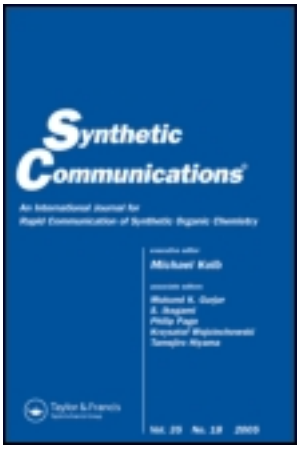

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One-Pot Synthesis of 3,4-Dihydropyridin-2-one via Michael Addition of in situ-Generated Enaminones

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ONE-POT SYNTHESIS OF 3,4-DIHYDROPYRIDIN-2-ONE VIA MICHAEL ADDITION OF IN SITU–GENERATED ENAMINONES

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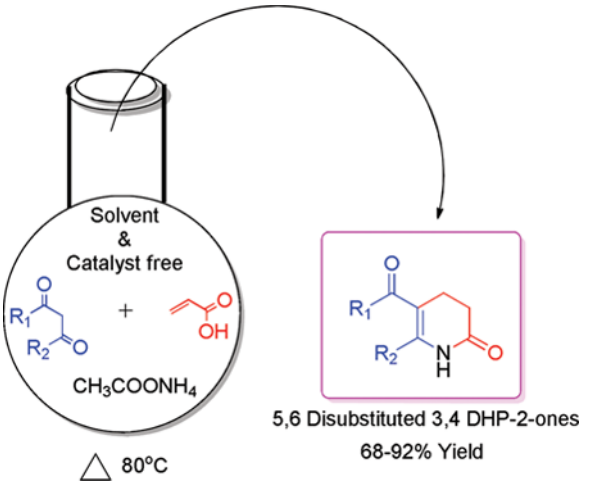
GRAPHICAL ABSTRACT



Abstract *Herein we have reported a facile solvent-, catalyst-, and aldehyde-free, one-pot synthesis of 3,4-dihydropyridin-2-one from 1,3-diones using simple and mild reaction conditions. The substrate scope has been also extended to* β*-ketoesters.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource: Full experimental and spectral details.]*

Keywords 3,4-DHP-2-ones; 1,3-dicarbonyls; enaminones; solvent free

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INTRODUCTION

Development of new synthetic approaches and solvent-free, one-pot, multi component reactions (MCRs) for the synthesis of N-heterocycles offer the products cost-effectively.[1] Because of the wide distribution of biologically active N-heterocycles in nature, the synthesis of novel bioactive nitrogen-containing heterocyclic compounds has been an important research target.[2] Among different N-heterocycles, pyridine-2--one derivatives and their partially reduced 3,4-dihyrdopyridin-2-ones (3,4-DHP-2-ones) possess a variety of biological properties and can act in pharmaceuticals such as Rho kinase inhibitor, $P2X_7$ antagonists, α-adrenergic receptor antagonists, and nonselective β-blockers[3] (Fig. 1).

Moreover 3,4-DHP-2-ones act as useful scaffolds for the synthesis of Clausena alkaloids[4] and calcium channel modulators.[5] 3,4-DHP-2-ones have been further elaborated by reduction to δ-lactams,[6] and oxidation to 2-pyridones,[7] giving further scope to the parent library. Wide-spectrum therapeutic effects associated with 3,4-DHP-2-ones have generated interest in the synthesis of these scaffolds. Substantial synthetic methods are documented for pyridine-2-one and its derivatives;[8] however, limited literature is available for the synthesis of 3,4-DHP-2-one and its derivatives.[9] Reports involve the Michael addition of the 1,3-dione intermediate to the arylidene Meldrum's acid condensate followed by intramolecular nucleophilic substitution,[9a] 1,4-dien-3-ones-mediated Nazarov electrocyclization and intermolecular trapping by various azides,[9b] reaction of 1-azabutadienes with enolates of substituted acetates,[9c] and solid-support aza anulation[9e] to form the cyclic amide. 3,4-DHP-2-one intermediate has been envisioned from the bicyclic vinylogous amide

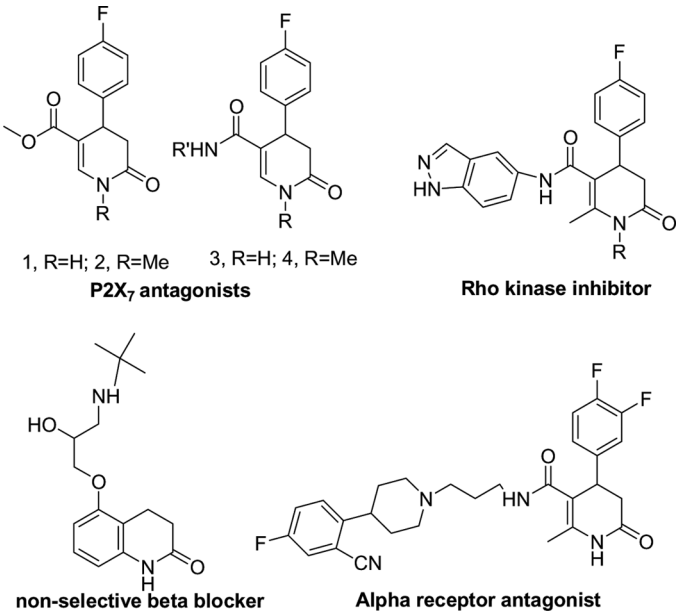
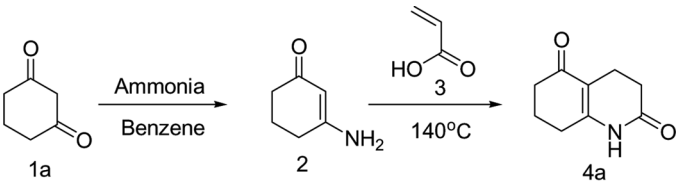


Figure 1. Biologically important 3,4-dihydropyridin-2-one.



Scheme 1. (a) Reported method for the synthesis of bicyclic vinylogous amide. (b) One-pot synthesis of bicyclic vinylogous amide.

(**4a**), which is used in the synthesis of aspidosperm-type alkaloids[10] and nonselective α-blocker carteolol.[3d] The classical method for the synthesis of **4a** involved the preparation of enaminone intermediate (**2**) by passing ammonia gas in the solution of cyclohexane-1,3-dione (**1a)** in benzene, followed by cyclization with acrylic acid to give **4a** in 95% yield[11] (Scheme 1a); however, less than 50% yield was obtained by us and other research groups[12] using same method. The use of ammonia gas and hazardous solvent benzene for the preparation of **2** involved special handling and safety procedures. We have developed a simple, versatile, efficient, and economically viable synthetic method, devoid of ammonia[13] gas and benzene,[14] for the preparation of 3,4-DHP-2-one (**4a**) (Scheme 1b). Further, the substrate scope of this methodology was investigated using various 1,3-dicarbonyls.

RESULTS AND DISCUSSION

Various parameters such as temperature, reaction duration, molar ratios, and nitrogen source were examined to optimize reaction conditions (Table 1**)**. The reaction of **1a** with ammonium chloride and **3** in equimolar ratios (entry 1, Table 1) for 3 h at 60 °C did not result in product formation; however, increasing temperatures to 80 °C and 110 °C afforded traces of **4a** (entries 2 and 3). Interestingly, the reaction of ammonium acetate with **1a** and **3** in equimolar ratio at 60 °C resulted in the formation of **4a** in 40% yield after 3 h (entry 4) and 55% yield after 5 h (entry 5), whereas further increase in reaction time (8 h) resulted in reduced yield (entry 6). Ammonium acetate is a salt of weak acid, and ammonia is easily released to form enaminone as compared to ammonium chloride, which is a salt of strong acid. It was noticed that reaction conditions with equimolar ratios of **1a** and **3** to the formation of **4a** always proceeded with the contamination of **1a**, which may be due to the escape of a small amount of NH_3 from the reaction vessel. The use of a slight excess of ammonium

Table 1. Optimization of reaction conditions

Entry	**1a–3**–ammonium acetate (mol ratio)	Nitogen source	T (°C)	Time (h)	Yield (%)[a]
1	1:1:1	NH_4Cl	60	3	No product
2	1:1:1	NH_4Cl	80	3	Trace[b]
3	1:1:1	NH_4Cl	110	3	Trace[b]
4	1:1:1	NH_4OAC	60	3	40[b]
5	1:1:1	NH_4OAC	60	5	55[b]
6	1:1:1	NH_4OAC	60	8	50[b,c]
7	1:1.2:1.2	NH_4OAC	60	5	65
8	1:1.2:1.2	NH_4OAC	80	5	92

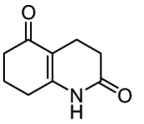
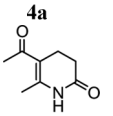
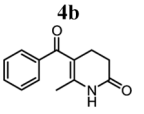
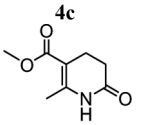
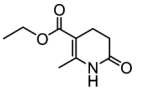
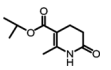
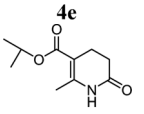
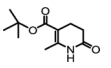
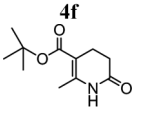
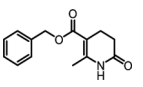
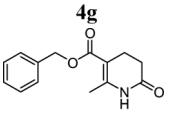
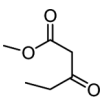
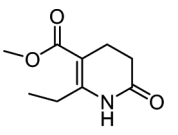
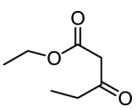
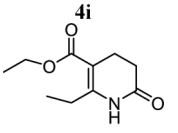
[a]Isolated yield.
[b]Starting materials were present.
[c]Polymerisation was observed.

acetate and **3** accomplished a complete transformation of the starting material to afford **4a** in quantitative yield (65%, entry 7). Subsequent optimization of the reaction temperature offered **4a** in 92% yield at 80 °C (entry 8). Further, modulating the reaction conditions did not result in an increase in yield. The product was isolated by vacuum filtration of the reaction mass followed by recrystallization with water. The sequence of reactions for the formation of **4a** involved are 1) disproportionate amount of ammonium acetate to give acetic acid and ammonia, (2) **1a** and ammonia under acidic conditions formed enaminone intermediate, and (3) Michael addition of the enaminone intermediate to acrylic acid to led to the formation of 3,4-DHP-2-one (**4a**).

This is modified E1cb mechanism. The initial reaction involves the protonation of enol form, generated from acetic acid, which favors the nucleophillic attack of ammonia, which results in in situ generation of enaminone intermediate, followed by Michael addition, leading to the formation of 3,4-DHP-2-one. The economically viable and significantly improved synthesis of **4a** has been developed by precluding the preparation of enaminone intermediate **2**. Furthermore, the scope and limitation of this method were evaluated using various 1,3-dicarbonyls to get 5,6-disubstituted products **4a–m** (Table 2). 1,3-Acyclic dione (entry 2, Table 2) afforded cyclized product in 87% yield, whereas 1,3-diketo moiety bearing an aryl substituent next to the carbonyl group did not form the cyclized product (entry 3, Table 2), which may be due to the predominant existence of *cis*-enol enaminone.[15] The reaction of benzoylacetone with ammonium acetate (entry 3) was investigated to envisage the failure of 3,4-DHP-2-one formation. The ^1H NMR showed (Fig. 2A) the acidic proton at δ 10.21 (OH) and an imino proton at δ 5.27 (NH). In ^{13}C NMR of the enaminone, the C=O carbon at δ 200 is slightly upfield at δ 190 due to the C-OH tautomer[15b], indicating that the intermediate occurs mainly as stable imine tautomer (Fig. 2B).

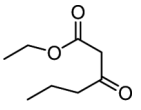
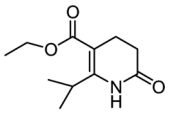
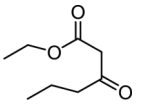
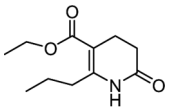
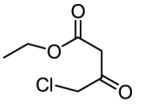
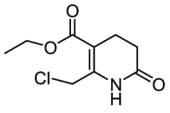
Various substituted acetoacetate esters (entries 4–12) afforded the cyclized product in 68–89% yield. The chloroethylacetoacetate (entry 13) afforded a mixture of unidentified products, which could be due to the negative inductive effect of the chlorine atom that favors the enol-enaminone formation, leading to an

Table 2. Synthesis of dihydropyridin-2-ones via Michalis addition of in situ–generated enamines

Entry	1,3 Dicarbonyls		Product	Yield (%)[a]	Melting point (°C)
	R_1	R_2			
1	R_1 and R_2= -$(CH_2)_3$-		 **4a**	92	193–195
2	CH_3	CH_3	 **4b**	87	146–148[b]
3	CH_3		 **4c**	-[b]	—
4	CH_3	-O-CH_3	 **4d**	89	150–153
5	CH_3	-O-CH_2CH_3	 **4e**	86	152
6	CH_3		 **4f**	81	115
7	CH_3		 **4g**	78	125
8	CH_3		 **4h**	68	128
9	 **1i**	-O-CH_3	 **4i**	81	120
10	 **1j**	-O-CH_2CH_3	 **4j**	79	119

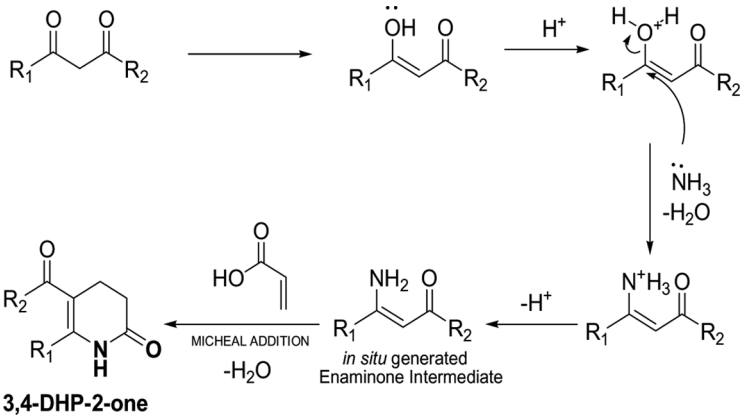
(*Continued*)

Table 2. Continued

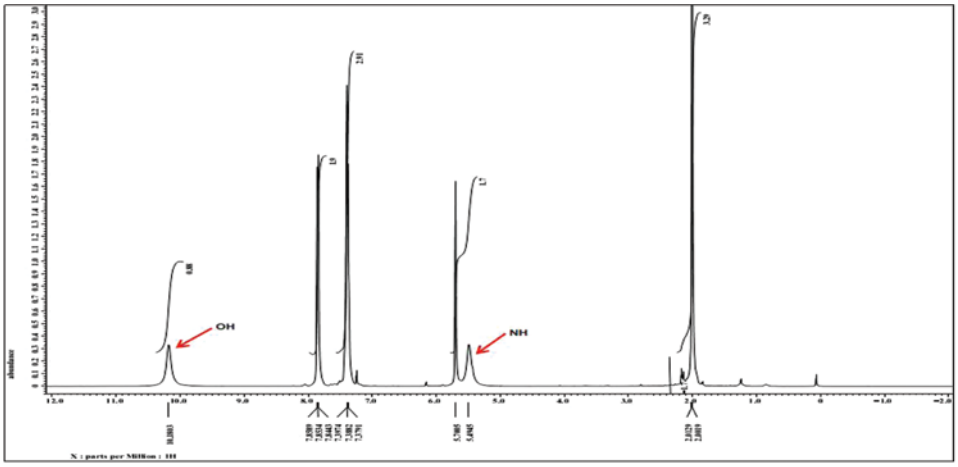
Entry	1,3 Dicarbonyls R_1	1,3 Dicarbonyls R_2	Product	Yield (%)[a]	Melting point (°C)
11	 **1k**	-O-CH_2CH_3	 **4k**	72	115–117
12	 **1l**	-O-CH_2CH_3	 **4l**	70	90
13	 **1m**	-O-CH_2CH_3	 **4m**	—[b]	

[a]Isolated yield.
[b]Inseparable mixture.

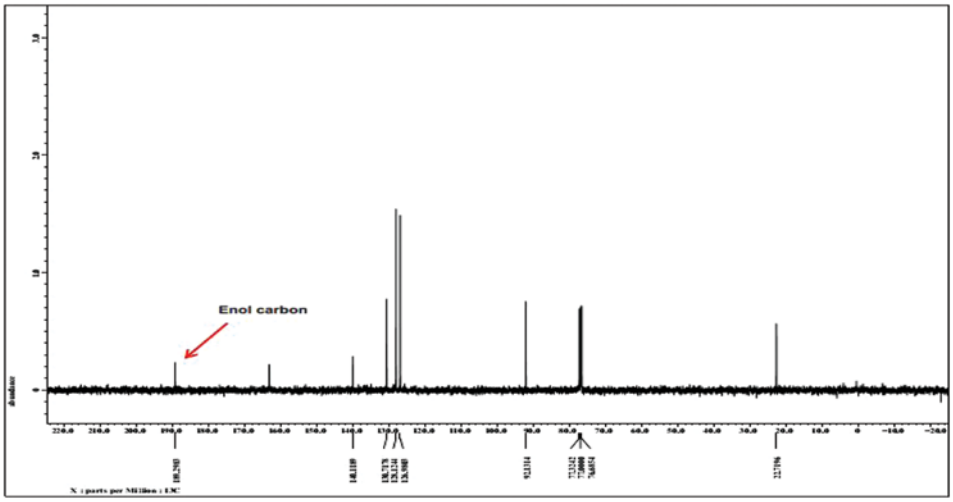
intractable mixture. It is evident from the table that by increasing the chain length at the ester (entries 4–8) and carbonyl groups (entries 9–12), the yield tends to be decreased. Compounds **4a, 4d**, and **4e** were reported earlier. Compound **4d** was synthesized by a two-step procedure involving condensation of 3-aza-4-(dimethylamino)-2-(methylthio)-l,3-pentadiene with methylacrylate followed by hydrolysis of the cyclic adduct,[16] whereas compound **4e** was synthesized (76%) by the reaction of ethyl α-acetoglutarate with ammonium acetate and glacial acetic acid in benzene.[17]



Scheme 2. Mechanism of enaminone intermediate in the formation of 3,4-DHP-2-one.



(A)



(B)

Figure 2. (A) Proton NMR; (B) Carbon-13 NMR. (Figure is provided in color online.)

CONCLUSION

In summary, we have developed a facile solvent-, catalyst-, and aldehyde-free, one-pot synthesis of 3,4-DHP-2-one from 1,3-diones using simple and mild reaction conditions. The substrate scope has been also extended to β-ketoesters. The compounds **4b**, **4f**, **4g**, **4h**, **4i**, **4j**, **4k**, and **4l** are novel and could be used to synthesize novel therapeutic scaffolds. The products were formed with a yield range of 68% to 92%. The substrate scope of other Michael acceptors such as methacrylate, methyl acrylate, and methacrylic acid is under investigation. The methodology could be

automated and applied to form the combinatorial library for the of synthesis of a wide array of biologically important dihydropyrolidine-2-ones.

EXPERIMENTAL

$^{1}H/^{13}C$ NMR (400/75 MHz; $CDCl_3$) spectra were recorded using commercially available deuterated solvents on a multinuclear spectrometer Bruker 400-MHz instrument using TopSpin software and Jeol 400-MHz instrument using Delta software. The NMR is reported as follows: chemical shifts (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), broad (br), and multiplet (m)], coupling constant [Hz], integration). High-resolution mass spectra (HRMS) were recorded on Bruker Daltonics MicroTof Focus spectrometer using Na-formate solution as calibrant. Infrared(IR) spectra were recorded on a Jasco FTIR 6300 spectrophotometer and only significant peaks are presented. Thin-layer chromatography (TLC) was performed on Merck (60 F_{254}, 0.2 mm) using an appropriate solvent system. The chromatograms were visualized under ultraviolet light. Separation of various products was carried out by column chromatography on silica gel (100–200 mesh). All solvents and liquid reagents were dried with appropriate reagents before use. Commercially available 1,3-dicarbonyls, acryllic acid, and ammonium acetate were used without any further purification. All the reactions were performed in Teflon-capped 4-ml glass vials under different temperatures with stirring.

General Procedure for Synthesis of 3,4,7,8-Tetrahydroquinoline-2,5(1H,6H)-dione (4a)

1,3-Dicarbonyls (8.9 mmol, 1 equiv.) followed by ammonium acetate (10.6 mmol, 1.2 mmol, 1.2 equiv.) were added to the solution of acrylic acid (10.6 mmol, 1.2 equiv.). The reactant mass was mixed thoroughly with a spatula and heated at 80 °C with stirring under a nitrogen atmosphere for 5 h. After cooling, the reaction mixture was diluted with 10 mL distilled water and extracted twice with ethyl acetate (2×10 mL). The organic extracts were dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure and subjected to column chromatography (ethyl acetate/hexane) to obtain pure products. The characterization data of the compounds are given.

3,4,7,8-Tetrahydroquinoline-2,5(1H,6H)-dione (4a)

Isolated yield 92%; white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.0 (m, 2H), 2.4–2.6 (m, 8H), 9.0 (brs 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.2, 21.3, 27.2, 30.2, 36.6, 112.5, 152.4, 173.0, 196.3; HRMS (ESI, Na-formate calibrant) calcd. for $C_9H_{11}NO_2$ $[MH]^+$: 166.0868; found $[MH]^+$ 166.0864.

(Z)-3-Imino-1-phenylbut-1-en-1-ol (4c Intermediate)

Isolated yield 55%; solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.1 (s, 3H), 5.25 (brs, 1H), 5.75 (s, 1H), 7.4 (m, 3H), 7.8 (m, 2H), 10.2 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.90, 92.32, 127.1, 128.2, 130.8, 140.2, 162.9, 189.5.

SUPPORTING INFORMATION

Full experimental detail, ^{1}H and ^{13}C NMR spectra of all synthesized compounds can be found via the Supplementary Content section of this article's Web page.

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