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Ultrasound-mediated, uranyl nitrate hexahydrate-catalyzed synthesis of 1,4-dihydropyridines under mild conditions

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Abstract Synthesis of 1,4-dihydropyridines by three-component condensation reaction of aldehyde, 1,3-dicarbonyl compounds, and ammonium acetate have been found to be efficiently catalyzed by uranyl nitrate hexahydrate [$UO_2(NO_3)_2{\cdot}6H_2O$] at room temperature under ultrasound irradiation. This novel synthetic method offers the advantages of high yields, short reaction times, simplicity, and easy workup compared to the conventional methods reported in the literature.

Keywords 1,4-DHPs · Uranyl nitrate hexahydrate · Ultrasound irradiation

Introduction

1,4-Dihydropyridine (1,4-DHPs) derivatives are known as an important class of heterocycles owing to their potential biological activity, and for their therapeutics use such as antihypertensive [1, 2], hypnotic, anti-inflammatory [3], antihypoxic, antiischemic drugs [4] and calcium channel modulators of the nifedipine type [5]. For synthesis of 1,4-DHPs, several methods have been reported [6–10]. The presence of ester groups at the 3- and 5-positions on the 1,4-DHPs ring is of crucial importance for its pharmacological effects. Recently, some new 3,5-disubstituted 1,4-DHPs were synthesized which exhibit pharmacological effects such as antihypertensive, bronchodilatory and antitubercular agent [11, 12]. DHPs are also have significant biological activities, ranging from anti-tumour, fungicidal, bactericidal and anti-inflammatory and antiviral activities [13, 14]. In continuation of our interest in 1,4-DHPs [15–22], we here report a simple and efficient protocol for the synthesis of 1,4-DHPs via three-component reaction of aldehydes, 1,3-

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dicarbonyls and ammoniumacetate in the presence of uranyl nitrate haxahydrate as a catalyst under ultrasonic irradiation. Uranyl nitrate hexahydrate is usually used as an electron-dense stain for transmission electron microscopy. However, it has also found application as a local catalyst in the polymerization of methacrylates [23].

Experimental

IR spectra were recorded using an AVATAR 330 equipped with DTGS detector. NMR spectra were measured on a Bruker AMX-400 instrument at RT in $CDCl_3$ using TMS as internal reference. The coupling constants *J* are in Hz. HRMS spectra were recorded on macromass spectrometer (Waters) by the electron-spray method (ES). Melting points were determined in open capillaries and are uncorrected. Sonication was performed in a Make (E-Chrom Tech, Taiwan), equipped with a 1.3×10^{-2}-m-long probe, which was immersed directly into the reaction mixture. The operating frequency was 22 kHz and the output power was 800 W through manual adjustment.

General procedure for synthesis of 1,4-DHPs

To a solution of aldehyde (1.0 mmol), ethyl/methyl acetoacetate/acetylacetone (2.0 mmol) and ammonium acetate (1.0 mmol) in ethanol (3 mL), uranyl nitrate (10 mol%) was added and the resultant reaction mixture was sonicated at room temperature for the required time (Table 1). The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into crushed ice. The obtained solid was filtered, washed thoroughly with water, dried, and purified by recrystallisation in ethanol. The plausible reaction mechanism was proposed for the $UO_2(NO_3)_2{\cdot}6H_2O$ catalyzed reaction of aldehyde, 1,3-dicarbonyl compound and ammonium acetate (Fig. 1).

Diethyl 2,6-dimethyl-4-(thiophen-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4 h)

Yield: 95 %. m.p.: 172–173 °C; IR (KBr, cm^{-1}):3,403, 3,327, 1,673, 1,633, 1,591, 1,528, 113. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 1.24 (*t*, $J = 7.2$ Hz, 6H), 2.31 (*s*, 6H), 4.10–4.19 (*m*, 4H), 5.32 (*s*, 1H), 5.81 (*s*, NH), 6.76–6.83 (*m*, 2H), 7.02 (*d*, $J = 6.0$ Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 14.00, 18.60, 33.91, 59.31, 102.25, 122.53, 122.57, 125.91, 145.36, 151.81, 167.22.HRMS (*m/z*): Calcd. for$C_{17}H_{21}NO_4S$: 335.1189. Found: 335.1180 (M^+).

Diethyl-4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4j)

Yellow solid. M.p. 227–229 °C. IR (KBr, cm^{-1}): 3,345, 2,981, 1,662 and 1,486. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.88 (*t*, $J = 7.5$ Hz, 6H), 2.77 (*s*, 6H), 3.66–3.76 (*q*,

Table 1 Optimization conditions of benzaldehyde (1.0 mmol), ethyl acetoacetate (2.0 mmol), and ammonium acetate (1.0 mmol), with ultrasonic irradiation

Entry	Catalyst	Mole (%)	Solvent	Time (min)	Yield (%)
1	$UO_2(NO_3)_2{\cdot}6H_2O$	Nil	EtOH	40	70
2	$UO_2(NO_3)_2{\cdot}6H_2O$	1	EtOH	40	70
3	$UO_2(NO_3)_2{\cdot}6H_2O$	2.5	EtOH	25	80
4	$UO_2(NO_3)_2{\cdot}6H_2O$	5	EtOH	20	85
5	$UO_2(NO_3)_2{\cdot}6H_2O$	10	EtOH	15	96
6	$UO_2(NO_3)_2{\cdot}6H_2O$	20	EtOH	15	96
7	$UO_2(NO_3)_2{\cdot}6H_2O$	10	MeCN	20	90
8	$FeCl_3{\cdot}6H_2O$	10	MeCN	40	75
9	$AlCl_3{\cdot}6H_2O$	10	MeCN	40	77
10	Nil	Nil	MeCN	120	45

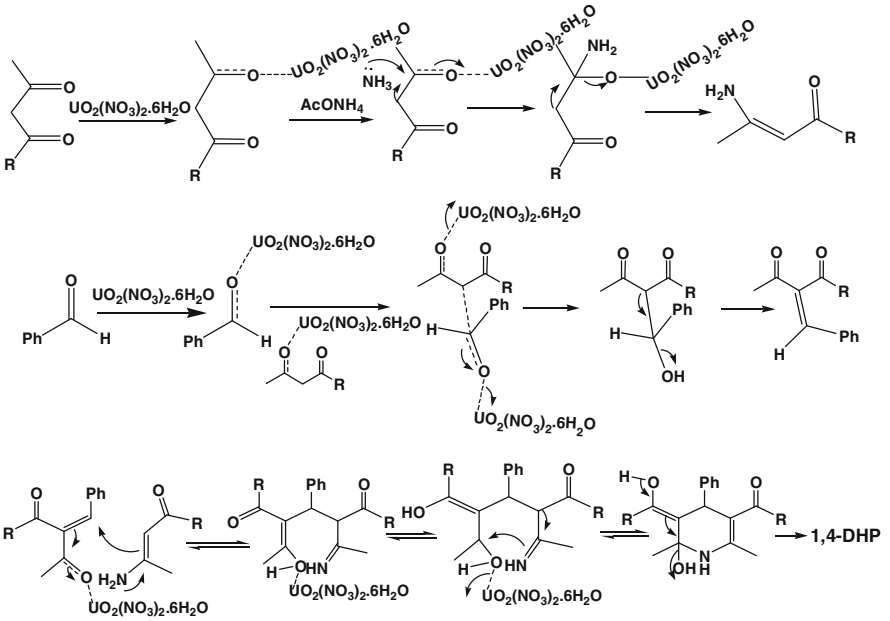


Fig. 1 Plausible mechanism for the uranyl nitrate hexahydrate-catalyzed synthesis of 1,4-dihydropyridines

$J = 6.0$ Hz, 4H), 4.49 (*s*, 1H), 6.30 (*d*, $J = 8.0$ Hz, 2H), 6.72 (*d*, $J = 8.0$ Hz, 2H), 7.60 (s, –NH, 1H), 8.27 (*s*, –OH, 1H). HRMS: Calcd. for$C_{19}H_{23}NO_5$: 345.1575. Found: 345.1582 (M^+).

Dimethyl-4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (5 h)

Yellow solid. M.p. 198–199 °C. IR (KBr, cm^{-1}): 3,339, 3,003, 2,950, 1,680, 1,647 and 1,611. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.86 (*s*, 6H), 3.28 (*s*, 6H), 4.51 (*s*, 1H), 6.31 (*d*, $J = 8.0$ Hz, 2H), 6.70 (*d*, $J = 8.0$ Hz, 2H), 7.73 (*s*, –NH, 1H), 8.35 (*s*, –OH, 1H). HRMS (*m/z)*: Calcd. for$C_{17}H_{19}NO_5$: 317.1,265. Found: 317.1,270 (M^+).

3,5-Diacetyl-2,6-dimethyl-1,4-dihydro-4-(4-ethylphenyl)-3,5-pyridine (6i)

Yellow solid. M.p. 179–181 °C. IR (KBr, cm^{-1}): 3,343, 3,008, 2,960, 1,689 and 1,649. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.88 (*t*, $J = 7.1$ Hz, 3H), 1.89 (*s*, 6H), 2.34 (*m*, $J = 7.0$ Hz, 2H), 2.37 (*s*, 6H), 4.81 (*s*, 1H), 6.63 (*d*, *m*, $J = 7.8$ Hz, 2H), 7.78 (*d*, *o*, $J = 7.5$ Hz, 2H). HRMS (*m/z)*:Calcd. for$C_{17}H_{19}NO_5$: 297.1725.Found:297.1725 (M^+).

Results and discussion

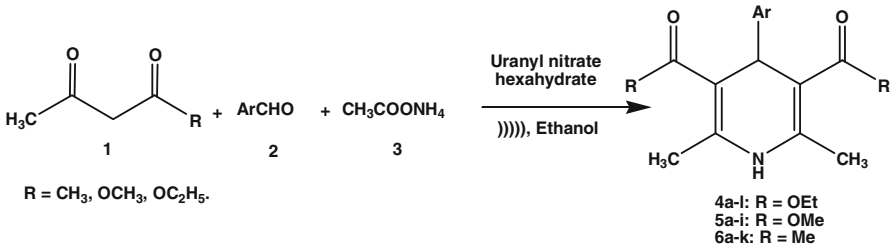
The formation of 1,4-DHPs using various aldehydes, ethyl/methyl acetoacetate/acetylacetone and ammonium acetate under ultrasonic irradiation was examined and the results are summarized in Table 2. Initially, the reactions were carried out at room temperature for 15–30 min in the presence of 10 mol% of the uranyl nitrate hexahydrate at 22 kHz under ultrasonic irradiation. To determine the amount of the catalyst required, the reaction of benzaldehyde, ethyl acetoacetate and ammonium acetate was selected as the model reaction and conducted under sonication in the presence of varying concentrations (mol%) of the uranyl nitrate and it was found that optimum yield was observed while using 10 mol% of the catalyst (Table 1). Using lesser amounts of the catalyst resulted in lower yields, while higher amounts of the catalyst did not affect reaction times and yields. In the absence of the catalyst, the yield was found to be low. The reaction was also carried out using different solvents such as methanol, ethanol, acetonitrile and chloroform, as well as a solvent-free system at reflux conditions with 10 mol% of $UO_2(NO_3)_2.6H_2O$ as the catalyst. Under these conditions, it was noticed that the highest yield and shorter reaction duration was achievable with ethanol (in 40 min, 90 % yield) while the others took longer durations to yield lesser products. Hence, the ultrasonic irradiation which required only 15 min duration to complete the reaction dominates the reflux reaction conditions. So the use of the ultrasound improves the yield as well as the rate of reaction. To prove the generality of the reaction, a wide range of substituted aldehydes with electron-donating as well as electron-withdrawing substituents were used and found to have excellent yields of 1,4-DHPs (Table 2). Unlike those of ethyl/methyl acetoacetate products, the reaction of acetyl acetone products proceeded at lower rates and less efficiency to afford the 1,4-DHPs. Known

Table 2 Synthesis of 1,4-DHPs using uranyl nitrate hexahydrate as catalyst under ultrasonic irradiation

Entry	Ar	R	Time (min)	Yield (%) d	mp (°C)
4a	C_6H_5	OEt	15	96	158–160 (158–160) [24]
4b	4-ClC_6H_4	OEt	20	92	145–146 (144–146) [24]
4c	4-$CH_3OC_6H_4$	OEt	20	89	153–155 (158–160) [24]
4d	3-$NO_2C_6H_4$	OEt	25	90	165–167 (162–164) [24]
4e	4-Pyridyl	OEt	25	87	181–182 (178–180) [25]
4f	3-Pyridyl	OEt	25	85	188–190 (190–192) [25]
4g	4-BrC_6H_4	OEt	20	91	162–164 (162–164) [26]
4h	2-Thienyl	OEt	25	89	172–173 (171–173) [24]
4i	4-$CH_3C_6H_4$	OEt	30	86	136–137 (135–138) [27]
4j	4-HOC_6H_4	OEt	30	90	227–229 (227–228) [28]
4k	3-HOC_6H_4	OEt	30	88	172–175 (180–182) [25]
4l	2,5-$Me_2C_6H_3$	OEt	25	86	147–148 (146–147) [29]
5a	C_6H_5	OMe	15	92	198–200 (197–198) [30]
5b	3-$NO_2C_6H_4$	OMe	20	90	210–212 (210–212) [31]
5c	4-$CH_3C_6H_4$	OMe	25	86	174–176 (174–176) [31]
5d	2-ClC_6H_4	OMe	30	87	185–186 (185–186) [30]
5e	4-$CH_3OC_6H_4$	OMe	30	88	173–174 (173–174) [30]
5f	2-Furyl	OMe	25	89	194–197 (195–196) [32]
5g	2-Thienyl	OMe	30	90	201–203 (200–202) [33]
5h	4-HOC_6H_4	OMe	30	92	198–199 (198–199) [30]
5i	4-ClC_6H_4	OMe	25	90	196–198 (195–196) [30]
6a	CH_3	Me	20	90	155–156 (150–152) [34]
6b	3-$NO_2C_6H_4$	Me	25	89	210–211 (210–211) [34]
6c	2-$NO_2C_6H_4$	Me	25	87	195–197 (195–197) [35]
6d	2-Furyl	Me	25	86	159–160 (158–159) [35]
6e	2-Thienyl	Me	25	90	169–172 (171) [36]
6f	3-Pyridyl	Me	30	88	262–263 (262–263) [37]
6g	3-ClC_6H_4	Me	25	90	222–224 (221–222) [35]
6h	3-$CH_3OC_6H_4$	Me	30	89	200–201 (196–198) [34]
6i	4-$C_2H_5C_6H_4$	Me	30	90	179–181 (179–181) [20]
6j	4-Pyridyl	Me	25	88	245–246 (245–246) [38]
6k	4-BrC_6H_4	Me	30	90	109–111 (109–111) [39]

Reaction conditions: aldehyde (1.0 mmol), ethyl/methyl acetoacetate/acetylacetone (2.0 mmol), ammonium acetate (1.0 mmol), uranyl nitrate hexahydrate (10 mol%)

compounds were identified by comparing their spectroscopic data and melting points with reported literature values, and hence only representative compounds were included in the "Experimental" section.



Conclusion

An efficient and simple alternative method for the synthesis of substituted 1,4-DHPs under ultrasonic irradiation using $UO_2(NO_3)_2{\cdot}6H_2O$ as the catalyst was developed with operational simplicity, good yields, shorter reaction time, low costs, and easy workup procedure.

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