	Temp (°C)	Time (h)	% yield[b] of 2a
1	0.50	50-55	24	77
2	0.25	50-55	24	80
3	0.10	50-55	24	62
4	0.0	50-55	24	Nil
5	0.25	50-55	12	59
6	0.25	Room temp	24	10

[a]All the reactions were carried out using aniline **1a** (1.0 mmol) and acetone (10 mL per 1.0 g of compound **1a**).
[b]Isolated yield.

temp and time. We observed that 0.25 equiv was the minimum amount of CAN necessary to achieve the maximum yield of product **2a** (Entry 1 *vs* 2 *vs* 3, Table **1**). The reaction was entirely suppressed in the absence of CAN (entry 4, Table **1**) indicating the key role of this catalyst. All these reactions were carried out at 50-55 °C for 24h. Decrease in reaction time (entry 5, Table **1**) or lowering of reaction temperature (entry 6, Table **1**) either decreased the product yield or suppressed the product formation significantly. It is worthy to mention that this reaction does not need the use of inert or anhydrous atmosphere and can be carried out in an open reaction vessel. In other words this reaction was not sensitive towards the atmospheric oxygen which is beneficial for a large scale synthesis.

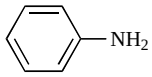
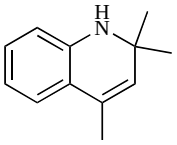
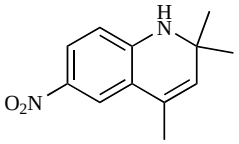
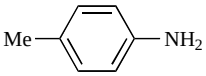
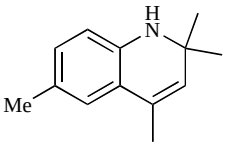
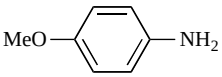
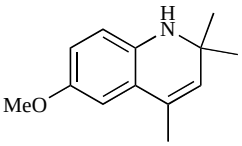
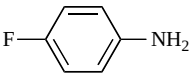
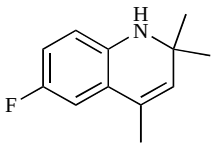
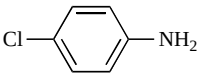
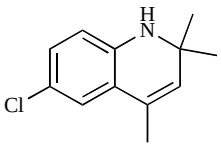
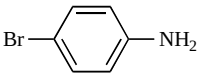
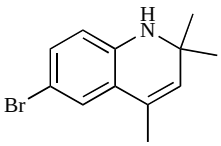
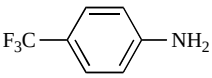
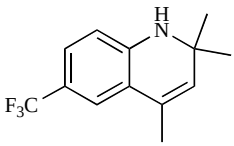
Having established the optimum reaction condition we then decided to examine the generality and scope of this CAN-catalyzed synthesis of dihydroquinoline. Thus a number of substituted anilines (**1**) were employed under the condition of entry 2 of Table **1** [27]. The reaction proceeded well in all these cases providing 2,2,4-trimethyl-1,2-dihydroquinolines (**2**) in good yield (entries 1-8, Table **2**). The aniline may contain an electron withdrawing groups such as NO_2 or CF_3 (entry 2 and 8, Table **2**) or electron donating substituents such as Me, OMe (entry 3 and 4, Table **2**) or halogens e.g. F, Cl or Br (entry 5, 6 and 7, Table **2**). The use of other ketone e.g. 2-butanone was also examined under the reaction condition employed and the corresponding dihydroquinoline **2i** was isolated in 70% yield (entry 9, Table **2**). Structures of all the compounds synthesized were confirmed by spectral (NMR, IR & MS) and analytical data. Appearance of a peak in the region 5.3-5.6 (1H), 1.9-2.0 (3H) and 1.2-1.3 δ (6H) in the ^{1}H NMR spectra of **2a-h** indicated the presence of a vinylic proton, a vinylic methyl and two other methyl groups.

Due to our continued interest in the synthesis of nimesulide derivatives of potential pharmacological interest we applied our present methodology for the preparation of compound **C**. Thus reduction of nimesulide **B** was carried out according to a known procedure [30] to afford the required aniline derivative **3** (Scheme **2**). The compound **3** was then treated with acetone in the presence of CAN to give the desired dihydroquinoline derivative **C** in 80% yield [31]. Notably, preparation of compound **C** was also attempted by using the conventional iodine-mediated method [16] in our laboratory but the reaction yielded an inseparable mixture of unidentified compounds instead of desired product **C**. The ^{1}H and ^{13}C NMR spectra of compound **C** is shown in Fig. (**2**).

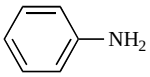
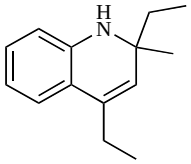
Mechanistically, this reaction seems to proceed *via* an imine intermediate **E1** generated in situ followed by an electrophilic attack at the *ortho* position by another ketone molecule in the presence of CAN (Scheme **3**). Presumably, the simultaneous interaction of CAN with imine nitrogen of **E1** and the carbonyl oxygen of the reacting ketone favored the *ortho* attack to give **E2**. An intramolecular cyclization of **E2** involving the imine and ene moiety promoted by CAN provided **E3** which on subsequent isomerization yielded the product **2**. A similar type of intramolecular cyclization of imine under photo irradiation has been reported earlier [32].

In conclusion, we have developed a new and practical method for the synthesis of 2,2,4-trimethyl-1,2-dihydroquinolines *via* a CAN mediated modified Skraup

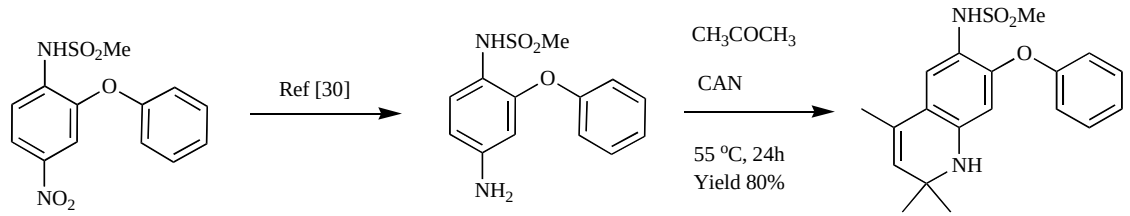
Table 2. CAN Catalyzed One-Pot Synthesis of 2,2,4-trimethyl-1,2-dihydroquinolines[a]

Entry	Arylamine (1)	Time	Product (2)	% Yield[b]	Ref.
1	 **1a**	24	 **2a**	80	[28]
2	 **1b**	24	 **2b**	65	[25]
3	 **1c**	20	 **2c**	70	[28]
4	 **1d**	20	 **2d**	75	--
5	 **1e**	24	 **2e**	72	--
6	 **1f**	24	 **2f**	70	[28]
7	 **1g**	24	 **2g**	75	[28]
8	 **1h**	24	 **2h**	68	--

(Table 2). Contd…..

Entry	Arylamine (1)	Time	Product (2)	% Yield[b]	Ref.
9	 **1a**	20	 **2i**[c]	70	[29]

[a]All the reactions were carried out using aniline **1** (1.0 mmol), acetone (10 mL per 1.0 g of compound **1**) and CAN (0.25 mmol) at 50-55 °C.
[b]Isolated yield.
[c]2-butanone was used in place of acetone.



B **3** **C**

Scheme 2. Synthesis of novel dihydroquinoline-based compound derived from nimesulide.

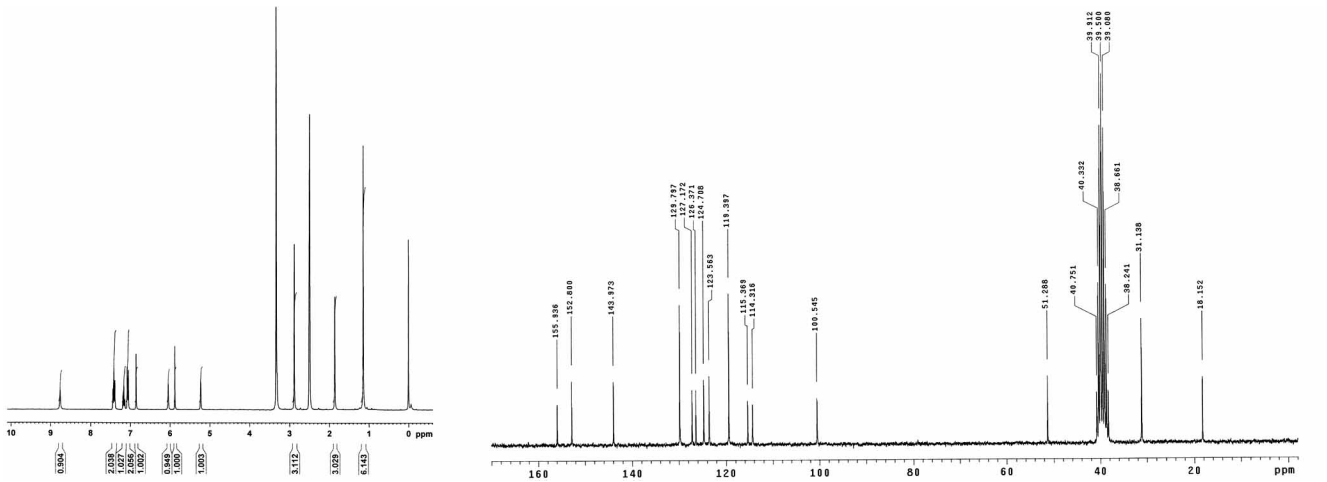
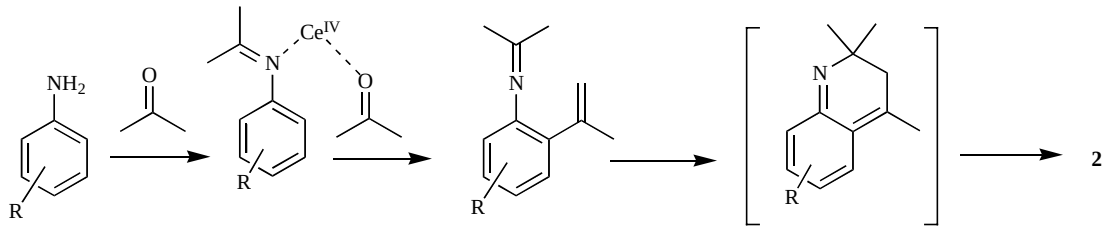


Fig. (2). ^{1}H and ^{13}C NMR of compound **C** in DMSO-d_6.



1 **E1** **E2** **E3**

Scheme 3. Proposed mechanism for CAN-mediated synthesis of 2,2,4-trimethyl-1,2-dihydroquinolines.

reaction. The reaction does not require the use of expensive catalyst or reagent and can be carried out in an open vessel. The methodology was used to synthesize a novel dihydroquinoline-based compound derived from anti-inflammatory agent nimesulide. Due to its operational simplicity and easy availability of required raw materials we expect that the present methodology would find wide usage in the preparation of dihydroquinoline-based library of small molecules.

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[27] General procedure for the preparation of compound **2a-h**: A solution of substituted aniline **1** (1.0 mmol) in acetone (10 mL per 1.0 g of compound **1**) was stirred for 5-10 min at 25-35 °C. To this was added CAN (0.25 mmol) and the mixture was stirred at 50-55 °C for the time indicated in Table **2**. After completion of the reaction (indicated by TLC), the mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with cold water (10 mmol) and extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were collected, washed with water (2 x 10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using hexane-EtOAc.

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[31] Spectral and analytical data of compound **C**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.76 (bs, D_2O exchangeable, 1H), 7.41 (t, J = 5.6 Hz, 2H), 7.18-7.04 (m, 3H), 6.85 (s, 1H), 6.04 (bs, D_2O exchangeable, 1H), 5.87 (s, 1H), 5.22 (s, 1H), 2.88 (s, 3H), 1.86 (s, 3H), 1.14 (s, 6H); ^{13}C NMR (50 MHz, DMSO-d_6) 155.9, 152.8, 143.9, 129.7, 127.2, 126.4, 124.7, 123.5, 119.4, 115.4, 114.3, 100.5, 51.2, 31.1, 18.2; IR (KBr, cm^{-1}) 3350 (bs, NH), 3223 (bs, NH), 2972, 1614 (C=C), 1587, 1487; MS (m/z, EI method) 359.0 (M+1, 100%); Elemental Analysis found: C, 63.41; H, 6.20; N, 7.94 $C_{19}H_{22}N_2O_3S$ Requires C, 63.66, H, 6.19, N, 7.82.

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