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ORIGINAL ARTICLE

One pot four component sequential synthesis of hexahydroquinoline derivatives in aqueous media via enaminone intermediates: A green protocol

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KEYWORDS

Enaminone;
Sequential reaction;
Hantzsch reaction;
Crystal structure;
Michael reaction

Abstract A convenient green chemistry method through one pot four component tandem synthesis of hexahydroquinoline via enaminone intermediate using dimedone, ammonium acetate, aryl aldehydes and malononitrile has been described in aqueous media without the use of any external catalyst. The excess of ammonium acetate used acts as a reagent as well as catalyst. The incorporation of water as solvent along with eradication of external catalyst renders the protocol to comply with the green chemistry aspects. Shorter reaction time, high atom economy, easy work up and purification of products by non-chromatographic method are the crucial features of this methodology. The crystal structure of hexahydroquinoline basically shaped by chromatographic free selective reaction was determined by single crystal X-ray diffraction analysis.

1. Introduction

MCRs with their requisition of substantially simpler method and operations as compared to the conventional multistep methods of heterocycle synthesis have gained enormous interest in diversity oriented synthesis in organic, medicinal and combinatorial chemistry [3,32]. Furthermore, the MCR tactics are determined to be economical owing to their reduction in steps thereby saving synthetic time, efforts and sustained expensive purification process besides the protection and deprotections [6,30]. Recently, MCRs have become an governing tool for atom efficient and waste free synthesis of complex building blocks of 'drug-like' motifs [13,14]. MCRs are tandem reactions which offer an influential approach for molecular complexity from simple preliminary materials. These reactions prevent the fall of overall steps by avoiding isolations of extremely reactive intermediates [4,10].

In recent days, aqueous mediated reactions have captured a considerable attention in organic synthesis as a result of both economic and environmental safety reasons. The consistent persuasion water as solvent for organic reaction arises due to

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its abundance, economical nature, high polarity, high reactivity, typical selectivity and existence of strong hydrogen bonding also supplemented by convenient work up and purification carried out by simple filtration or extraction [13,14,28]. In addition to this large surface tension, high specific heat capacity and the high cohesive energy, salting in or salting out effect, variation of pH and chemo enzymatic strategies are some of the unique properties of water that can significantly impact the conversions performed in this media. In particular, reactions with negative activation volume are reported to occur faster in water than in organic solvents [7,24].

Breslow, in 1980 rediscovered the use of water as solvent in organic reaction which proved that hydrophobic effects might strongly increase the rate of organic reaction [1]. Consequently the use of water as an environmentally benign solvent for chemical transformation has developed into the demand of the present day researchers.

Quinoline and their derivatives performing as a core unit in several natural products and drugs attributing to their diverse applications in the pharmaceutical industries uphold a remarkable place among the heterocyclic compounds [12]. Quinolines having 1,4-DHP nucleus have been reported as significant compounds due to their therapeutic and pharmacological properties such as vasodilator, antitumor, bronchodilator, geroprotective, antimalarial, anti-inflammatory, antiasthematic, and antibacterial activities [17,29].

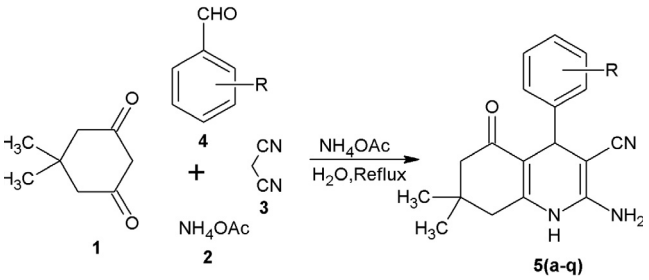
In particular, now days 1, 4-DHP nucleus containing drugs nimodipine, lacidipine posses improved calcium channel antagonist activity [18,21] (Fig. 1) and the cardiovascular agents such as nifedipine, nicardipine, and amlodipine are effective against treatment of hypertension [16].

Hantzsch and Liebigs reported the synthesis of 1,4-dihyropyridine by traditional method which involved cyclocondensation of aldehyde with ethyl acetoacetate and ammonia reflux in alcohol or in acetic acid for a prolonged time [8].

A brief review on the literature reveals that the synthesis of quinoline derivatives can be achieved by using organocatalysts [15], CAN [25], ionic liquids [11], $Sc(OTf)_3$ [5], iodotrimethylsilane (ITMS) [26], microwave irradiation [19,28,31], $Yb(OTf)_3$ [33], L-proline [9], $Bi(NO_3)_3{\cdot}5H_2O$ [20] etc.

Nevertheless, most of the reported methods still suffer from several drawbacks, such as the long reaction time, unsatisfactory yields, drastic reaction condition, use of organic solvents as well as expensive catalysts and tedious work up procedures. Hence there emerges a through need to develop an ecological and efficient methodology for the synthesis of hexahydroquinoline derivatives.

In prolongation of our efforts for the development of synthetic methodologies for the synthesis of heterocyclic compounds [23], we report herein an eco-friendly, expedient, atom economic and highly efficient protocol for the tandem synthesis of hexahydroquinoline derivatives via four component condensation of dimedone, aryl aldehydes, malononitrile and excess of ammonium acetate as a reagent and neutral catalyst in aqueous media (Scheme 1).



Scheme 1 Synthesis of hexahydroquinoline derivatives from tandem reaction.

2. Experimental

2.1. General

All reagents were purchased from Thomas Baker and S.D. fine chemicals. Melting points were measured by a Labstar melting apparatus and were uncorrected. Monitoring the progress of all reactions was carried out by the thin layer chromatography (TLC). Infrared spectra were recorded on a Perkin-Elmer, FTIR-1600 spectrophotometer in KBr with absorption in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were determined on a Bruker Avance (300 and 75 MHz) spectrometer as DMSO-d_6 solutions, using tetramethylsilane (TMS) as the internal standard. Chemical shifts (δ) are expressed in ppm and Coupling constants J are given in Hz. Mass spectra were recorded on a Performa spectrometer.

2.2. X-ray structure analysis

X-ray diffraction data of compound **5m** was collected at $T = 298$ K on a Bruker APEXII CCD diffractometer with graphite monochromated Mo Kα ($\lambda = 0.71073$ Å) radiation. Table 4 shows the unit cell parameters and other crystallographic details. The determination of cell refinement and data reduction were performed with program SAINT [2]. The structure was solved using direct methods of program SHELXS97 and refined anisotropically by full-matrix least-square on F^2 carried out with the program SHELXL97 [27].

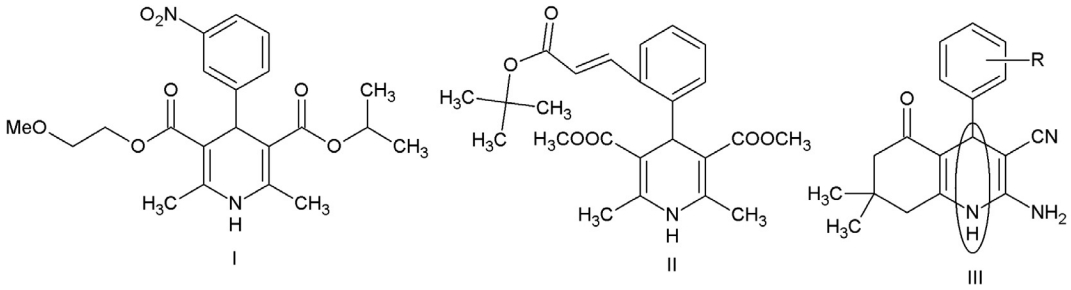


Figure 1 Nimodipine (I), Lucidipine (II) and Hexahydroquinoline (III) containing 1, 4-DHP Nucleus.

2.3. General procedure for the synthesis of substituted hexahydroquinoline (**5a–5q**)

In a 50 ml round bottom flask 5,5-dimethylcyclohexane-1,3-dione (1 mmol) and excess of ammonium acetate (3.3 mmol) in water (10 ml) were added. Then the reaction mixture was stirred at 100 °C for approximately 35–40 min. Afterward, malononitrile (1 mmol), and aryl aldehyde (1 mmol) were charged, and the mixture was stirred at 100 °C for 30 min. After completion of reaction [monitored by TLC, ethyl acetate: *n*-hexane (3:7)], the reaction mixture was stirred at RT. The generated solid was filtered off and recrystallized from ethanol to afford pure product.

2.4. Characterization data of some novel representative compounds

2.4.1. 2-Amino-4-[4-(nitro) phenyl]-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**5i**)

Yellow solid; m.p. 290–292 °C; IR (KBr, cm^{-1}): 3487, 3393, 3325, 3222, 2959, 2177, 1654, 1603, 1517, 1479; ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.88 (s, 3H, CH_3), 1.0 (s, 3H, CH_3), 1.95–2.19 (dd, 2H, J = 16.2 Hz, CH_2), 2.29–2.46 (dd, 2H, J = 17.1 Hz, CH_2), 4.45 (s, 1H, CH), 5.95 (s, 2H, NH_2), 7.36–7.39 (d, 2H, J = 8.7 Hz, Ar–H), 8.11-8.14(d, 2H, J = 8.7 Hz, Ar–H), 9.0 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.1, 29.2, 32.5, 38.0, 50.4, 57.8, 108.19, 121.6, 124.0, 128.5, 146.3, 150.8, 150.9, 158.1, 194.4; ESI-MS (m/z): 339.2 ($M+H^+$); Anal. Calcd. for $C_{18}H_{18}N_4O_3$ (338.360): C, 63.89; H, 5.36; N, 16.56%. Found: C, 63.86; H, 5.31; N, 16.60%.

2.4.2. 2-Amino-4-[3-(fluoro) phenyl]-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline(**5j**)

Yellow solid; m.p. 262–265 °C; IR (KBr, cm^{-1}): 3418, 3326, 3236, 2960, 2181, 1639, 1599, 1477; ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.89 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.97–2.19 (dd, 2H, J = 15 Hz, CH_2), 2.29–2.43 (dd, 2H, J = 17.1 Hz, CH_2), 4.33 (s, 1H, CH), 5.83 (s, 2H, NH_2), 6.83–6.97 (m, 3H, Ar–H), 7.24-7.31(m, 1H, Ar–H), 8.84 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.0, 29.2, 32.4, 37.4, 50.4, 58.5, 108.7, 121.8, 123.3, 130.4, 150.4, 161.0, 164.2, 194.4; ESI-MS (m/z): 312.2 ($M+H^+$); Anal. Calcd. for $C_{18}H_{18}FN_3O$ (311.353): C, 69.44; H, 5.83; N, 13.50%. Found: C, 69.39; H, 5.79; N, 13.54%.

Table 1 Optimization of the catalyst for one-pot tandem synthesis of hexahydroquinolines.[a]

Entry	Catalyst (loading)	Condition	Time (h)	Yield (%)[b]
1	–	RT	12	–[c]
2	–	70	9	–[c]
3	–	80	6	–[c]
4	–	Reflux	7	30
5	$AcONH_4$ (0.5 mmol)	Reflux	4	45
6	$AcONH_4$ (1 mmol)	Reflux	3.5	55
7	$AcONH_4$ (1.5 mmol)	Reflux	2	67
8	$AcONH_4$ (2 mmol)	Reflux	1	89[b],79[d]
9	$AcONH_4$ (2.5 mmol)	Reflux	1	88

[a] Reaction condition: 5,5-dimethyl 1,3-cyclohexadione (1 mmol), ammonium acetate (1.3 mmol), 3-trifluoro methyl benzaldehyde (1 mmol), and malononitrile (1 mmol) in water (10 ml).
[b] Isolated yield.
[c] No reaction occurred.
[d] % Atom economy = (MW of desired product/$\sum$ of all reactants) × 100 = 79%.

2.4.3. 2-Amino-4-[3-(trifluoromethyl) phenyl]-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**5k**)

Light yellow solid; m.p. 285–287 °C; IR (KBr, cm^{-1}): 3392, 3335, 3225, 2922, 2180, 1657, 1605, 1478: ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.87 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 2.15–2.34 (dd, 2H, J = 18 Hz, CH_2), 2.42–2.49 (dd, 2H, J = 17.4 Hz, CH_2), 4.42 (s, 1H, CH), 5.89 (s, 2H, NH_2), 7.38–7.55 (m, 4H, Ar–H), 9.09 (br s, 1H,NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 26.6, 29.4, 32.4, 37.7, 50.4, 58.4, 108.5, 121.7, 122.9, 123.3, 123.5, 126.5, 129.0, 129.5, 129.7, 131.4, 148.9, 150.7, 150.8, 194.5; ESI-MS (m/z): 362.2 ($M+H^+$); Anal. Calcd. for $C_{19}H_{18}F_3N_3O$ (361.360): C, 63.15; H, 5.02; N, 11.63%. Found: C, 63.12; H, 4.97; N, 11.67%.

2.4.4. 2-Amino-4-[3,4-(dimethyl) phenyl]-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**5l**)

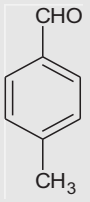
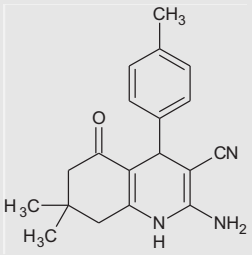
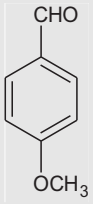
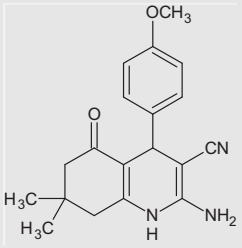
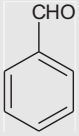
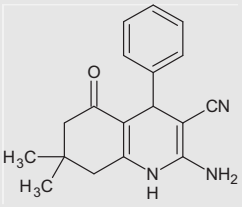
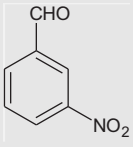
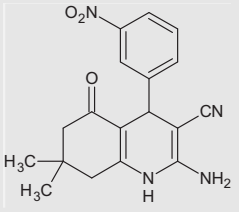
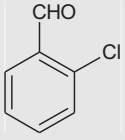
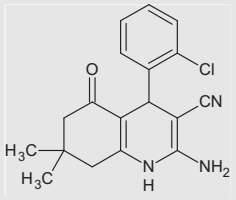
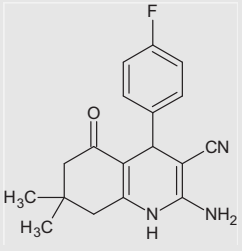
Yellow solid; m.p. >300 °C; IR (KBr, cm^{-1}): 3394, 3332, 3226, 2964, 2192, 1661, 1603, 1476; ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.94 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.93–2.17 (dd, 2H, J = 16.2 Hz, CH_2), 2.26–2.43 (dd, 2H, J = 17.4 Hz, CH_2), 2.13 (s, 3H, Ar–CH_3), 2.15 (s, 3H, Ar–CH_3), 4.20 (s, 1H, CH), 5.71 (s, 2H, NH_2), 6.80–6.85 (m, 2H, Ar–H), 6.95–6.98 (m, 1H, Ar–H), 8.90 (br s, 1H, NH); ^{13}C NMR

Table 2 Screening of solvents using 2 mmol of NH_4OAc catalyst for tandem synthesis of hexahydroquinolines.[a]

Entry	Solvent	Temperature °C	Time (h)	Yield (%)[b]
1	Water	100	1	89
2	Water:EtOH (1:1)	85	2	75
3	EtOH	78	4	55
4	MeOH	65	5	47
5	IPA	85	5.5	45
6	DMF	110	7	–[c]
7	DMSO	100	5	40

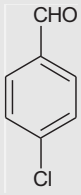
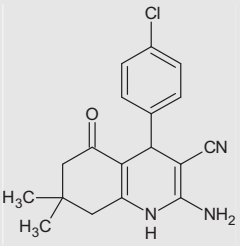
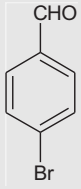
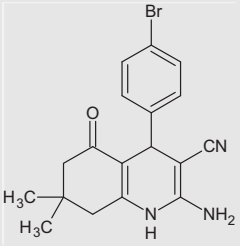
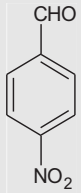
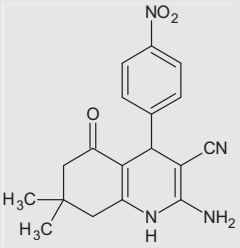
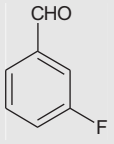
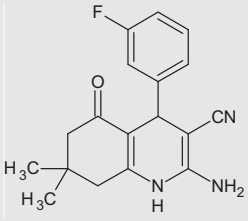
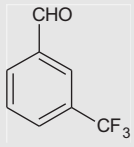
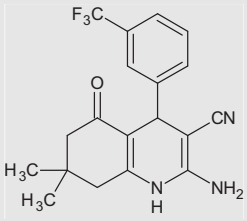
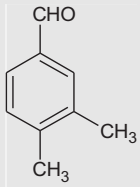
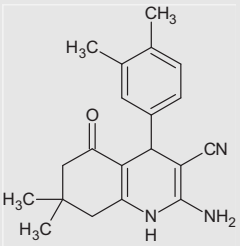
[a] Reaction condition: 5,5-dimethyl 1,3-cyclohexadione (1 mmol), ammonium acetate (1.3 mmol),3-trifluoro methyl benzaldehyde (1 mmol), malononitrile (1 mmol).
[b] Isolated yield.
[c] No reaction occurred.

Table 3 Synthesis of hexahydroquinoline derivatives (**5a**–**5q**) from tandem reaction with different aryl aldehydes.[a]

Entry	Aldehyde (R) **4**	Product **5**		Time (min)	Yield (%)[b]	Atom economy (%)[c]	M.P. °C (observed)	M.P. °C (Lit.)[Ref.]
1			**5a**	75	80	76.20	293–296	294–295[e]
2			**5b**	80	83	77.10	285–287	289–293[e]
3			**5c**	70	84	75.33	285–288	280–281[d]
4			**5d**	57	88	77.88	280–281	282–283[d]
5			**5e**	65	84	77.33	275–277	273–276[e]
6			**5f**	57	90	76.42	298–299	299–300[d]

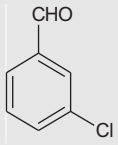
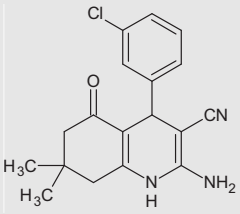
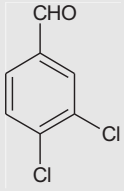
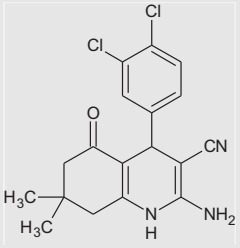
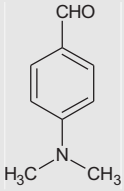
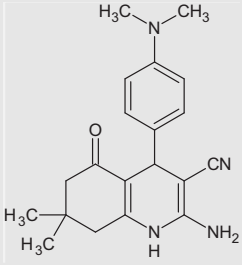
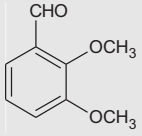
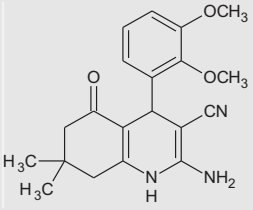
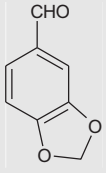
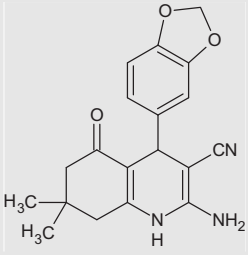
(continued on next page)

Table 3 *(continued)*

Entry	Aldehyde (R) **4**	Product **5**		Time (min)	Yield (%)[b]	Atom economy (%)[c]	M.P. °C (observed)	M.P. °C (Lit.)[Ref.]
7			**5g**	60	85	77.33	288–290	290–291[d]
8			**5h**	62	86	79.49	297–299	295–296[d]
9			**5i**	59	88	77.88	290–292	–
10			**5j**	60	87	76.42	262–265	–
11			**5k**	58	89	79.00	285–287	–
12			**5l**	75	82	77.00	> 300	–

(continued on next page)

Table 3 *(continued)*

Entry	Aldehyde (R) **4**	Product **5**		Time (min)	Yield (%)[b]	Atom economy (%)[c]	M.P. °C (observed)	M.P. °C (Lit.)[Ref.]
13			**5m**	62	87	77.33	> 300	–
14			**5n**	57	84	79.04	> 300	> 300[d]
15			**5o**	77	85	77.79	> 300	> 300[e]
16			**5p**	85	81	78.63	272–275	269–270[d]
17			**5q**	81	83	77.83	> 300	> 300[d]

[a] Reaction condition: 5,5-dimethyl 1,3-cyclohexadione (1 mmol), ammonium acetate (1.3 mmol), aryl aldehyde (1 mmol), malononitrile (1 mmol) and excess of NH_4OAc (2 mmol) as a catalyst in 10 ml water.

[b] Isolated yield.

[c] % Atom economy = (MW of desired product/$\sum$ of all reactants) × 100.

[d] Litvic et al. [19].

[e] Tu et al. [31].

(75 MHz, DMSO-d_6): δ 19.3, 20.0, 27.0, 29.4, 32.4, 37.2, 50.6, 59.5, 109.4, 122.1, 124.7, 128.5, 129.6, 134.0, 135.0, 145.2, 149.8, 150.5, 194.3; ESI-MS (m/z): 322.2 ($M+H^+$); Anal. Calcd. for $C_{20}H_{23}N_3O$ (321.416): C, 74.74; H, 7.21; N, 13.07%. Found: C, 74.70; H, 7.18; N, 13.11%.

*2.4.5. 2-Amino-4-[3-(chloro) phenyl]-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**5m**)*

Yellow solid; m.p. >300 °C; IR (KBr, cm^{-1}): 3355, 3199, 2967, 2185, 1657, 1602, 1487, 1368; ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.90(s, 3H, CH_3), 1.01(s, 3H, CH_3), 1.98–2.21 (dd, 2H, J = 15 Hz, CH_2), 2.36–2.50 (dd, 2H, J = 18 Hz, CH_2), 4.35 (s,1H,CH), 5.85 (s, 2H, NH_2), 7.10–7.12 (d, 2H, J = 6 Hz, Ar–H) 7.18–7.21 (d, 1H, J = 9 Hz, Ar–H), 7.26–7.31 (m, 1H, Ar–H), 8.96 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.3, 29.3, 32.5, 37.6, 50.4, 58.6, 108.7, 121.8, 126.1, 126.5, 127.0, 130.5, 133.2, 150.0, 150.4, 150.8, 194.4; ESI-MS (m/z): 350.2 ($M+Na^+$); Anal. Calcd. for $C_{18}H_{18}ClN_3O$ (327.808): C, 65.95; H, 5.53; N, 12.82%. Found: C, 65.91; H, 5.46; N, 12.86%.

3. Results and discussion

Herein we have reported a one pot tandem reaction and a new synthetic strategy for selectively substituted hexahydroquinoline derivatives using dimedone, malononitrile, aryl aldehydes and ammonium acetate via enaminone intermediate. To study this latest method, we explored the reaction of dimedone and excess of ammonium acetate in water at reflux condition which afforded the expected enamine adduct intermediates. Further the sequential addition of malononitrile and aldehyde successfully gave hexahydroquinoline derivatives in excellent yields as well as good atom economy (Scheme 1).

Initially, we engaged dimedone (1 mmol), ammonium acetate (1.3 mmol), 3-trifluoro methyl benzaldehyde (1 mmol) and malononitrile (1 mmol) as model substrates for the optimization of reaction conditions. In the beginning we tried to establish a protocol for the above model reaction without any catalytic assistance in aqueous media varying the temperature criteria from room temperature to reflux condition, however the reaction failed to proceed even after prolonged stirring at RT to 80 °C (Table 1, Entries 1–3), although trace amount (30%) of desired product was afforded at reflux condition after 7 h (Table 1, Entry 4). Moreover the same reaction was employed incorporating excess addition of NH_4OAc as a catalyst from 0.5 to 2.5 mmol under reflux condition (Table 1, Entries 5-9), then we got the desired product hexahydroquinoline in excellent yield (89%) at 2 mmol of excess addition of NH_4OAc and the time of reaction completion becomes only 1 h (Table 1, Entry 8).

Interestingly we found that the reaction using water as solvent (Table 2, Entry 1) resulted in excellent yield (89%) of desired product than any other solvents (Table 2, Entries 2–7). Our optimization studies revealed that the yield increased with catalyst loading up to 2 mmol and then remained with no improvement in the yield with 2.5 mmol of catalyst loading (Table 1, Entry 9).

With the standard optimized parameter, we next concentrated on the scope of this reaction which was investigated by synthesizing a library of hexahydroquinoline derivatives in the presence of 2 mmol NH_4OAc at reflux condition using water as a reaction medium (Table 3).The optimized tandem methodology tolerated a wide spectrum of aldehydes with good to excellent yields of the targeted molecules. From Table 3 it is evident that the reaction proceeded smoothly

Table 4 Crystal data and structure refinement for **5m**.

Identification code	**5m**
Empirical formula	$C_{18}H_{18}ClN_3O$
Formula weight	327.80
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 7.5314(3) Å α = 103.039(2)^0 b = 9.3764(4) Å β = 94.004(2)^0 c = 12.3556(5) Å γ = 99.177(2)^0
Volume	834.05(6) A^3
Z, Calculated density	2, 1.305 mg/m^3
Absorption coefficient	0.237 mm^{-1}
F(000)	344
Crystal size	0.20 × 0.15 × 0.11 mm
Theta range for data collection	2.27–25.00^0
Limiting indices	$-8 \leqslant h \leqslant 8$, $-11 \leqslant k \leqslant 11$, $-14 \leqslant l \leqslant 14$
Reflections collected/unique	8471/2756 [R(int) = 0.0275]
Completeness to theta	25.00 94.0%
Absorption correction Multi-scan	0.9744 and 0.9542
Max. and min. transmission	
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2756/0/210
Goodness-of-fit on F^2	1.035
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0739, w$R2$ = 0.1231
R indices (all data)	$R1$ = 0.0739, w$R2$ = 0.1231
Largest diff. peak and hole	0.278 and −0.442 e A^{-3}
CCDC number	CCDC 960507

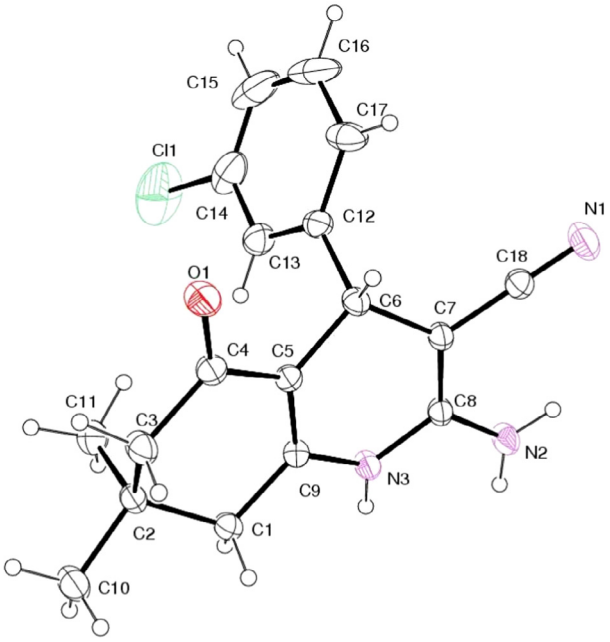
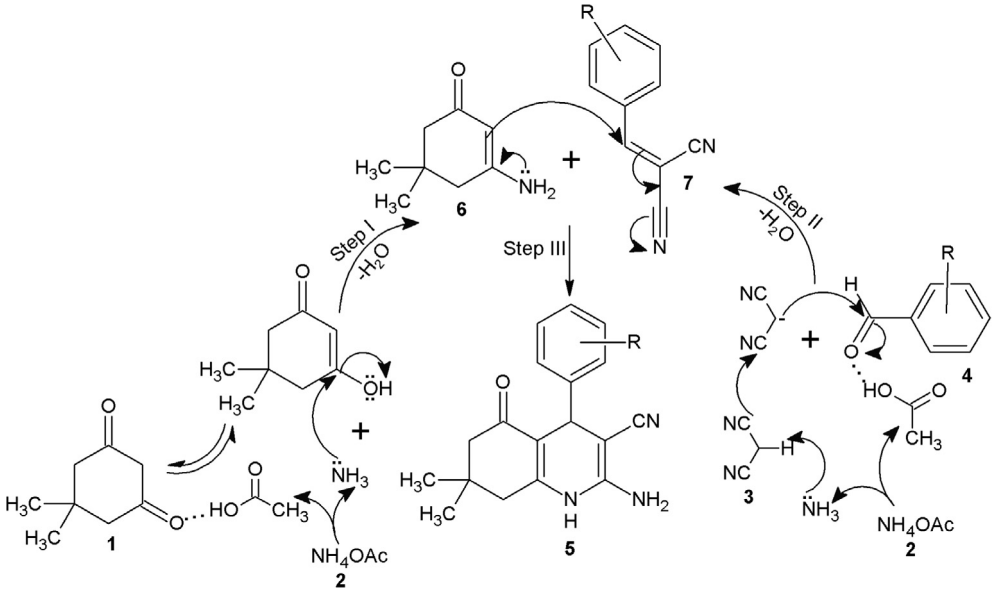


Figure 2 X-ray crystal structure of **5m** with atom-labeling scheme.

Table 5 Intramolecular hydrogen bonds for **5m**.

D-H...A	D-H (Å)	H...A (Å)	D...A (Å)	[D-H...A(°)]
N3-H3...O1#1	0.86	2.13	2.912	150.5
N2-H2B...O1#1	0.86	2.18	2.958	150.5
N2-H2A...N1#2	0.86	2.26	3.089	161.0

Symmetry code: #1 $x + 1, y, z$. #2 $-x + 2, -y-1, -z$.



Scheme 2 A plausible mechanism for the formation of hexahydroquinoline.

for both electron rich and electron deficient aromatic aldehydes.

The crude products were further purified by recrystallization from ethanol to afford the pure substituted hexahydroquinoline **5a**–**5q** in good to excellent yields.

All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR, LC–MS and by elemental analysis and well matched with literature reported compounds [19,31].The stereochemistry and structure of 2-amino-4-[3-(chloro) phenyl]-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline motif was further confirmed by single crystal X-ray analysis (Fig. 2, **5m**).

The stereochemistry of structure **5m** exposes that both six membered rings of the hexahydroquinoline derivative adopt half chair conformation with atoms C_2 and C_6 forming flaps in the each ring. The proton attached to nitrogen N_3 forms a H-bond with the oxygen O_1 (>C=O) such that the N_3-H_3...O_1 distance is 2.912 Å, while that of N2-H_{2B}...O_1 (>C=O) distance is 2.958 Å. As well as the proton attached to nitrogen N_2 forms an H-bond with nitrogen N_1 (−CN) screening N_2-H_{2A}...N_1 distance 3.089 Å (Table 5).

A tentative mechanism for this transformation is proposed in Scheme 2. The reaction proceeds through three different steps. Step 1 involves the formation of enaminone **6** from dimedone and excess of ammonium acetate. The excess of ammonium acetate act as a source of acetic acid, which can protonate carbonyl group to create a more reactive species. Enaminone contains nucleophilic character of enamine and nucleophilic character of enone [22].

In step 2 there is formation of arylidenemalononitrile **7** by Knoevenagel reaction of aldehyde and malononitrile, finally step 3 involves Michael addition reaction with intramolecular cyclization between enaminone **6** and arylidenemalononitrile **7** affording the final product hexahydroquinoline **5**.

The luxuriance of the procedure was confirmed by using the percent atom economy (Fig. 3). It was observed that percent atom economy of the reaction is good which pointed out that maximum quantity of raw materials finished in to the product and a minimum quantity of waste was formed.

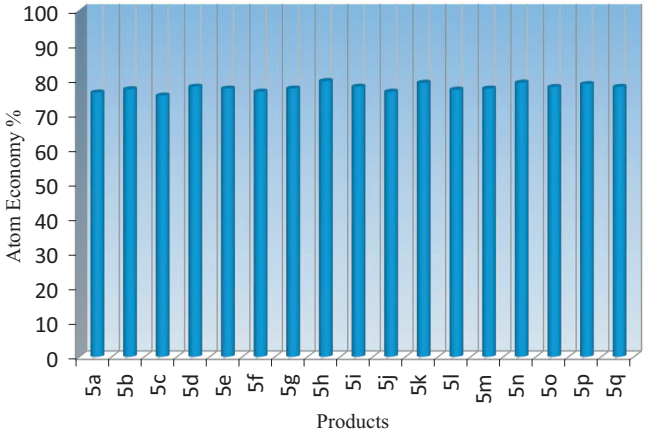


Figure 3 Percent atom economy of products.

Table 6 Results obtained using large scale synthesis of hexahydroquinoline derivatives from tandem reaction with different aryl aldehydes.

Entry	Aldehydes	Aldehydes amount (mmol)	Product	Time (min)	Yield[a] (%)
1	4-OCH_3 C_6H_4	20	5b	80	88
2	C_6H_5	20	5c	70	89
3	4-F C_6H_4	20	5f	60	93

[a] Isolated yield.

To sustain this protocol, we explored the efficiency of our procedure using three representative aryl aldehydes containing in their structure hydrogen, electron-donating groups and weak electron-withdrawing groups. Reactions were performed in aqueous media at reflux temperature and the reactants were used in the same ratio as formerly determined.

Thus, a large-scale synthesis of compound **5b**, **5c** and **5f** was carried out on 20 mmol scale (Table 6).The reaction mixture was refluxed for reported time and the desired product was obtained in 88%, 89% and 93% yield, respectively.

4. Conclusion

In conclusion we have provided an efficient and diversity oriented four component route using readily available starting materials for the tandem synthesis of a series of hexahydroquinoline derivatives in aqueous media using ammonium acetate as an inexpensive and neutral catalyst. The experimental simplicity, excellent yields in small and large scale, shorter reaction time, simple work up procedure, no need of external catalyst, purification of products by non-chromatographic method and high atom economy are the captivating features of this protocol.

Supplementary information

Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC 960507. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (www.ccdc.cam.ac.uk/data_request/cif or e-mail: deposit@ccdc.cam.ac.Uk).

Acknowledgments

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