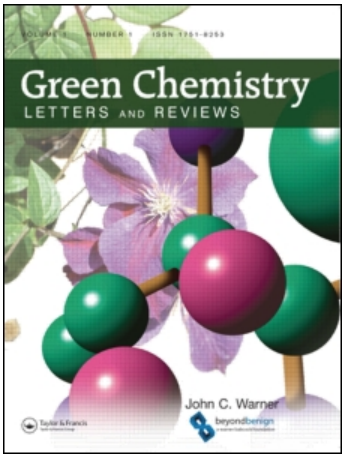

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One pot synthesis of unsymmetrical dihydropyridines by green, catalyst free and environmentally benign protocol

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ORIGINAL ARTICLE

One pot synthesis of unsymmetrical dihydropyridines by green, catalyst free and environmentally benign protocol

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A facile and ecofriendly synthesis of β-enamino esters is reported by reaction of both aliphatic and aromatic amines with β-keto esters by refluxing in ethanol in absence of any catalyst. Addition of α,β-unsaturated aldehydes to the reaction mixture leads to the formation of unsymmetrical dihydropyridine derivatives which generally are metal free hydrogen sources for asymmetric reduction reactions.

Keywords: β-enamino esters; β-keto esters; dihydropyridines; α,β-unsaturated carbonyl compounds; reflux

Introduction

Green chemistry is a concept that reduces the use of hazardous chemicals and formation of waste products, taking environment into concern. This concept has clinched an important position in the field of research over the last few years (*1–5*). The major priority of this branch of chemistry is given to the E-factor (*1*) and the 12 fundamental processes (*6*). The key requirement of a green synthetic methodology is the use of ecofriendly solvents, catalysts and nontoxic chemicals. Addressing the demand for a environmentally benign and green methodology, we wish to report the synthesis of enamino esters, followed by the formation of 1,4-dihydropyridine (DHP) derivatives under reflux without any catalyst.

β-Enamino esters and β-enaminones are an important class of biologically active (*7–11*) molecules synthesized from the β-dicarbonyl compounds. A variety of catalysts like Al_2O_3 (*12*), ceric ammonium nitrate (CAN) (*13*), ytterbium triflate (*14*), erbium triflate (*15*), $NaAuCl_4$ (*16*), $Zn(ClO_4)_2.6H_2O$ (*17*), acetic acid under ultrasound (*18*), $ZrCl_4$ (*19*) have been reported lately. However, these methodologies suffer from limitations when considered from a green point of view.

Recent literature unveils the importance of DHPs due to their interesting pharmacological and pharmaceutical activities (*20–22*). They have been used as calcium channel modulators (*21*) and NADH mimics (*23*) and consequently the DHP derivatives are transformed to pyridines (*24*). Classically symmetrical dihydropyridines are synthesized using Hantzsch synthesis (*25*). However, the synthesis of unsymmetrical DHPs is an important area in recent times as these compounds can be used as hydrogen source for asymmetric reduction (*26*). Very few methods, using Lewis acid and Bronsted acid as catalysts, have been reported for the synthesis of unsymmetrical DHP (*27*).

In continuation of our research for the development of new synthetic methodologies (*28*), we wish to report herein an easy, green and environmentally benign procedure for the synthesis of a series of β-enaminones and its application for the synthesis of DHP derivatives under reflux in absence of catalyst as indicated in Scheme 1.

Results and discussion

Initially, we conducted the reaction in some chosen green solvents among which ethanol was found to be the most effective of all. In a typical procedure, a solution of benzylamine (1.2 mmol) in ethanol and methyl acetoacetate (1 mmol) was refluxed for two hrs. After the completion of the reaction as monitored by thin layer chromatography (TLC), ethanol was evaporated from the reaction mixture. The crude reaction mixture was dried and was characterized directly by ^1H, ^{13}C NMR and mass spectrometry. Encouraged by the result, we next tried to synthesize some DHP derivatives under the same condition. Hence, after the formation of the enamino ester as indicated by TLC, equimolar amount of α,β-unsaturated aldehyde was added to the reaction mixture and refluxed, devoid of any catalyst. As anticipated, we

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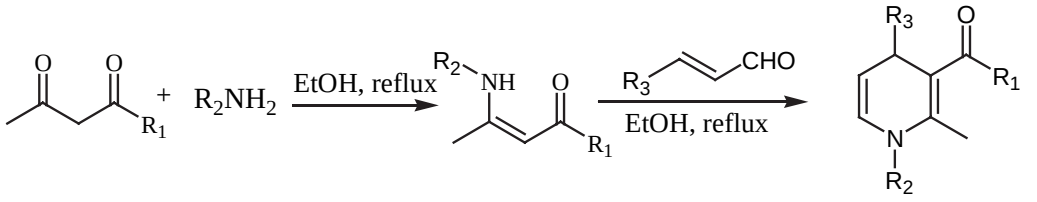


R_1 = Me, OMe, OEt, Ocyclohexyl, Ocinnamyl R_2 = Benzyl, 2-$OMeC_6H_4$, *n*-butyl R_3 = Me, Ph

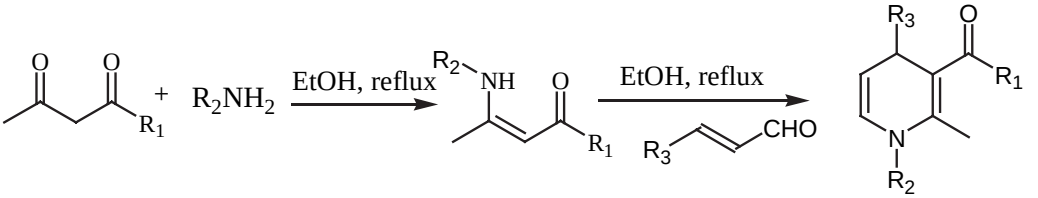
Scheme 1.

observed complete formation of dihydropyridine derivatives within one hr. Subsequently, a variety of DHP derivatives were synthesized by adding cinnamaldehyde and crotonaldehyde to the series of enamino esters as shown in Table 1.

It is to be noted that nucleophilic benzyl amines reacted faster with variety of β-keto esters to give the corresponding β-enamino esters in excellent yields than substituted anilines and aliphatic amines. Both the resonance and conjugation effect induces the exclusive formation of the products. The enamino esters (Table 1, entry 1u) derived from aliphatic amines and aniline reacted with crotonaldehyde under the same condition but with considerably lesser yields.

Remarkably, this method was applicable for enaminations of linear long chain and bulky β-keto esters (Table 1, entry 1g–1l), which reacted smoothly

Table 1. Synthesis of dihydropyridine derivatives.



1 2

Entry	R_1	R_2	1(Time) (hr)	R_3	D(Time) (min)	Yield of 2 (%)[a,b]
a	Me	$PhCH_2$	1.5	Me	30	92
b	Me	$PhCH_2$	1.5	Ph	30	92
c	Et	$PhCH_2$	2	Me	35	93
d	Et	$PhCH_2$	2	Ph	35	93
e	CMe_3	$PhCH_2$	2	Me	35	89
f	CMe_3	$PhCH_2$	2	Ph	35	89
g	$C_{10}H_{21}$	$PhCH_2$	2.5	Me	45	85
h	$C_{10}H_{21}$	$PhCH_2$	2.5	Ph	45	85
i	$C_{16}H_{33}$	$PhCH_2$	2.5	Me	50	88
j	$C_{16}H_{33}$	$PhCH_2$	2.5	Ph	50	88
k	cyclohexyl	$PhCH_2$	2	Me	30	91
l	cyclohexyl	$PhCH_2$	2	Ph	30	91
m	Benzyl	$PhCH_2$	1.5	Me	60	90
n	Benzyl	$PhCH_2$	1.5	Ph	60	90
o	Allyl	$PhCH_2$	1.5	Me	60	90
p	Allyl	$PhCH_2$	1.5	Ph	60	90
q	cinnamyl	$PhCH_2$	2.5	Me	65	85
r	cinnamyl	$PhCH_2$	2.5	Ph	65	85
s	Me	2-$OCH_3C_6H_4$	3	Me	90	75
t	CMe_3	2,6-$(CH_3)_2C_6H_3$	3	Me	100	72
u	Me	*n*-Bu	5	Me	180	70

[a]Isolated yield.
[b]The compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR and elemental analyses.

but slowly to give the desired dihydropyridine derivatives (Table 1, entry 2g–2l) in considerably good yields.

The carbonyl group of the acetyl part is probably activated by refluxing. Subsequently, nucleophilic addition of amines to the carbonyl group takes place with the formation of enaminoesters, which are further stabilized by the intramolecular hydrogen bonding. The enamine thus synthesized probably acts as the catalyst to push forward the formation of DHP derivatives under reflux condition. In order to claim the catalyst free version of the reaction, a set of reaction was carried out with equimolar amount of amine, β-keto ester and aldehyde under the same reaction condition. The DHP product was isolated as anticipated, but with a lesser yield and in longer time, which thereby strengthens the catalyst free point of view.

Experimental section

General

Chemicals were purchased from Fluka, Merck, and Aldrich chemical companies. Some of the β-keto esters were prepared by reported procedure (*28b*). Yields refer to isolated pure products. The products were characterized by comparison of their spectral (IR, UV, ^{1}H NMR, and ^{13}C NMR) and physical data with the authentic samples.

Typical procedure for the synthesis of enamine (1a) from benzyl amine and methyl acetoacetate

Benzylamine (1.2 mmol) was dissolved in ethanol to which methyl acetoacetate (1 mmol) was added and the reaction mixture was refluxed for two hrs. After the completion of the reaction as monitored by TLC, the ethanol was evaporated under reduced pressure. The crude mixture was directly analyzed.

Typical procedure for the synthesis of DHP (2a)

Benzylamine (1.2 mmol) was dissolved in ethanol to which methyl acetoacetate (1 mmol) was added and the reaction mixture was refluxed for two hrs. After the completion of the reaction as monitored by TLC, crotonaldehyde (1 mmol) was dissolved in ethanol and was added to the reaction mixture which was refluxed further for 30 mins. The ethanol was evaporated under reduced pressure. The crude mixture was purified through column chromatography (Hexane:EtOAc::9:1), and analyzed by ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analyses.

Spectral data of some enamines

1i: Hexadecyl-3-(benzylamino) but-2-enoate: White crystals, mp 57°C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (t, 3H, $J = 7.2$ Hz), 1.25 (s, 26H), 1.62 (quin, 2H, $J = 7.6$ Hz), 1.91 (s, 3H), 4.01 (t, 2H, $J = 6.8$Hz), 4.41 (d, 2H, $J = 6.4$ Hz), 4.52 (s, 1H), 7.23 – 7.25 (m, 3H), 7.29–7.33 (m, 2H), 8.91 (br s, 1H, NH) .^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.49$, 19.73, 23.05, 26.44, 29.43, 29.70, 29.95 (4C), 30.03 (5C), 32.27, 47.09, 62.99, 83.45, 126.81 (2C), 127.42, 128.86 (2C), 138.84, 161.73, 170.63.Anal. Calcd for $C_{27}H_{45}NO_2$: C, 78.02; H, 10.91; N, 3.37. Found: C, 77.93; H, 11.09.; N, 3.42.

1k: Cyclohexyl-3-(benzylamino)but-2-enoate: White crystals, mp 72°C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 1.25–1.30 (m, 1H), 1.33–1.44 (m, 3H), 1.55(bs, 2H), 1.71–1.73 (m, 2H), 1.85–1.89 (m, 2H), 1.91 (s, 3H), 4.41 (d, 2H, $J = 6.4$Hz), 4.51 (s, 1H), 4.71(br, 1H), 7.24–7.25 (m, 3H), 7.30–7.33 (m, 2H), 8.92 (br s, 1H, NH) .^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.68$, 24.36, 25.86, 31.73, 32.46, 47.07, 50.78, 70.64, 83.85, 126.83 (2C), 127.38, 128.81 (2C), 138.76, 161.57, 170.09.Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.50; H, 8.59.; N, 5.28.

1q: Cinnamyl-3-(benzylamino)but-2-enoate: White crystals, mp 95°C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.93$ (s, 3H), 4.43 (d, 2H, $J = 6.4$ Hz), 4.58(s, 1H), 4.71(d, 2H, $J = 6.0$ Hz), 6.27–6.34 (m, 1H), 6.62 (d, 1H, $J = 16$ Hz), 7.19–7.38 (m, 10 H), 8.93 (br s, 1H, NH) .^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.76$, 47.09, 63.37, 83.03, 124.84, 126.62 (2C), 126.79 (2C), 127.44, 127.78, 128.57 (2C), 128.86 (2C), 132.93, 136.66, 138.66, 162.24, 170.11. Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.28; H, 6.92; N, 4.69.

Spectral data of some dihydropyridine derivatives

2c: 1-Benzyl-2,4-dimethyl-1,4-dihydropridine-3-carboxylic acid ethyl ester: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.04$ (d, 3H, $J = 6.4$ Hz), 1.26 (t, 3H, $J = 6.4$ Hz), 2.31(s, 3H), 3.45(pent, 1H, $J = 6.4$ Hz), 4.11–4.18(m, 2H), 4.49 (AB, 1H, $J = 16.8$ Hz), 4.63 (AB, 1H, J = 16.8 Hz), 4.89 (dd, 1H, $J = 6.0$ Hz, $J = 7.6$ Hz), 5.86 (d, 1H, $J = 7.6$ Hz), 7.17(d, 2H, $J =$ 7.2 Hz), 7.26 (t, 1H, $J = 7.2$ Hz), 7.34(t, 2H, $J = 7.2$ Hz).^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.67$, 16.09, 25.37, 28.61, 53.69, 59.45, 101.80, 109.28, 126.18(2C), 127.53, 129.04(2C), 130.13, 138.65, 149.15, 169.52. Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.42; H, 7.73; N, 5.21.

2d: 1-Benzyl-2-methyl-4-phenyl-1,4-dihydropridine-3-carboxylic acid ethyl ester: ^{1}H NMR (400 MHz,

$CDCl_3$): δ = 1.13 (t, 3H, *J* = 6.8 Hz), 2.48 (s, 3H), 4.04 (q, 2H, *J* = 6.8 Hz), 4.57 (AB, 1H, *J* = 16.8 Hz), 4.65 (AB, 1H, J = 16.8 Hz), 4.75 (d, 1H, *J* = 5.2 Hz), 5.02 (dd, 1H, *J* = 5.2 Hz, *J* = 7.6 Hz), 5.98 (d, 1H, *J* = 7.6 Hz), 7.22–7.58 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.49, 16.25, 40.64, 53.95, 59.58, 100.63, 108.32, 126.29 (2C), 126.50(2C), 127.76, 127.82 (2C), 128.52 (2C), 129.17(2C), 129.78, 138.42, 149.16, 169.27. Anal. Calcd. for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.39; H, 6.82; N, 4.29.

2e: 1-Benzyl-2,4-dimethyl-1,4-dihydropridine-3-carboxylic acid *tert*-butyl ester: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (d, 3H, *J* = 6.4 Hz), 1.49 (s, 9H), 2.26(s, 3H), 3.41(pent, 1H, *J* = 6.4 Hz), 4.45 (AB, 1H, *J* = 17.2 Hz), 4.60 (AB, 1H, J = 17.2 Hz), 4.85 (dd, 1H, *J* = 5.0 Hz, *J* = 7.7 Hz), 5.84 (d, 1H, *J* = 7.6 Hz), 7.19(d, 2H, *J* = 7.6 Hz), 7.26 (t, 1H, *J* = 7.2 Hz), 7.33(t, 2H, *J* = 7.2 Hz) .^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.04, 25.46, 28.65(3C), 29.10, 53.61, 78.89, 103.53, 108.83, 126.19(2C), 127.47, 129.02(2C), 130.24, 138.87, 147.77, 169.06. Anal. Calcd. for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N,4.68 Found: C, 76.39; H, 8.31; N, 4.73.

2p: 1-Benzyl-2-methyl-4-phenyl-1,4-dihydropridine-3-carboxylic acid allyl ester: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3H), 4.46(dd, 2H, *J* = 1.6 Hz, *J* = 4.0 Hz), 4.59 (AB, 1H, *J* = 16.8 Hz), 4.66 (AB, 1H, J = 16.8 Hz), 4.79 (d, 1H, *J* = 5.6 Hz), 5.06 (dd, 1H, *J* = 5.2 Hz, *J* = 7.6 Hz), 5.13 (dd, 2H, *J* = 8.8 Hz, *J* = 10.0 Hz), 5.77–5.87 (m, 1H), 5.99 (d, 1H, *J* = 7.6 Hz), 7.26–7.42 (m, 10H) .^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.36, 40.46, 54.02, 64.41, 100.12, 108.54, 117.15, 126.37,126.50, 127.03, 127.12, 127.76 (2C), 127.80, 128.25, 128.61, 129.19, 129.75, 133.36, 138.32, 149.00, 149.88, 168.81. Anal. Calcd. for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N,4.05. Found: C, 80.09; H, 6.62; N, 4.13.

Conclusion

In conclusion, we present a simple and efficient protocol for the formation of β-enamino esters with both aromatic and aliphatic amines and β-keto esters followed by the synthesis of DHP derivatives under reflux in catalyst free condition. The reaction is clean without the formation of any byproducts. Moreover, the operational simplicity, lesser reaction time, and the environmentally benign condition will contribute to the realms of greener synthetic organic chemistry.

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