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Atomized Sodium Catalyzed, Ultrasound Assisted, One-pot four-component Synthesis of a Series of Polysubstituted-tetrahydroquinolines

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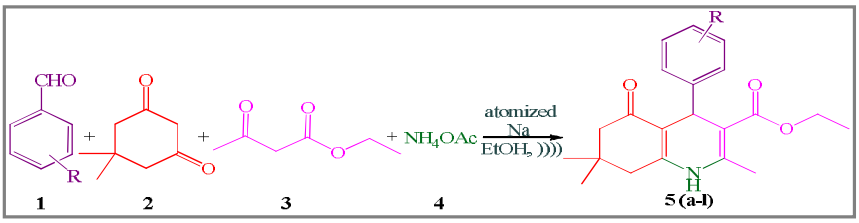
ABSTRACT

Ultrasound-assisted, atomized sodium catalysed, sustainable, one-pot four-component approach offers a series of polysubstituted-tetrahydroquinolines. The protocol is a green organic synthetic method which works under mild reaction conditions. The ease imparted by ultrasound in the present method divulges the facile, efficient, economical, eco-friendly and clean approach to afford excellent yield of the products in short durations.

Graphical Abstract



Highlights

- Ultrasound-assisted, atomized sodium mediated, sustainable, one-pot four-component approach has been developed.
- A series of polysubstituted-tetrahydroquinolines have been synthesized in ethanol.
- The protocol is a green organic synthetic method which works under mild reaction conditions.
- The method is energy efficient, facile, economical and eco-friendly.
- The approach is clean and affords excellent yield of the products in short durations.

Keywords: Polysubstituted tetrahydroquinolines, Aryl aldehydes, Ethyl acetoacetate, Dimedone, Atomized sodium, Ultrasonication.

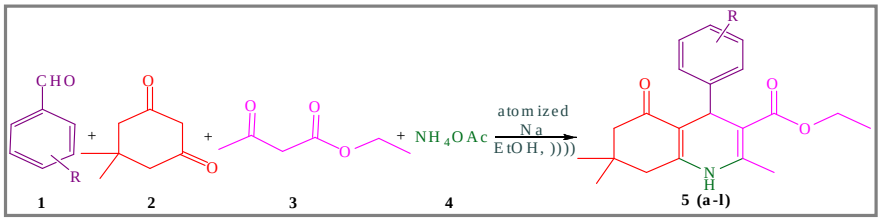
INTRODUCTION

Green chemistry has clearly made us understand the fascinating developments in the synthesis of large libraries of simple and complex organic molecules; and successful use of the green principles in

the modern organic synthesis has received considerable attention in the recent past [**1, 2**]. The most important high look in the academic research is to develop green and energy efficient methods for the synthesis of a varied and highly functionalized heterocyclic scaffolds using readily available substrates and reagents under simple and efficient reaction conditions. One-pot multi-component reactions (MCRs) on the other hand, have emerged as a powerful tool towards the synthesis of complex, fused and highly functionalized heterocyclic compounds [**3**]. The major advantages of MCRs include: atom economy, ease in optimization of reaction conditions and easy access to several heterocyclic compounds in shorter reaction durations.

In recent years, ultrasonication, an energy efficient and green technique, has played a major role in carrying out various organic transformations [**4, 5**]. Ultrasound assisted, one-pot MCRs in a heterogeneous system have been known to improve the reaction rates and the yield of the products when compared with the traditional methods [**6–10**]. Sonication of solid-liquid system leads to formation of micro bubbles; and their collapse is termed as acoustic cavitation, which can create extreme chemical and physical changes. The short-lived localized hot-spots produce very high temperatures and pressures during implosive collapse of bubbles which assist the chemical species to react and afford the products through a most favorable transition state [**11**] .Thus, the ultrasound-assisted one-pot MCR is an effective method for the synthesis of numerous complex heterocyclic compounds.

The design and synthesis of substituted quinolines is documented in the literature, and these compounds are known to possess a wide range of biological properties and pharmaceutical activities such as: antimicrobial, [**12**] antitumor, antiatherosclerotic, antidiabetic, antimutagenic, vasodilator, bronchodilator, hepatoprotective and geroprotective activities, [**13**, **14**] and are known as calcium channel blockers. [**15**, **16**] Thus, the synthesis of structurally varied quinolines is of great interest. A few reports on the synthesis of these molecules in the presence of catalysts such as: mesoporous silica; mobil composition of matter (MCM-41) [**17**], silica based SBA-15 [**18**]; nano materials such as: titanium dioxide [**19**], iron oxide [**20**], nickel and zinc oxide [**21**, **22**], boehmite-silica sulphuric acid (boehmite-SSA) [**23**] and carbon nanotubes-supported cobalt oxide (Co_3O_4-CNT) [**24**] are available in the literature. A few more methods report the use of other catalysts such as: trimethyl silyl chloride (TMSCl) [**25**], L-proline [**26**], different polymeric agents [**27**], ytterbium triflate [**28**], silica supported perchloric acid ($HClO_4$-SiO_2) [**29**], heteropoly acid [**30**], ceric ammonium nitrate [**31**], *p*-toulenesulphonic acid [**32**], indium chloride [**33**], molecular iodine [**34**], tinphosphonate nanoparticles [**35**], triphenylamine and α,α-dibromo-*p*-xylene [**36**], Baker's yeast [**37**] and ZnO [**38**]; and under the conditions such as: conventional heating [**39**, **40**], grinding [**41**], microwave irradiation [**42**], PEG-ultrasonication [**43**] and by a solid phase solvent-free reaction [**44**]. However, some of the reported methods suffer from drawbacks such as: catalyst preparation, elevated temperatures, inert atmosphere, tedious and time consuming methodologies, use of volatile and ecologically harmful solvents, conventional heating, low yields and long reaction durations. Our efforts are promising and in continuation of our work on the use of atomized sodium under sonic conditions [**45**], we have succeeded in overcoming most of the drawbacks, and herein, we report anatomized sodium catalysed, clean, simple, efficient, ultrasound-assisted, one-pot, four-component synthesis of polysubstituted-tetrahydroquinolines in EtOH from dimedone, ethyl acetoacetate, ammonium acetate and substituted benzaldehydes and heteroaromatic aldehydes as depicted in the Scheme 1.



Scheme 1. Synthesis of polysubstituted-tetrahydroquinolines.

MATERIALS AND METHODS

All reagents are commercial and were used as received, except liquid reagents which were distilled before use. Melting points were determined on a Raaga, Indian make melting point apparatus. The progress of the reactions was monitored by thin layer chromatography [(TLC) analytical silica gel plates (Merck 60 F_{250}), observed under ultraviolet (UV) light]. Infrared (IR) spectra were recorded using an Agilent Cary 630 and Bruker FT-IR spectrophotometers. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury Spectrophotometer in DMSO-d_6 and $CDCl_3$ at 400 MHz and 100 MHz respectively with TMS as an internal standard. The chemical shifts are expressed in δ parts per million (ppm) and the coupling constants (J) are given in hertz (Hz). LC-Mass spectra were recorded on an Agilent Technologies 1200 series instrument. Ultrasonication was performed using SIDILU, Indian make sonic bath operating at 35 kHz (constant frequency, 80 W) maintained between 28–30 °C by continuously circulating water.

General experimental procedure for the synthesis of polysubstituted tetrahydroquinolines (5a–5l) under ultrasonication: A 50 mL flask containing aromatic/heteroaromatic aldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), ammonium acetate (1.5 mmol), atomized sodium (0.03 g) and EtOH (10 mL) was sonicated in a cleaning bath working at 35 kHz for an appropriate time at 25°C. After the completion of the reaction [TLC (eluent: 8–10 % ethyl acetate in light petrol)], the reaction mixture was poured onto crushed ice. The precipitate thus formed was filtered, repeatedly washed with water and allowed to dry in the open atmosphere. Ethyl acetate (8 mL) was then added to dissolve the solid and the solution was dried over anhydrous Na_2SO_4, the solvent was distilled and the crude solid thus obtained was further purified by recrystallization using ethyl acetate. The structures of all the products were confirmed by IR, ^{1}H NMR, ^{13}C NMR and LC-Mass spectral analysis.

RESULTS AND DISCUSSION

Firstly, a mixture of the model substrates 4-chlorobenzaldehyde (**1**), dimedone (**2**), ethyl acetoacetate (**3**) and ammonium acetate (**4**) were sonicated in EtOH without any catalyst. The observation inferred the formation of the desired polysubstituted-tetrahydroquinoline (**5a**) in 20% yield (Table 1, entry 1), hence, EtOH was selected as a solvent for further studies. For increasing the yield of the product, various acidic and basic catalysts were then screened in EtOH under ultrasonication (Table 1, entries 2–14). As illustrated in table 1, the reaction using catalysts such as: $ZnCl_2$, $Ba(OH)_2$, SiO_2, *p*-TSA and CAN (entries 2–6) afforded the desired product in low yields. The catalysts such as: $FeCl_3$, TiO_2, ZnO

Table 1. Effect of various catalysts on the synthesis of Ethyl-4-(4′-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,6,8-tetrahydroquinoline-3-carboxylate (**5a**)

Entry	Catalyst[a,b]	Time (min)	Yield (%)[e,f]
1	No catalyst	120	20
2	$ZnCl_2$	120	26
3	$Ba(OH)_2$	120	32
4	SiO_2	120	34
5	*p*-TSA	120	48
6	CAN	120	45
7	$FeCl_3$	120	55
8	TiO_2	120	57
9	ZnO	120	60
10	L-Proline	120	65
11	I_2	50	67
12	NaOMe[c,d]	50	74
13	NaOEt[c]	50	87
14	**Atomized sodium**	**30**	**98**

[a] 0.03 g; [b] EtOH (10 mL); [c] 0.05 g; [d] MeOH (10 mL); [e] Compared on TLC; [f] Isolated yield.

and L-proline (entries 7–10) improved the yield of **5a** after prolonged reaction duration. Molecular iodine in EtOH (10 mL) gave 67% of the product; Sodium methoxide (NaOMe) in methanol (MeOH, 10 mL) yielded 74% and Sodium ethoxide (NaOEt) in EtOH (10 mL) furnished 87% of the desired product (Table 1, entries 11–13) in 50 min. As can be seen from the data provided in the table 1, the best result with enhanced yield and short reaction time to get **5a** was use of atomized sodium (0.03 g) in EtOH (10 mL) under ultrasonic condition (entry 14).

In the presence of atomized sodium, the effect of various solvents such as *n*-hexane, dichloromethane (DCM), acetonitrile (CH_3CN), acetone, *o*-xylene, THF, methanol and ethanol under sonication was then evaluated on the model reaction; and it was found that, *n*-Hexane was not a suitable solvent (Table 2, entry 1); solvents such as: DCM, CH_3CN, acetone and xylene in the presence of atomized sodium rendered very low yield of the product (entries 2–5). Reaction in THF gave 67% yield, in MeOH (78%) and in ethanol 98% of the product was obtained (entries 6–8).

Table 2: Effect of solvent on the atomized sodium catalysed synthesis of Ethyl-4-(4′-chlorophenyl) -2,7,7-trimethyl-5-oxo-1,4,6,8-tetrahydroquinoline-3-carboxylate (**5a**)

Entry	Solvent[a]	Time (min)	Yield (%)[b]
1	*n*-Hexane	30	ND[c]
2	DCM	30	20
3	CH_3CN	30	20
4	Acetone	30	25
5	*o*-Xylene	30	34
6	THF	30	67
7	MeOH	30	78
8	**EtOH**	**30**	**98**

[a] 10 mL; [b] Isolated yield; [c] ND-Not Detected.

In order to determine the appropriate feed ratio of atomized sodium in the model reaction, different amounts was selected (0.010 g, 0.015 g, 0.020 g, 0.025 g, 0.030 g and 0.035 g) and the reaction was performed under sonication, and the product was obtained in 57%, 62%, 70%, 73%, 98% and 95% yield respectively (Table 3, entries 1–6). From table 3 (entry 5), it is clear that, 0.03 g of atomized sodium is sufficient for the synthesis of **5a** in 98% yield.

Table 3: Optimization of the feed ratio of atomized sodium for the synthesis of **5a** under sonication

Entry	Catalyst load (g)	Yield (%)[a]
1	0.010	57
2	0.015	62
3	0.020	70
4	0.025	73
5	**0.030**	**98**
6	0.035	95

[a] Isolated yield.

Under the optimized condition, we extended the study to different aromatic aldehydes and heteroaromatic aldehydes and a series of various polysubstituted-tetrahydroquinolines were obtained in excellent yields. The results of this study are presented in the table 4, as can be seen, the functional groups, either electron donating or electron withdrawing does not have any adverse effect on the rate of the reaction or the yield of the products.

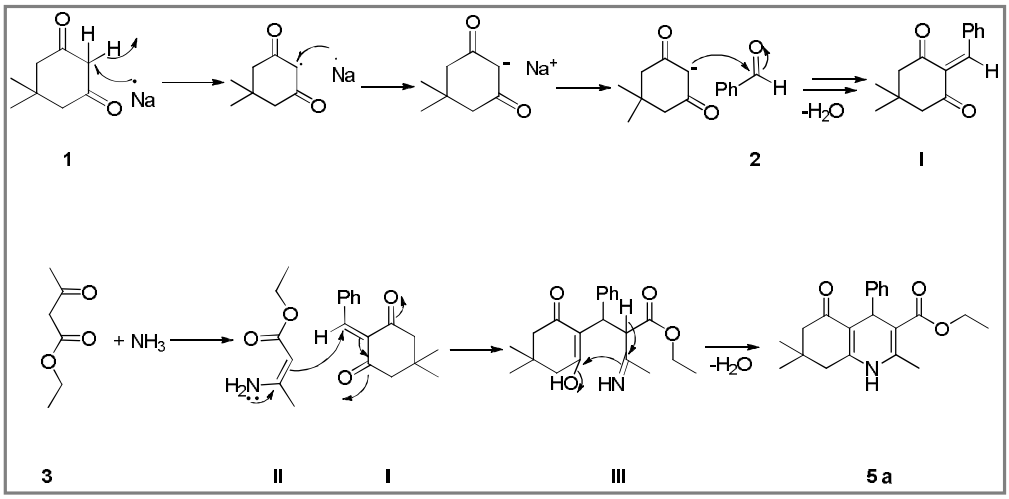
A Plausible Mechanism: A plausible mechanism for the formation of product **5a** is depicted in the scheme 2. The first step of the reaction may involve the formation of dimedone (**1**) radical by the transfer of an electron from the sodium metal; transfer of another electron from the metal may lead to the formation of dimedone anion which may react with a molecule of benzaldehyde (**2**) to give the

Knoevenagel adduct: benzylidene-dimedone (**I**). Ammonia (from ammonium acetate, **4**) may then react with a molecule of ethyl acetoacetate (**3**) to give the enamine **II**; in the next step the enamine (**II**) may undergo condensation with the adduct **I** by a Michael addition reaction to give the intermediate **III**. The intermediate **III** may then undergo an internal cyclization under ultrasonication to give the desired product **5a** after the elimination of a molecule of water as shown in the scheme 2.

Table 4. Synthesis of polysubstituted-tetrahydroquinolines using atomized sodium in EtOH under ultrasonication

Entry	Aromatic/ heteroaromatic aldehyde	Product	Time (min)	Yield (%) [a,b]
1	4-ClC_6H_4CHO	**5a**	30	98
2	3-$NO_2C_6H_4CHO$	**5b**	30	97
3	4-$NO_2C_6H_4CHO$	**5c**	30	97
4	3,4-$(CH_3O)_2C_6H_3CHO$	**5d**	30	95
5	1*H*-Indol-3-yl-CHO	**5e**	30	94
6	4-$(CH_3)_2NC_6H_4CHO$	**5f**	30	96
7	3,4,5-$(CH_3O)_3C_6H_2CHO$	**5g**	30	96
8	5-Butyl-1*H*-imidazole-2-yl-CHO†	**5h**	30	94
9	4-(Methylsulfonyl)C_6H_4CHO†	**5i**	30	95
10	3,5-$(I)_2$-2-HOC_6H_2CHO†	**5j**	30	96
11	3-pyridyl-CHO	**5k**	30	97
12	4-(CH_3O)-3-Br-C_6H_3CHO†	**5l**	30	96

[a] Characterized by IR, ^{1}H NMR, ^{13}C NMR and LC-Mass spectral analysis;
[b] Isolated yield; †Novel compound.



Scheme 2. A plausible mechanism for the formation of **5a.**

Spectral data of 5a–5l

Ethyl-4-(4′-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,6,8-tetrahydroquinoline-3-carboxylate (5a): Yellow crystals; m.p 238–240°C; IR (KBr, ν cm^{-1}): 3272, 3206, 2967, 1704, 1647, 1486, 1380, 1230, 1106, 972, 730, 606; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.06 (s, 1H, NH), 7.22 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.13 (d, *J* = 8.40 Hz, 2H, Ar-H), 4.81 (s, 1H, CH), 3.945 (q, *J* = 6.8 Hz, 2H, CH_2), 2.41–1.93 (m,4H, CH_2 × 2), 2.26 (s, 3H, CH_3), 1.095 (t, *J* = 6.8 Hz, 3H, CH_3), 1.02 (s, 3H, CH_3), 0.81 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.21, 19.28, 27.10, 32.86, 39.58, 41.68, 50.55, 61.00, 103.30, 111.97, 128.00, 130.10, 131.10, 143.71, 151.61, 167.51, 196.01 ppm; MS: m/z: 374.1 $[M+H]^+$.

Ethyl-2,7,7-trimethyl-4-(3′-nitrophenyl)-5-oxo-1,4,6,8-tetrahydroquinoline-3-carboxylate (5b): Colourless crystals; m.p 179–181°C; IR (KBr, ν cm^{-1}): 3261, 2959, 1702, 1632, 1481, 1378, 1350, 1209, 1101; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.32 (s, 1H, NH), 8.29 (s, 1H, Ar-H), 8.11 (d, *J* = 8

Hz, 1H, Ar-H), 7.78 (d, *J* = 8 Hz, 1H, Ar-H), 7.63 (t, *J* = 8 Hz, 1H, Ar-H), 4.88 (s, 1H, CH), 3.945 (q, *J* = 6.8 Hz, 2H, CH_2), 2.41–1.95 (m, 4H, CH_2 × 2), 2.25 (s, 3H, CH_3), 1.075 (t, *J* = 6.8 Hz, 3H, CH_3), 0.99 (s, 3H, CH_3), 0.90 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.20, 19.42, 27.04, 32.71, 37.22, 40.33, 50.60, 60.09, 104.84, 111.01, 120.61, 121.03, 122.03, 133.98, 144.58, 146.18, 149.02, 154.47, 166.88, 195.49 ppm; MS: m/z: 385.1 $[M+H]^+$.

Ethyl-2,7,7-trimethyl-4-(4′-nitrophenyl)-5-oxo-1,4,6,8-tetrahydroquinoline-3-carboxylate (5c): Colourless crystals; m.p 242–244°C; IR (KBr, ν cm^{-1}): 3263, 2958, 1728, 1576, 1450, 1368, 1341, 1250, 1110; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.09 (s, 1H, NH), 6.885 (d, *J* = 6.8 Hz, 2H, Ar-H), 6.7 (d, *J* = 6.8 Hz, 2H, Ar-H), 5.07 (s, 1H, CH), 3.975 (q, *J* = 7.2 Hz, 2H, CH_2), 2.40–1.88 (m, 4H, CH_2 × 2), 2.22 (s, 3H, CH_3), 1.12 (t, *J* = 7.2 Hz, 3H, CH_3), 0.99 (s, 3H, CH_3), 0.98 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.20, 19.42, 27.05, 32.80, 39.52, 40.93, 50.60, 60.09, 104.79, 111.01, 123.33, 126.98, 144.88, 149.02, 152.00, 154.47, 166.88, 197.19 ppm; MS: m/z: 384.1 $[M]^+$.

Ethyl-4-(3′,4′-dimethoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,6,8-tetrahydroquinoline-3-carboxylate (5d): Yellow crystals; m.p 204–206°C; IR (KBr, ν cm^{-1}): 3279, 2962, 1729, 1684, 1577, 1461, 1300, 1237, 1144; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.82 (s, 1H, NH), 7.37 (s, 1H, Ar-H), 7.115(d, *J* = 22 Hz, 1H, Ar-H), 6.725 (d, *J* = 22 Hz, 1H, Ar-H), 4.89 (s, 1H, CH), 4.14 (q, *J* = 6.8 Hz, 2H, CH_2), 3.92 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 2.48–1.85 (m, 4H, CH_2 × 2), 2.24 (s, 3H, CH_3), 1.115 (t, *J* = 6.8 Hz, 3H, CH_3), 0.93 (s, 3H, CH_3), 0.88 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.38, 19.02, 27.08, 32.30, 39.89, 41.06, 51.05, 56.01, 59.66, 103.75, 109.60, 110.08, 110.87, 121.55, 130.0, 144.01, 146.78, 149.40, 150.88, 168.72, 196.44 ppm; MS: m/z: 399.2 $[M]^+$.

Ethyl-4-(1H-indol-3′-yl)-2,7,7-trimethyl-5-oxo-1,4,6,8-tetrahydroquinoline-3-carboxylate (5e): Yellow solid; m.p 168–170 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.82 (s, 1H, NH), 9.04 (s, 1H, NH), 7.61 (d, *J* = 25.6 Hz, 1H, Ar-H), 7.29 (s, 1H, Ar-H), 7.165 (d, *J* = 20.8 Hz, 1H, Ar-H), 6.81–6.60 (m, 2H, Ar-H), 4.96 (s, 1H, CH), 4.24 (q, *J* = 18.4 Hz, 2H, CH_2), 2.40–1.85 (m, 4H, CH_2 × 2), 2.24 (s, 3H, CH_3), 1.075 (t, *J* = 18.4 Hz, 3H, CH_3), 0.93 (s, 3H, CH_3), 0.89 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.20, 19.37, 27.33, 33.42, 40.92, 41.0, 50.88, 60.09, 102.22, 104.79, 111.99, 112.26, 115.75, 116.11, 123.35, 123.47, 127.48, 136.94, 150.60, 154.62, 166.90, 195.74 ppm; MS: m/z: 378.1 $[M]^+$.

Ethyl-4-[4′-(N,N-dimethylamino)phenyl]-2,7,7-trimethyl-5-oxo-1,4,6,8-tetrahydroquinoline-3-carboxylate (5f): Brown solid; m.p 229–231°C; IR (KBr, ν cm^{-1}): 3277, 2965, 1699, 1681, 1597, 1478, 1308, 1214, 1105; ^{1}H NMR (400 MHz, DMSO-d_6): 9.20 (s, 1H, NH), 6.415 (d, *J* = 8.4 Hz, 1H, Ar-H), 6.24 (d, *J* = 8.4 Hz, 1H, Ar-H), 4.15 (q, *J* = 7.6 Hz, 2H, CH_2), 3.18 (s, 6H, CH_3 × 2), 2.38–1.85 (m, 4H, CH_2 × 2), 2.24 (s, 3H, CH_3), 1.06 (t, *J* = 7.6 Hz, 3H, CH_3), 0.95 (s, 3H, CH_3), 0.89 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 14.20, 19.26, 28.35, 32.41, 40.89, 42.52, 43.64, 50.97, 61.21, 106.02, 112.00, 112.90, 127.92, 132.03, 143.61, 147.21, 149.88, 169.50, 196.02 ppm; MS: m/z: 382.2 $[M]^+$.

Ethyl-2,7,7-trimethyl-5-oxo-4-(3′,4′,5′-trimethoxyphenyl)-1,4,6,8-tetrahydroquinoline-3-carboxy late (5g): Yellow solid; m.p 220–222°C; IR (KBr, ν cm^{-1}): 3268, 2947, 1695, 1630, 1585, 1488, 1300, 1265, 1118; ^{1}H NMR (400 MHz, DMSO-d_6): 9.86 (s, 1H, NH), 6.49 (s, 2H, Ar-H), 4.80 (s, 1H, CH), 4.01 (q, *J* = 7.2 Hz, 2H, CH_2), 2.45–1.98 (m, 4H, CH_2 × 2), 2.24 (s, 3H, CH_3), 1.17 (t, *J* = 7.2 Hz, 3H, CH_3), 1.01 (s, 3H, CH_3), 0.92 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 14.01, 19.32, 27.01, 32.87, 39.51, 40.95, 50.72, 56.10, 60.09, 61.52, 102.12, 106.30, 111.12, 136.10, 136.36, 149.16, 152.01, 154.52, 166.85, 197.21 ppm; MS: m/z: 430.2 $[M+H]^+$.

Ethyl-4-(5′-butyl-1H-imidazol-2′-yl)-2,7,7-trimethyl-5-oxo-1,4,6,8-tetrahydroquinoline-3-carboxylate (5h): Yellow solid; m.p 160–162°C; ^{1}H NMR (400 MHz, DMSO-d_6): 10.95 (s, 1H, NH), 9.12 (s, 1H, NH), 7.08 (s, 1H, Ar-H), 4.81 (s, 1H, CH), 4.04 (q, *J* = 14 Hz, 2H, CH_2), 2.545 (t, *J* = 12.8 Hz, 2H, CH_2), 2.385 (d, *J* = 20 Hz, 1H, CH), 2.305 (d, *J* = 20 Hz, 1H, CH), 2.24 (s, 3H, CH_3), 2.15 (d, *J* =

18 Hz, 1H, CH), 1.91 (d, *J* = 18.4 Hz, 1H, CH), 1.50–1.37 (m, 2H, CH_2), 1.31–1.19 (m, 2H, CH_2), 1.115 (t, *J* = 14 Hz, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.80 (s, 3H, CH_3), 0.73 (t, J = 10 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 14.12, 14.32, 19.01, 22.01, 27.01, 29.57, 30.50, 31.85, 32.21, 40.07, 51.04, 60.22, 105.36, 111.65, 120.17, 144.22, 146.17, 148.91, 150.07, 167.75, 195.52 ppm; MS: m/z: 386.2 $[M]^+$.

Ethyl-2,7,7-trimethyl-4-[4′-(methylsulfonyl)phenyl]-5-oxo-1,4,6,8-tetrahydroquinoline-3-carboxylate (5i): Yellow solid; m.p 229–231°C; ^{1}H NMR (400 MHz, DMSO-d_6): 9.06 (s, 1H, NH), 7.57 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.43 (d, *J* = 8.4 Hz, 2H, Ar-H), 4.81 (s, 1H, CH), 3.945 (q, *J* = 6.8 Hz, 2H, CH_2), 3.19 (s, 3H, CH_3), 2.41–1.93 (m, 4H, CH_2 × 2), 2.23 (s, 3H, CH_3), 1.095 (t, *J* = 6.8 Hz, 3H, CH_3), 0.98 (s, 3H, CH_3), 0.88 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 14.20, 19.42, 27.04, 32.71, 40.93, 41.12, 47.73, 50.60, 60.09, 104.84, 111.01, 128.98, 130.33, 138.26, 149.02, 149.18, 154.47, 166.88, 195.49 ppm; MS: m/z: 417.1 $[M]^+$.

Ethyl-4-(2′-hydroxy-3′,5′-diiodophenyl)-2,7,7-trimethyl-5-oxo-1,4,6,8-tetrahydroquinoline-3-carboxylate (5j): Pale yellow solid; m.p 168–170°C; ^{1}H NMR (400 MHz, DMSO-d_6): 9.44 (s, 1H, NH), 7.60 (s, 1H, Ar-H), 7.45 (s, 1H, Ar-H), 5.46 (s, 1H, OH), 4.91 (s, 1H, CH), 4.125 (q, *J* = 6.8 Hz, 2H, CH_2), 2.41–1.89 (m, 4H, CH_2 × 2), 2.26 (s, 3H, CH_3), 1.185 (t, *J* = 6.8 Hz, 3H, CH_3), 0.99 (s, 3H, CH_3), 0.97 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 14.29, 19.28, 27.23, 32.62, 33.13, 40.71, 51.00, 61.40, 88.89, 89.61, 106.38, 112.19, 125.59, 140.22, 143.19, 149.30, 150.26, 153.69, 167.76, 194.91 ppm; MS: m/z: 606.9 $[M]^+$.

Ethyl-2,7,7-trimethyl-5-oxo-4-(pyridin-3-yl)-1,4,6,8-tetrahydroquinoline-3-carboxylate(5k): Yellow solid; m.p 147–148°C; ^{1}H NMR (400 MHz, DMSO-d_6): 9.12 (s, 1H, NH), 8.40 (s, 1H, Ar-H), 8.27 (d, *J* = 9.6 Hz, 1H, Ar-H), 7.18–7.49 (m, 2H, Ar-H), 4.81 (s, 1H, CH), 4.04 (q, *J* = 14.4 Hz, 2H, CH_2), 2.48–1.93 (m, 4H, CH_2 × 2), 2.24 (s, 3H, CH_3), 1.115 (t, *J* = 14.4 Hz, 3H, CH_3), 0.98 (s, 3H, CH_3), 0.90 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 14.20, 19.42, 27.04, 32.71, 40.93, 41.18, 50.60, 60.09, 104.84, 111.01, 123.33, 132.85, 134.18, 144.58, 146.18, 149.02, 154.47, 166.88, 195.49 ppm; MS: m/z: 341.2 $[M+H]^+$.

Ethyl-4-(3′-bromo-4′-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,6,8-tetrahydroquinoline-3-carboxylate (5l): Brown solid; m.p 189–190°C; IR (KBr, ν cm^{-1}): 3276, 2939, 1670, 1599, 1489, 1323, 1279, 1107; ^{1}H NMR (400 MHz, DMSO-d_6): 9.02 (s, 1H, NH), 7.26 (s, 1H, Ar-H), 7.06 (d, *J* = 7.6 Hz, 1H, Ar-H), 6.91 (d, *J* = 8.4 Hz, 1H, Ar-H), 4.75 (s, 1H, CH), 3.955 (q, *J* = 6.8 Hz, 2H, CH_2), 3.74 (s, 3H, OCH_3), 2.42–1.96 (m, 4H, 2×CH_2), 2.28 (s, 3H, CH_3), 1.12 (t, *J* = 6.8 Hz, 3H, CH_3), 0.99 (s, 3H, CH_3), 0.86 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 14.22, 19.13, 27.19, 32.74, 40.0, 40.91, 51.26, 55.99, 61.73, 102.32, 111.98, 112.87, 113.81, 129.23, 134.72, 138.94, 149.32, 150.11, 154.03, 167.37, 194.98 ppm; MS: m/z: 448.1 $[M+H]^+$.

Effect of ultrasound on the reaction: Sonication of heterogeneous liquid–solid media proceeds with nucleation, which depends largely on the intermolecular attractive forces of the liquid causing cohesion. The gas present in the micro bubbles experiences the variation of vapour pressure and simultaneous decrease in the liquid pressure creates convex bubble surface, and the unstable pressure in the gas pocket leads to implosion of bubbles which produces enormous amounts of heat and pressure. Further, the micro bubbles present in the liquid medium leads to the physical effects of cavitation. Eventually, the acoustic cavitation is through the formation of gas pockets in the crevices of the solid materials. In the liquid medium, several mechanisms such as: micro streaming, microturbulence, formation of acoustic waves and microjets (non-linear bubble) accelerate the dissolution, heat flow (induces randomness in chemical species) and mass transfer in the medium. Thus, ultrasonic irradiation accelerates the rates of the chemical reactions by inducing high local temperatures and pressures generated inside the cavitation bubble and near its interface when it collapses [**4, 5**]. In the present heterogeneous reaction, the asymmetric bubble collapse may progress in the vicinity of the atomized sodium (solid) surface and may give rise to high-speed liquid jets

which can accelerate the collisions between the substrate molecules in the presence of the catalyst and hence, the formation of the products takes place rapidly. Owing to the associated chemical and mechanical effects, the efficient role of atomized sodium pronounces effectively the synthesis of polysubstituted-tetrahydroquinolines in EtOH under ultrasonication.

APPLICATION

Quinoline and a number of derivatives of quinoline exhibit a wide range of biological properties including: antimalarial, antimicrobial, antitumor, antiatherosclerotic, antidiabetic, antimutagenic, vasodilator, bronchodilator, hepatoprotective and geroprotective activities, and are known to show calcium channel blocking property; due to which they find application in the medical and pharmaceutical industries. A series of known and novel substituted quinolinones have been prepared by a one-pot four-component reaction under ultrasonication, which is considered to a highly energy efficient and green technique. The prepared heterocyclic compounds may also exhibit biological activity and find application in the pharmaceutical industries.

CONCLUSION

In conclusion, we have developed a clean, simple, economical, ultrasound-assisted, energy efficient, atomized sodium catalyzed, one-pot four-component synthesis of polysubstituted-tetrahydro quinolines in EtOH as a medium from dimedone, ethyl acetoacetate, ammonium acetate and substituted benzaldehydes/ heteroaromatic aldehydes in shorter reaction durations. The outcome of our effort is: excellent yield of the products, sustainability of the reaction and promotion of reaction rates. The reaction is green as it involves use of a simple and readily available sodium metal as a catalyst and a green solvent: ethanol; and is a rational approach towards the synthesis of nitrogen based-polysubstituted quinolines under ultrasonic conditions.

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