Synlett F. Tamaddon, A. Khorram Letter

Advanced Catalyst-Free Pseudo-Six-Component Synthesis of Tetrahydrodipyrazolopyridines in Water by Using Ammonium Carbonate as an Ecofriendly Source of Nitrogen

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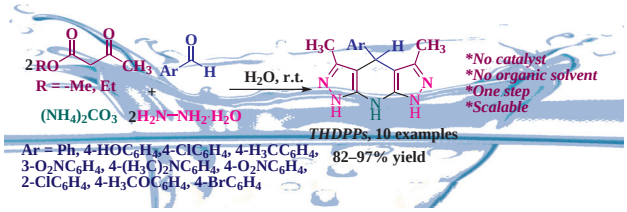

Received: 16.10.2019
Accepted after revision: 04.01.2020
Published online: 04.02.2019
DOI: 10.1055/s-0039-1691600; Art ID: st-2019-k0447-l

Abstract This work describes an improved environmentally friendly method for the synthesis of tetrahydrodipyrazolopyridines (THDPPs) in water through a catalyst-free pseudo-six-component reaction of alkyl acetoacetates, hydrazine hydrate, and ammonium carbonate with an aldehyde in a mole ratio of 2:2:1:1 at room temperature. The ammonium carbonate serves as a green source of nitrogen for the central 1,4-dihydropyridine ring in the THDPPs. Methyl acetoacetate reacts faster than either ethyl or propyl acetoacetate in this method. The product precipitates during the reaction and is simply collected by filtration. Advantages of this environmentally benign method include no use of an organic solvent, no hazardous waste, rapid clean reactions, and excellent yields of products.

Keywords dipyrazolopyridines, water-based synthesis, catalyst-free synthesis, multicomponent reaction, green chemistry, ammonium carbonate

The development of water-based procedures for the synthesis of valuable biologically active compounds and pharmaceuticals is an ecofriendly approach to green chemistry.[1] The unique properties of water as a promising sustainable solvent serve as the main impetus for developing such reactions.[2] Although aqueous organic transformations profit from rate enhancement from the hydrophobic association of organic materials,[3] most catalysts and reagents used in promoting reactions are water sensitive. Furthermore, surfactant catalysts used in improving aqueous organic reactions are usually nonrenewable and nonbiodegradable, creating further problems for water-based organic transformations. Therefore, catalyst-free organic reactions in water[4] that give filterable solid products would be ideal for synthesis.[5] Such safe reactions have attracted growing interest for synthesis of designed multifunctional organic materials with minimal chemical waste.[6]

Multicomponent reactions (MCRs) permit atom-economic and flexible assembly of more than two components to give functionalized molecules such as pyrazolopyridines.[5b,7,8] In particular, MCRs are of interest for the synthesis of heterocycles, which constitute 60% of all marketed medicines.[9] Moreover, a combination of MCRs with water-based organic synthesis leads to synergistic environmental advantages.[10] In this context, we have developed water-based organic transformations by MCRs under catalyst-free conditions[11] or by using biocompatible enzyme catalysts[12] or surfactants.[13]

The 1,4-dihydropyridine (1,4-DHP) skeleton is an important pharmacophore in some coenzymes,[14a] clinical antihypertensive drugs,[14b] and hexahydroquinolines.[14c] Generally, 1,4-DHPs are prepared by the conventional pseudo-four-component Hantzsch reaction under various conditions,[14d] so we developed a green version of this reaction by using ammonium carbonate in water.[11] Recently, the 1,4-DHP ring has been conjugated to two pyrazole rings to give the biologically active tetrahydrodipyrazolopyridines (THDPPs) that contain both 1,4-DHP[14b] and pyrazole pharmacophores.[15] THDPPs are also the fused heterocycle products of a modified pseudo-six-component reaction of hydrazine and 1,3-dicarbonyl compounds with aldehydes and ammonium acetate, and they are formed via a pyrazolone intermediate produced in situ.[15–20] In addition to the use of various catalysts and organic solvents for the synthesis of THDPPs, an ultrasound-assisted version of an MCR has also recently been documented.[15b] However, there is still a need for cleaner and more-efficient ecofriendly routes for large-scale synthesis of THDPPS in water.

To overcome the problems of dispersing organic components in water and the moisture sensitivity of ammonium acetate, we replaced this hygroscopic salt with ammonium carbonate as a less-toxic nonhygroscopic and safer buffered source of nitrogen for the synthesis of THDPPs in water.

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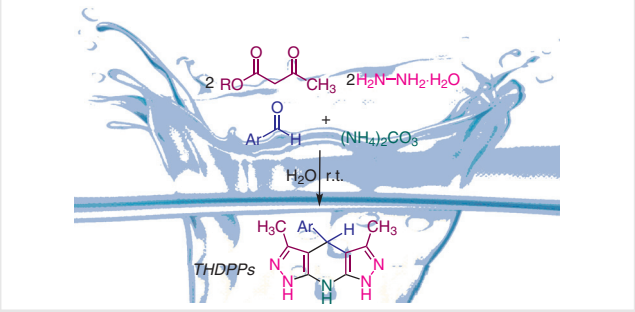
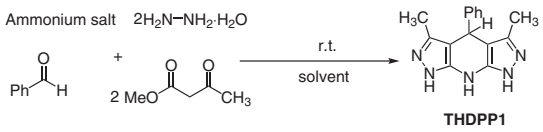
Ammonium carbonate [$(NH_4)_2CO_3$], is a sublimable solid source of ammonia with a low melting point (58 °C) and an LD_{50} of 1497 mg/kg that decomposes in water to give two moles of ammonia at a buffered pH.[11] Here, we report an operationally simple, catalyst-free, water-based, room-temperature synthesis of THDPPs by using ammonia formed in situ from $(NH_4)_2CO_3$ under completely safe conditions (Scheme 1).



Scheme 1 Environmentally friendly catalyst-free synthesis of THDPPs in water

Initially, we attempted to synthesize 3,5-dimethyl-4-phenyl-1,4,7,8-tetrahydrodipyrazolo[3,4-*b*:4′,3′-*e*]pyridine (**THDPP1**) as a model product by the catalyst-free room-temperature reaction of methyl acetoacetate, hydrazine hydrate, and benzaldehyde in the presence of various ammonium salts in a mole ratio of 2:2:1:1 (Table 1). Among the ammonium salts screened, a maximum 96% yield of **THDPP1** was obtained by running the reaction in the presence of $(NH_4)_2CO_3$ in water (Table 1, entry 6), and the product could be isolated by simple filtration. The lower yield of **THDPP1** under solvent-free conditions was due to sublimation of ammonium carbonate on stirring the reaction mixture (entry 9). The mild buffered pH of the reaction medium, hydrogen bonding, and the in situ release of NH_3 from $(NH_4)_2CO_3$ in water are the reasons for the superiority of this salt to other organic ammonium salts, including ammonium formate (entry 5) and nonvolatile ammonium oxalate (entry 10). The rapid reaction and the less-laborious product isolation are additional advantages of this salt-based method.

Table 1 NH_3-Source Optimization for Catalyst-Free Synthesis of **THDPP1** in Water



Entry	Ammonium salt	Solvent	Time (h)	Yield (%)
1	NH_4Cl	H_2O	3	0
2	NH_4NO_3	H_2O	3	0
3	NH_4VO_3	H_2O	5	0
4	NH_4HCO_3	H_2O	1	78
5	$NH_4OC(O)H$	H_2O	1.5	81
6	$(NH_4)_2CO_3$	H_2O	0.25	96
7	$(NH_4)_2CO_3$	H_2O–EtOH	1	89
8	$(NH_4)_2CO_3$	EtOH	1	90
9	$(NH_4)_2CO_3$	–	2	65
10	$[(NH_4)OC(O)]_2$	H_2O	2	65
11	$[(NH_4)OC(O)]_2$	–	2	76

To check the scale-up of this method, we performed the model reaction on a 10 mmol scale of benzaldehyde under the optimized conditions and we isolated the product **THDPP1** in 95% yield after 20 minutes.

To show the performance of $(NH_4)_2CO_3$ in this method, the result was compared with those of previous methods for synthesis of **THDPP1** (Table 2) and found to be superior to earlier methods in terms of the reaction time, yield, and conditions.

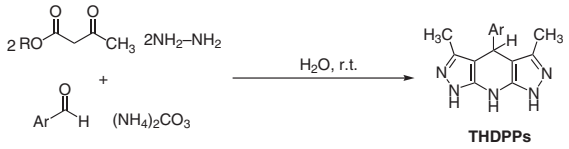
Because of the advantages of this metal- and catalyst-free technique, the optimized conditions were extended to the synthesis of other THDPPs by the pseudo-six compo-

Table 2 Performance of Syntheses of THDPP1 from Ammonium Carbonate

Entry	Conditions	N Source	Time (h)	Yield[a] (%)
1	H_2O, r.t. (this work)	$(NH_4)_2CO_3$	0.25	96
2	nano-$CdZr_4(PO_4)_6$ (0.6 mol%), EtOH, reflux	NH_4OAc	0.66	94[16]
3	$CuFe_2O_4$@HNTs (5 mg)b, EtOH, r.t	NH_4OAc	0.33	96[17]
4	EtOH, reflux	NH_4OAc	5	86[15a]
5	EtOH, reflux	NH_4OAc	5	96[19]
6	$FeNi_3$-ILs MNPsc (2 mg)b, EtOH, reflux	NH_4OAc	0.70	92
7	$CuCr_2O_4$ (4 mg)b, EtOH	NH_4OAc	0.75	93

[a] Isolated yield.
[b] Amount of catalyst per millimole of aldehyde.
[c] Ionic liquid immobilized on a FeNi3 nanocatalyst.

Table 3 The Scope of Catalyst-Free Synthesis of THDPPs from $(NH_4)_2CO_3$ in Water

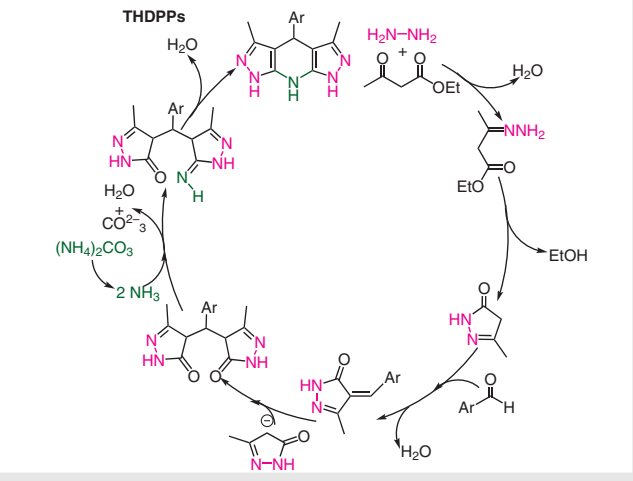


Entry	Ar	R	Time (min)	Yield (%)	Mp (°C) (Lit.[15,16])
1	Ph	Et	15	97	235–237 (240–242)
2	Ph	Me	10	98	239–241
3	4-HOC_6H_4	Et	20	92	265–267 (267–268)
4	4-ClC_6H_4	Et	25	94	254–256 (254–256)
5	4-Tol	Et	18	88	244–246 (244–246)
6	4-Tol	Me	15	92	243–245
7	3-$O_2NC_6H_4$	Et	25	91	285–286 (282–284)
8	3-$O_2NC_6H_4$	Me	18	93	283–285
9	4-$Me_2NC_6H_4$	Et	17	97	242–244 (240–242)
10	4-$Me_2NC_6H_4$	Me	18	97	243–244
11	4-$O_2NC_6H_4$	Et	10	94	333–335 (>300)
12	4-$O_2NC_6H_4$	Me	10	95	334–335
13	2-ClC_6H_4	Et	12	86	220–222 (164–165)
14	4-$MeOC_6H_4$	Et	30	82	182–184 (185–187)
15	4-$MeOC_6H_4$	Me	20	90	183–185
16	4-BrC_6H_4	Et	30	83	165–167 (165–167)

nent reaction of several aryl aldehydes with hydrazine hydrate, ammonium carbonate, and various alkyl acetoacetates in water to afford the desired products (Table 3).[21] Although methyl acetoacetate reacted faster than ethyl acetoacetate, this green method was compatible with various substrates. The isolated products in each case were sufficiently pure to show the expected characteristics. However, the reaction with phenylhydrazine was ineffective under our reaction conditions.

A probable reaction mechanism for the catalyst-free synthesis of THPPs with ammonium carbonate as the source of ammonia is shown in Scheme 2. We presumed that the reaction begins with hydrazonation of ethyl acetoacetate, pyrazolone formation, and further condensation with the other reaction components.

In summary, after evaluation of various organic and inorganic ammonium salts as sources of nitrogen in a water-based catalyst-free synthesis of the model compound **THDPP1** at room temperature, we selected ammonium carbonate as the optimal salt. This solid source of ammonia was used in a catalyst-free and fully biocompatible synthesis of THDPPs in water through a pseudo-six-component reaction of alkyl acetoacetates, hydrazine hydrate, and ammonium carbonate with an aldehyde in a mole ratio of 2:2:1:1. The advantages of this environmentally friendly protocol are simple isolation of the product by filtration, no use of any organic solvent, clean and rapid reactions, excellent yields, and its ecofriendly nature.



Scheme 2 Proposed mechanism for catalyst-free synthesis of THDPPs in water

Funding Information

We gratefully thank the Yazd University Research Council for financial support.

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(21) **Tetrahydrodipyrazolopyridines; General Procedure**
$(NH_4)_2CO_3$ (2.0 mmol) was added to a stirred mixture of the appropriate aldehyde (2.0 mmol), alkyl acetoacetate (4.0 mmol), and hydrazine hydrate (4.0 mmol) in H_2O (1.0 mL), and the mixture was stirred vigorously at r.t. for the appropriate time (Table 3). The precipitated product was separated by simple filtration.
4-(3,5-Dimethyl-1,4,7,8-tetrahydrodipyrazolo[3,4-*b*:4′,3′-*e*]pyridin-4-yl)phenol (Table 3, Entry 3)
White solid; yield: 244.1 mg (92%); mp 267–269 °C (Lit.[15] 267–268 °C). FTIR (KBr): 3234 (overlapped NH and OH stretching), 2935 (CH stretching), 1600 cm^{-1} (C=N stretching). ^1H NMR (400 MHz, DMSO-d_6): δ = 2.05 (s, 6 H, 2 CH_3), 4.68 (s, 1 H, CH), 6.57 (d, *J* = 8 Hz, 2 H, H_{arom}), 6.89 (d, *J* = 8 Hz, 2 H, ArH), 9.15 (s, OH), 11.52 (s, 3 H, 3 NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.35, 31.76, 104.51, 114.45, 128.25, 133.36, 139.75, 155.05, 161.05.
3,5-Dimethyl-4-(4-tolyl)-1,4,7,8-tetrahydrodipyrazolo[3,4-*b*:4′,3′-*e*]pyridine (Table 3, Entry 5)
White solid: 245.8 mg (88%); mp 244–246 °C (Lit.[15] 244–246 °C). FTIR (KBr): 3170 (NH stretching), 2920 (CH stretching), 1610 (C=N stretching), 1520 (C=C aromatic), 1139 cm^{-1} (C–N stretching). ^1H NMR (400 MHz, DMSO-d_6): δ = 2.1 (s, 6 H, 2 CH_3), 2.20 (s, 3 H, *p*-CH_3), 4.78 (s, 1 H, CH), 6.99–7.00 (m, 4 H, H_{arom}), 11.25 (s, 3 H, 3 NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.85, 20.98, 32.85, 104.85, 127.82, 128.83, 134.70, 140.20, 140.75, 161.50.
[4-(3,5-Dimethyl-1,4,7,8-tetrahydrodipyrazolo[3,4-*b*:4′,3′-*e*]pyridin-4-yl)phenyl]dimethylamine (Table 3, Entry 9)
Yellow-orange solid: 299.1mg (97%); mp 250–252 °C. FTIR (KBr): 3514, 3168 (NH stretching), 2942 (CH stretching), 1608 (C=N stretching), 1520 (C=C arom), 1139 cm^{-1} (C–N stretching). ^1H NMR (400 MHz, DMSO-d_6): δ = 2.26 (s, 6 H, 2 CH_3), 2.91 (s, 6 H, 2 *p*-CH_3), 4.9 (s, 1 H, CH), 6.75 (d, *J* = 8 Hz, 2 H, H_{arom}), 7.3 (d, *J* = 8 Hz, 2 H, H_{arom}), 11.54 (s, 3 H, 3 NH).
3,5-Dimethyl-4-(4-nitrophenyl)-1,4,7,8-tetrahydrodipyrazolo[3,4-*b*:4′,3′-*e*]pyridine (Table 3, Entry 11)
Cream solid: 291.7 mg (94%); mp 333–335 °C (Lit.[15] >300 °C). FTIR (KBr): 3250 (NH stretching), 2985 (CH stretching), 1605 (C=N stretching), 1489 (overlapped asymm stretching NO_2 with C=C arom), 1352 (NO_2 symm stretching), 753 cm^{-1} (out-of-plane bending C–H, *para*-substituted). ^1H NMR (400 MHz, DMSO-d_6): δ = 2.1 (s, 6 H, 2 CH_3), 4.95 (s, 1 H, CH), 7.35 (d, *J* = 8 Hz, 2 H, H_{arom}), 8.1 (d, *J* = 8 Hz, 2 H, H_{arom}), 11.20 (s, 3 H, 3 NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.70, 33.40, 103.60, 123.40, 129.20, 140.20, 146.1, 152.25, 161.35.

