

RESEARCH ARTICLE

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Catalyst-free synthesis of tetrahydrodipyrzolo-pyridines via an one-pot tandem and green pseudo-six-component reaction in water

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Abstract

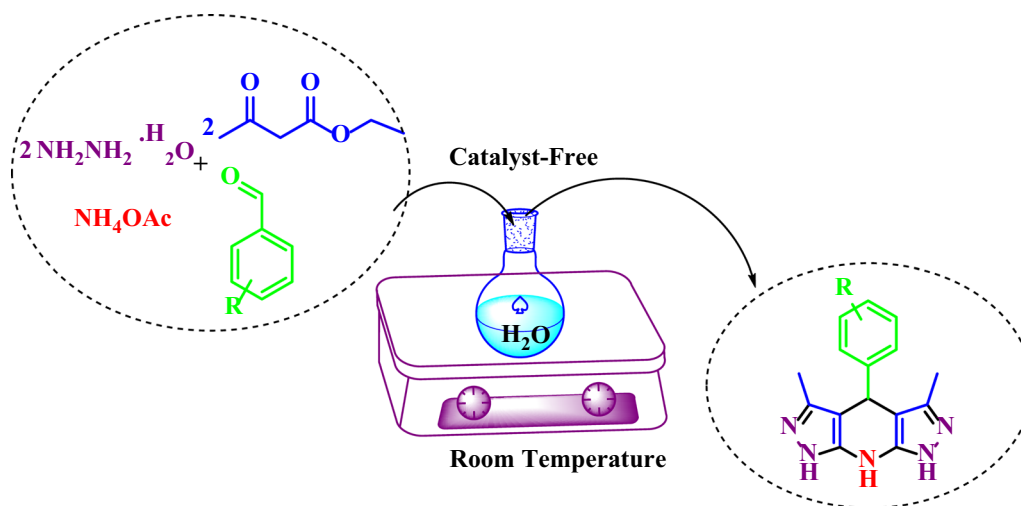
Background: A new, green and environmentally friendly protocol has been developed for the synthesis of tetrahydrodipyrzolo-pyridine derivatives. The structures of these products were determined in terms of melting point, FTIR, NMR and Mass spectroscopy.

Results: The tetrahydrodipyrzolo-pyridine derivatives were synthesized in water through a catalyst-free pseudo-six-component reaction of hydrazine hydrate, ethyl acetoacetate, ammonium acetate and aldehyde at room temperature.

Conclusions: This novel procedure has some advantages such as aqueous media, high yield and simple work-up.

Keywords: Tetrahydrodipyrzolo-pyridines (THDPP's), Multicomponent reaction, Environmentally friendly protocol, Catalyst-free reaction

Graphical Abstract



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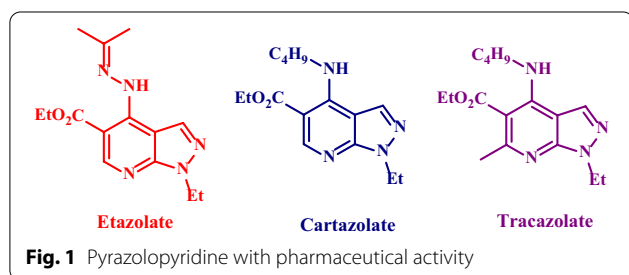
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Introduction

Multicomponent reactions (MCRs) are selective, simple and effective as compared to the conventional multistep synthesis [1–4]. They have been utilized to reduce environmental pollution. Water, as a green solvent, is presumed to speed up some organic reactions through hydrophobic effects [5]. Therefore, catalyst-free organic reactions in water that yield resolvable products are attractive for many organic chemists [6, 7]. THDPPs fuse the heterocyclic moieties of pyrazolopyridine with pharmaceutical activities, which exist in Etazolate, Cartazolate and Tracazolate drugs [8] (Fig. 1).

Meanwhile, Due to the existence of two biologically active moieties, namely pyrazole and 1,4-dihydropyridine pyrazole in the structure of THDPPs, these compounds have various pharmaceutical applications such as anti-allergic, anti-herpetic and anxiolytic effects [9, 10], anti-Leishmania activities [11] and HIF 1 α -prolyl hydroxylase inhibition [12].



A common protocol for the synthesis of THDPP is the reaction of aldehydes, hydrazine hydrate, ethyl acetoacetate, and ammonium acetate in a multi-component manner with the presence of a catalyst. Previously, pseudopolymeric magnetic nanoparticles [13], KCC-1-NH₂-DPA [14], CuFe₂O₄@HNTs [15], acetic acid [16], and carbonaceous material (CSO₃H) [17], Fe₃O₄/KCC1/IL/HPWMNPs [24], Nano-CdZr₄(PO₄)₆ [25], Nano-Fe₃O₄@SiO₂-SO₃H [23], FeNi₃-ILs MNPs [21], Nano-CuCr₂O₄ [26], Nano-ovalbumin [20], M(II)/Schiff base@MWCNT-Fe₃O₄/SiO₂ [27]. Meanwhile, a catalyst free protocol using ammonium carbonate instead of ammonium acetate has been reported [16], Ammonium carbonate is a basic salt and can catalysis the synthesis of THDPP's. In here, we have used ammonium acetate as neutral salt for production of ammonia in water and absence of any catalyst.

In this study, THDPPs are synthesized with a green catalyst-free protocol implemented in a water medium at room temperature (Scheme 1).

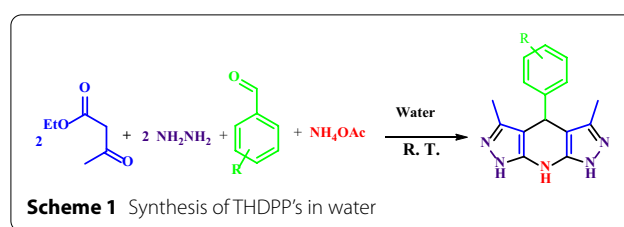
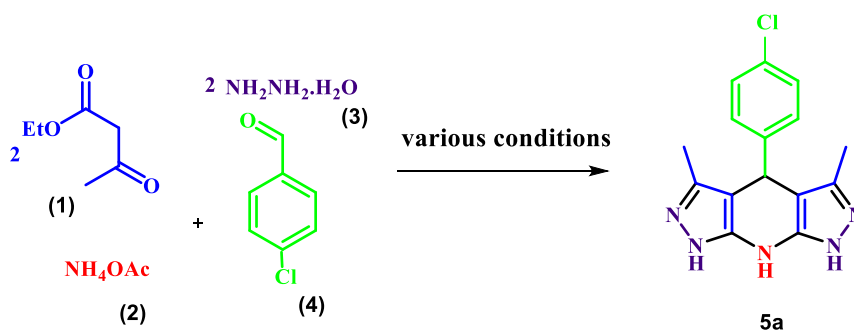


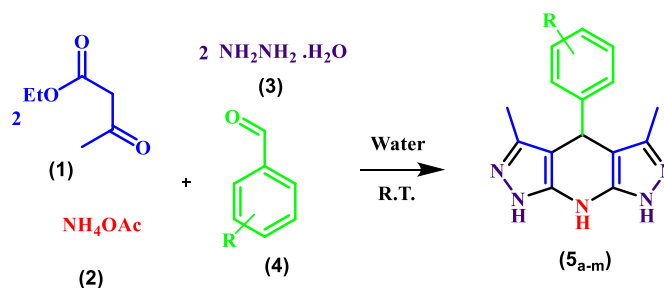
Table 1 Optimization of the reaction conditions for the synthesis of 4-(4-chlorophenyl)-3,5-dimethyl-1,4,7,8-tetrahydrodipyrzolo[3,4-b:4',3'-e]pyridine



Entry	Solvent	Conditions ^a	Time (min)	Yield (%) ^b
1	EtOH	rt	180	–
2	EtOH	Reflux	120	23
3	H ₂ O	Reflux	60	53
4	H ₂ O	rt	45	98 [This work]

^a The molar ratio of hydrazine hydrate (2 mmol), ethyl acetoacetate (2 mmol), 4-chlorobenzaldehyde (1 mmol) and ammonium acetate (4 mmol) is equal to 2:2:1:4

^b Isolated yields

Table 2 Synthesis of THDPP's (5_{a-m}) in water in room temperature

Entry	R	Product	Time (min)	Yield (%) ^b	M.P (°C)	Lit. M.P. (C) [Reference]
1	4-Cl	5a	45	98	244–246	254–256 [19]
2	4-NO ₂	5b	60	96	274–276	278–283 [19]
3	3-NO ₂	5c	50	98	268–270	282–284 [20]
4	4-OH	5d	80	96	266–268	267–268 [21]
5	4-Br	5e	75	96	222–224	221–224 [19]
6	2-Cl	5f	105	94	162–164	164–165 [22]
7	4-N(CH ₃) ₂	5g	90	85	238–239	240–242 [19]
8	4-Me	5h	180	95	240–242	241–243 [20]
9	4-F	5i	75	97	255–257	258–260 [18]
10	4-OCH ₃	5j	90	98	187–189	188–190 [20]
11	3-OMe-4-OH	5k	90	98	256–258	256–258 [20]
12	3,4-(OH) ₂	5l	90	83	208–210	208–210 [20]
13	4-CHO	5 m	120	91	> 300°	> 300° [23]

Reaction conditions: hydrazine hydrate (2 mmol), ethyl acetoacetate (2 mmol), 4-chloro benzaldehyde (1 mmol) and ammonium acetate (4 mmol), water (3 mL) at room temperature

Experimental

Materials and methods

General

A Bruker, Equinox 55 spectrometer was used to record the Fourier transforms infrared (FT-IR) spectra. A Bruker (DRX-400 Avance) nuclear magnetic resonance (NMR) instrument was also used to record the NMR spectra. In addition, a Buchi B-540 B.V.CHI apparatus served to determine the melting points of the compounds. Mass spectrometry spectra were recorded with a Agilent

Technology (HP), Model: 5793, Ion source: Electron Impact (EI), 20-EV, 230 °C, and Quadrupole analyzer.

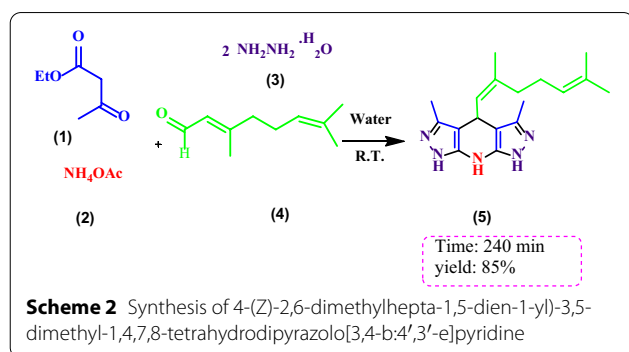
Chemistry

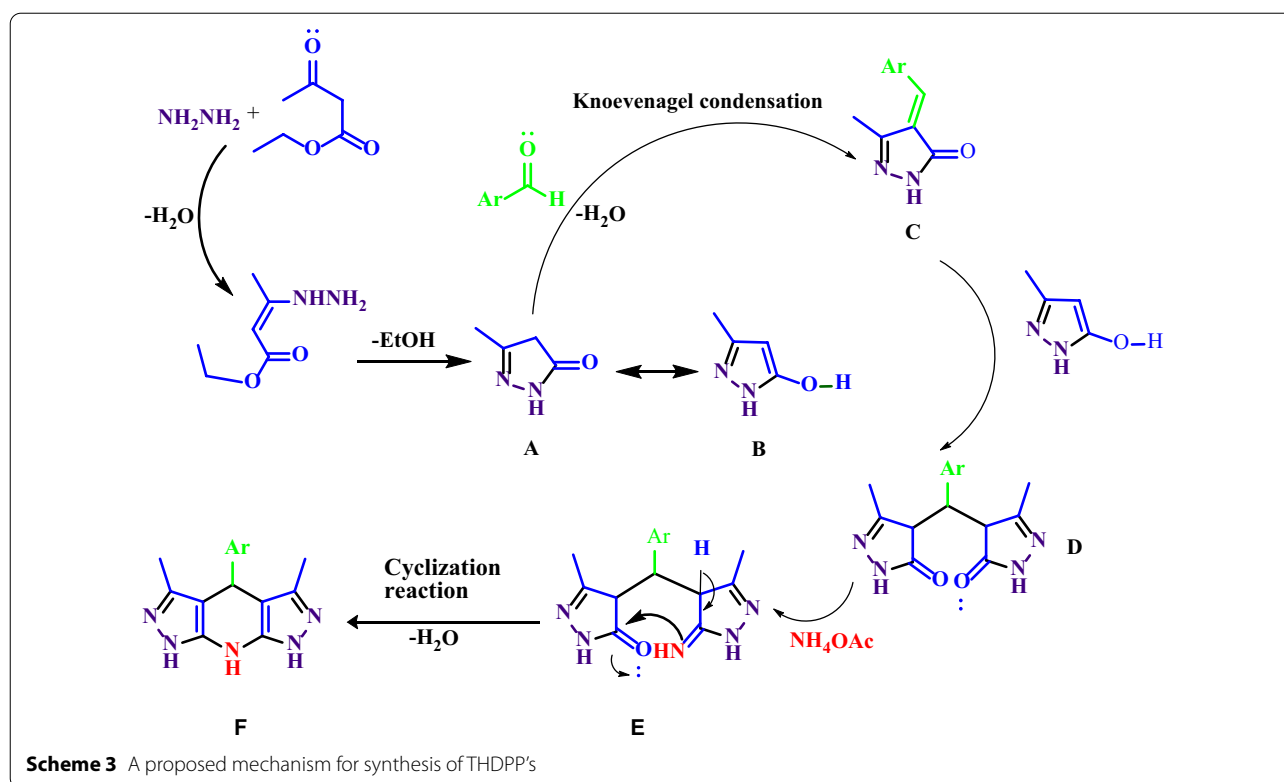
General procedure for the synthesis of THDPP's

Firstly, a solution of 2.0 mmol of hydrazine hydrate, 2.0 mmol of ethyl acetoacetate and 3 mL of water was stirred in a 25-mL round-bottom flask at room temperature. Secondly, 1.0 mmol of aldehyde and 4.0 mmol of ammonium acetate were added to it and stirred at room temperature. The reaction was monitored by thin-layer chromatography (TLC; *n*-hexane:EtOAc, 70:30). After the completion of the reaction, the solution was diluted with cold water, and the product was appeared as water insoluble solid which isolated by simple filtration.

Results and discussion

Although, catalytic synthesis of THDPPs protocols have many advantages such as high yields of products and short reaction time. But the hard work-up and expensive catalysts are some of drawbacks of them. Therefore, we





have decided to design a catalyst-free protocol for synthesis of THDPPs.

In order to optimize the reaction conditions for the preparation of THDPPs in the absence of a catalyst, some reactions were performed between ethylacetoacetate, ammonium acetate, 4-chlorobenzaldehyde and hydrazine hydrate in the presence of different solvents (Table 1). As the results indicated, tetrahydropyridopyridines could be synthesized in good-to-high yields and short reaction times.

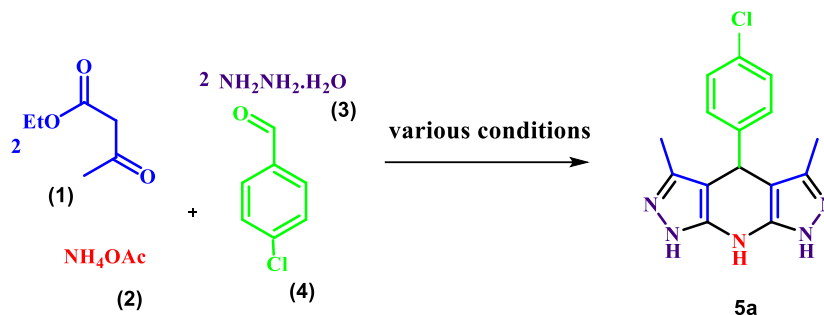
Hydrazine and ammonium acetate are soluble in water, ethyl acetoacetate is partially soluble and aldehyde is insoluble in water. In the first step, hydrazine hydrate and ethyl acetoacetate react in water to produce a insoluble intermediate which react with aldehyde in water cage.

Regarding the conditions for the synthesis of THDPPs, the optimization process was implemented with different aldehydes, hydrazine hydrate, ethyl acetoacetate and ammonium acetate (Table 2).

Meanwhile, we have synthesis THDPP using citral as aliphatic aldehyde (Scheme 2).

A mechanism proposed for the catalyst-free synthesis of THDPPs is shown in Scheme 3. Ammonium acetate was used as a source of nitrogen for the formation of 1,4-dihydropyridine ring in the THDPPs. Hydrazine is soluble and ethylacetoacetate is partially soluble (2.86 g/100 mL) in water. Initially, the reaction was begun with the versatile condensation of ethyl acetoacetate with hydrazine and then the elimination of ethanol to form pyrazolone A (B, tautomer of A) as a water insoluble solid. The A (B) and aldehyde are hydrophobia materials and react in a water cage to form the intermediate C through the Knoevenagel condensation. Then, the second molecule of B was condensed with C via Michael reaction to produce bipyrazolone D. Ammonia, which was produced from ammonium acetate, condensed with D to form imine E which produced product F through intramolecular cyclization, tautomerization and water removal.

In order to show the superiority of the THDPPs synthesis process in the absence of catalysts, this process was compared to some others in terms of conditions, reaction time and yield. The results are listed in Table 3.

Table 3 The comparison of catalyst-free protocol with other methods for synthesis of 5a

Entry	Catalyst	Conditions	Time (min)/yield ^a (%) [Reference]
1	Fe ₃ O ₄ /KCC1/IL/HPWMNPs (0.0001 mg)	H ₂ O/r.t	30/96 [24]
2	Nano-CdZr ₄ (PO ₄) ₆ (0.6 mol%)	EtOH/reflux	43/88 [25]
3	Nano-Fe ₃ O ₄ @SiO ₂ -SO ₃ H (0.004 g)	EtOH/MW	20/90 [23]
4	FeNi ₃ -ILs MNPs (0.002 g)	EtOH/reflux	48/86 [21]
5	Nano-CuCr ₂ O ₄ (4 mol%)	EtOH/25 °C	50/90 [26]
6	Nano-ovalbumin (0.05 g)	H ₂ O/55 °C	45/93 [20]
7	M (II)/Schiff base@MWCNT-Fe ₃ O ₄ /SiO ₂ (0.02 g)	-/r.t	90/85 [27]
8	Pseudopolymeric magnetic nanoparticles (10 mg)	EtOH/r.t	10–180/45–92 [13]
9	KCC-1-NH ₂ -DPA (0.1 g)	EtOH, reflux	30/95 [14]
10	CuFe ₂ O ₄ @HNTs (5 mg)	EtOH, r.t	20/90–96 [15]
11	acetic acid	AcOH/reflux	300/90 [16]
12	carbonaceous material (CSO ₃ H) (10 mg)	H ₂ O/60 °C	360/86 [17]
13	Catalyst-free	H ₂ O/r.t	45/98 [This work]

^a Isolated yields

Conclusions

In this study, an environmentally friendly protocol is introduced for the synthesis of THDPPs in a neutral aqueous medium without using any catalyst or organic solvent. In this green versatile protocol hydrophobia intermediate and aldehyde had been reacted under high pressure condition in water cage. In solubility of products in water caused having a simple work-up and purification of them. The attractive advantages of the protocol are excellent yields, mild reaction conditions, less pollution, short time reaction, simple workup and high-purity products.

Abbreviations

THDPP's: Tetrahydrodipyrzolo[3,4-b:4',3'-e]pyridines; MCRs: Multi-component reactions; FT-IR: Fourier transform infrared; NMR: Nuclear magnetic resonance; TLC: Thin layer chromatography.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13065-022-00802-4>.

Additional file 1: Spectroscopic data for the synthesized tetrahydrodipyrzolo[3,4-b:4',3'-e] pyridine derivatives.

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Authors' contributions

M.K. wrote the main manuscript and prepared figures. B.F.M. edited the manuscript and submit it as corresponding author. All authors read and approved the final manuscript.

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This study was financially supported by Yazd University. The funding bodies played no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations**Ethics approval and consent to participate**

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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