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ORIGINAL PAPER

Triethanolamine–sodium acetate as a novel deep eutectic solvent for promotion of tetrahydrodipyrazolopyridines synthesis under microwave irradiation

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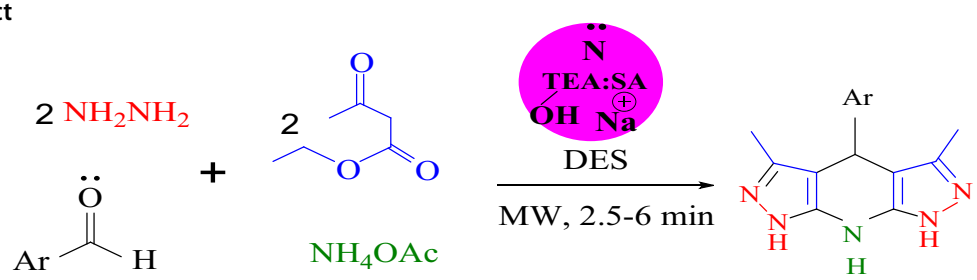
Abstract
Deep eutectic solvents like ionic liquids were used as solvent or catalyst in organic synthesis. In this work, a novel deep eutectic solvent containing triethanolamine and sodium acetate was prepared and studied by Fourier-transform infrared spectroscopy (FTIR), thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), potential of hydrogen (pH), viscosity and conductivity. This deep eutectic solvent was applied for the synthesis of tetrahydrodipyrazolopyridines as an efficient reusable catalyst under microwave irradiation. The advantages of this method include easy catalyst preparation, low catalyst consumption, short reaction time, excellent product yields and safe operation.

Graphic abstract



Keywords Pyrazolopyridines · Tetrahydrodipyrazolopyridines · Deep eutectic solvents · Microwave irradiation · Triethanolamine · Sodium acetate

Introduction

Similar to ionic liquids (ILs), deep eutectic solvents (DES) as binary mixtures almost are liquids at room temperature. DES are attractive substituents for hazardous solvents in organic synthesis. Insignificant vapor pressure, biodegradability, low cost, task-specific engineering and high absorption of gases such as CO_2 are the most important characteristics of DESs. The mixture of choline chloride and urea with eutectic temperature of 12 °C is the first DES that was prepared by Abbott [1]. Preparation of new DES with low melting point is an important field in organic chemistry [2, 3]. For introduction of a new DES, its thermal stability, electrochemical potential window, viscosity, conductivity, melting point and decomposition temperature should be measured.

Pyrazolopyridines have a wide range of biological and pharmacological activities, including antiviral [4], antitumor [5], hypoglycemic [6], anti-inflammatory [7], anxiolytic [8], antileishmania [9], antiherpetic [10], antiallergic [11] and protein kinase inhibitors [12]. A few synthesis protocols for tetrahydrodipyrazolo-pyridines have been reported in the chemical literature. The most straightforward process for the synthesis of tetrahydrodipyrazolopyridines is

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multicomponent reaction of ethyl acetoacetate, hydrazine, aldehyde and ammonium acetate. Previously, nano-Fe_3O_4/KCC-1/IL/HPW [13], nano-$CdZr_4(PO_4)_6$ [14], nano-$CuCr_2O_4$ [15], nano-$FeNi_3$ [16], nano-Fe_3O_4@SiO_2-SO_3H [17], nano-ovalbumin [18], $CuFe_2O_4$@HNTS [19] and Cu(II)/Schiff base@MWCNT-Fe_3O_4/SiO_2 [20] were used as catalysts for the above-mentioned process. Despite the remarkable achievements, biocompatible synthesis of these potent pyridines using an inexpensive, easily available and metal-free catalyst is still in demand. This work focuses on the developing triethanolamine–sodium acetate (TEA:SA) as a new deep eutectic solvent and application of it in the synthesis of dipyrazolopyridines.

Experimental

General

All chemicals were purchased from Merck, Fluka and were used without further purification. A conventional cell was used for studying the electrochemical behavior of DES. Platinum electrode was used as working electrode, Ag/AgCl, KCl (3 M) as reference electrodes and platinum as counter electrode. A computer-controlled potentiostat [Sama, IRAN] was used for electrochemical experiment. Thermogravimetric analysis (TGA/DTA) was done with "STA 504" instrument. Differential scanning calorimeter (DSC-60, Shimadzu Japan) was used for the study of phase transition of TEA:SA (0.88:0.12 mol) mixture. The pH and conductivity of DES were measured by Metrohm pH meter model 691 and Metrohm 912 conductometer. The viscosity of DES was measured Brookfield DV-E viscometer (spindle, 2 RV and rotating speed 50 RPM). Fourier transform infrared (FT-IR, ATR) spectra were run on a Bruker, Equinox 55 spectrometer. A Bruker (DRX-400 Avance) nuclear magnetic resonance (NMR) instrument was used to record the ^{1}H-NMR spectra. Melting points were determined by a Buchi melting-point B-540 B.V.CHI apparatus.

General procedure for the synthesis of dipyrazolopyridines

A mixture of hydrazine hydrate (0.5 mmol), ethyl acetoacetate (0.5 mmol), aldehyde (0.25 mmol), ammonium acetate (1 mmol) and TEA:SA (0.88:0.12), (0.01 g) was charged in the microwave Teflon vessel and allowed to react under microwave irradiation. The progress of the reaction was monitored by thin-layer chromatography (*n*-hexane:EtOAc, 50:50). After completion of the reaction, the reaction mixture was cooled to room temperature. Then, the solid product was obtained by adding water to reaction mixture. The product was filtered and dried at room temperature.

Some selected spectroscopic data

3,5-Dimethyl-4-(4-bromophenyl)-1,4,7,8-tetrahydrodipyrazolo [3,4-b; 4′,3′-e] Pyridine (5e)

Cream solid, m.p. 221–224 °C. FT-IR (ATR), $\bar{\upsilon}$ (cm^{-1}): 3333, 3272, 1596, 1518, 1474, 833, 663. ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm), 2.06 (s, 6H, $2CH_3$), 4.78 (s, 1H, CH),7.03 (d, J = 8 Hz, 2 H, ArH), 7.39 (d, J = 8 Hz, 2H, ArH), 11.50 (s, 3H, 3NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6), δ (ppm): 10.23, 32.43, 104.45, 118.30, 129.62, 130.34, 131.85, 142.66, 157.00.

3,5-Dimethyl-4(3-hydroxyphenyl)-1,4,7,8- tetrahydrodipyrazolo [3,4-b; 4′,3′-e]Pyridine (5d)

Pink solid, m.p. 225–228 °C. FT-IR (ATR) $\bar{\upsilon}$ (cm^{-1}): 3464, 3336, 1607, 1449, 1395, 1262, 875, 832, 686. ^{1}H NMR (400 MHz, DMSO-d_6) /δ ppm: 11.32 (s, NH, 3H), 9.11 (s, OH, 1H), 6.99 (t, J = 7.6 Hz, 1H), 6.57 (s, 1H), 6.53 (d, J = 8.8 Hz, 1H), 6.51 (d, J = 8.4 Hz, 1H), 4.74 (s, 1H), 2.07 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) /δ ppm: 161.58, 157.41, 145.32, 140.29, 128.98, 118.71, 115.05, 112.84, 104.73, 33.04, 10.86.

3,5-Dimethyl-4(3,4-dihydroxy phenyl)-1,4,7,8- tetrahydrodipyrazolo [3,4-b; 4′,3′-e] Pyridine (5 l).

Cream solid, m.p. 204–207 °C, FT-IR (ATR), $\bar{\upsilon}$ (cm^{-1}): 3343, 3297, 1600, 1511, 1439, 1172, 1075, 834, 787, 737. ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm) 11.30 (s, NH, 3H), 8.63 (s, OH, 1H), 8.52 (s, OH, 1H), 6.56 (d, J = 8 Hz, 1H), 6.55(s, 1H), 6.35 (d, J = 8 Hz, 1H), 4.67 (s, 1H), 2.06 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6), δ (ppm): 161.59, 144.97, 143.43, 140.21, 134.55, 118.56, 115.61, 115.32, 105.18, 32.36, 10.86.

Results and discussion

The eutectic temperature of triethanolamine (TEA), as hydrogen bond donor, and sodium acetate trihydrate (SA), as hydrogen bond acceptor, initially, was determined by freezing and defreezing of various mole fractions of them. The melting point of every mole fraction of TEA and SA was determined by digital thermometer (−50–150 °C). The obtained data are shown in Fig. 1. The eutectic point of this system was obtained as 4 °C in 0.91 mol fraction of triethanolamine.

For the determination of eutectic point of TEA:SA, the DSC diagrams of two mole fractions of TEA:SA (0.9:0.1 and 0.88:0.12) from −100 to + 250 °C were obtained (Fig. 2a–b).

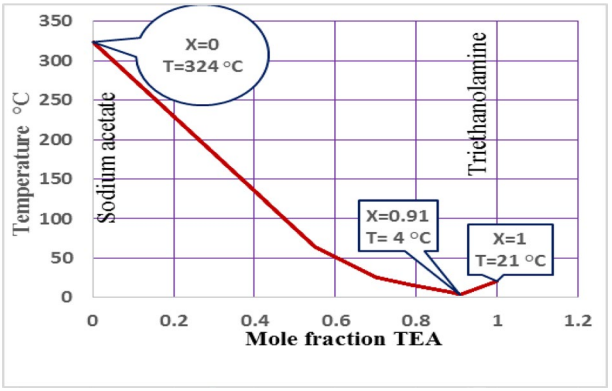


Fig. 1 Melting-point diagram of TEA:SA system

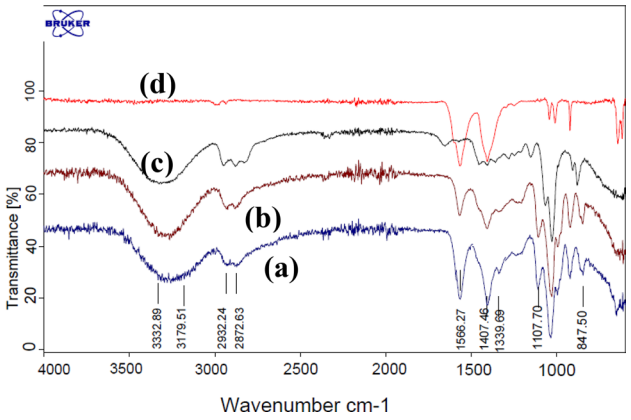


Fig. 3 FTIR spectrum of **a** TEA:SA (0.88:0.12 mol), **b** recovered TEA:SA (0.88:0.12 mol), **c** triethanolamine, **d** sodium acetate trihydrate

According to DSC diagrams, we have found that TEA:SA (O.88:0.12) involves lower melting point (1.18 °C, Fig. 2b) and can be mentioned as a DES.

FTIR spectrum of TEA:SA is shown in Fig. 3. According to Fig. 3a, TEA:SA has TEA and SA absorption bands.

Thermogravimetric diagram of DES of TEA:SA was studied for thermal behavior of the DES system (Fig. 4).

The TEA:SA (0.88:0.12 mol, 89:11% w/w) heating to 120 °C caused losing 10% of its weight due to elimination of water in triethanolamine and sodium acetate trihydrate. The TEA:SA (0.88:0.12 mol, 89:11% w/w) mixture under heating from 234 to 320 °C has lost 83% of its weight. This weight loss is due to degradation of TEA to produce 2 mol of ethylene oxide and ethanolamine and degradation of sodium acetate to acetic anhydride and sodium oxide. A small residual amount or char yield is 5% of TEA:SA (0.88:0.12 mol) system) which still remained at 817 °C; it is attributed to the fact that Na_2O was produced from decomposition of sodium acetate.

Cyclic voltammogram of TEA:SA (0.88:0.12 mol) system was studied for the determination of oxidation–reduction potential range in Fig. 5. Oxidation–reduction potential range of TEA:SA (0.88:0.12 mol) is −2.4 V to + 0.5 V referring to reference electrode (Ag/AgCl/KCl, 3 M). The measured pH of DES (TEA:SA (0.88:0.12 mol)) was 10.2. Ionic conductivity of DES was 220 MS/cm and the viscosity was 554 cp (30 °C). It should be pointed that the viscosity of triethanolamine is 404 cp (30 °C).

Sodium acetate is connected to triethanolamine by hydrogen bonding (Scheme 1). Hence, the interaction between sodium and acetate ions is lower than the pure sodium acetate trihydrate. The free sodium ions and triethanolamine can

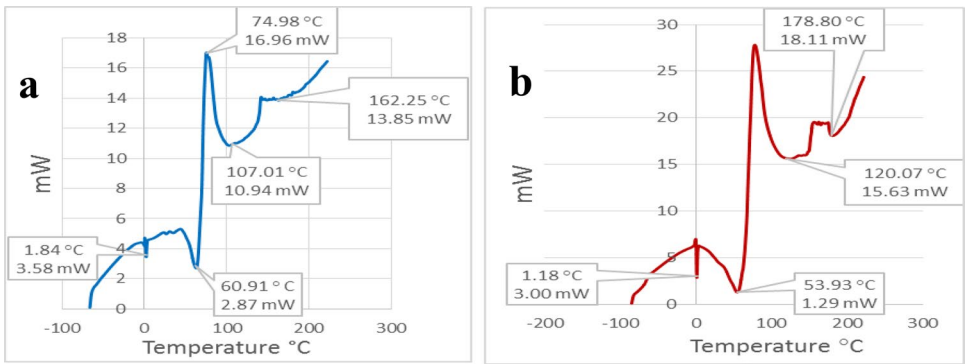


Fig. 2 DSC analysis of **a** TEA:SA (0.9:0.1 mol) and **b** TEA:SA (0.88:0.12 mol) system

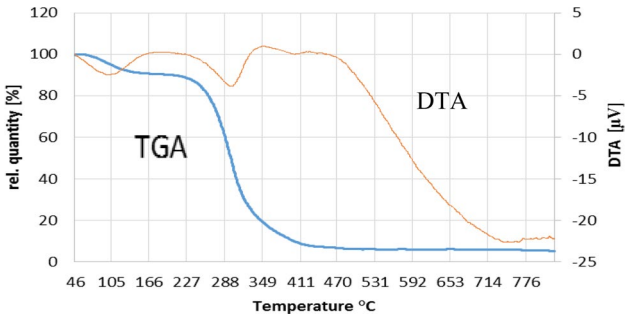


Fig. 4 Thermogravimetric mass loss (TGA) and differential thermal analysis (DTA) for the decomposition of TEA:SA (0.88:0.12 mol) system with a heating rate of 10 °C min^{-1}

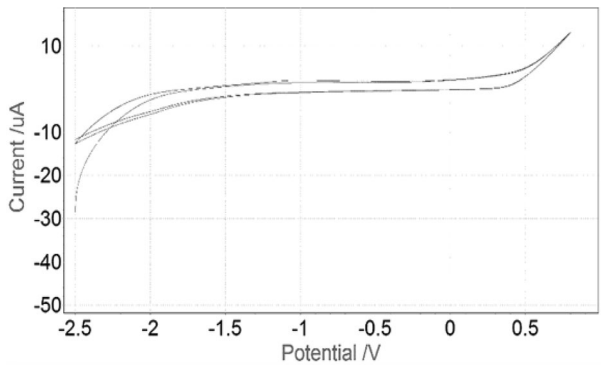
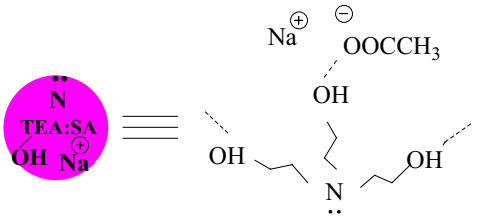


Fig. 5 Cyclic voltammogram of TEA:SA (0.88:0.12 mol) system at the scan rate of 50 Mv/sec. Working electrode (Pt), reference electrode (Ag/AgCl, (KCl, 3 M)) and counter electrode (Pt)

activate carbonyl groups for nucleophilic addition reaction via dipole–ion interaction or hydrogen bonding, respectively. Meanwhile, triethanolamine acts as a base for deprotonation of OH groups.

Various catalysts and conditions were applied for the synthesis of dipyrazolopyridines (Table 1). By comparison of catalysts and due to the best efficiency, 0.01 g of TEA:SA (0.88:0.12) system under microwave irradiation was selected (Table 1, entry 16).



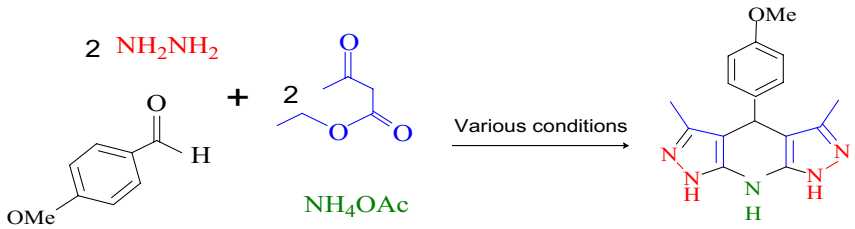
Scheme 1 The schematic form of TEA:SA as DES

We have used the above-mentioned catalyst to synthesis of different dipyrazolopyridines via condensation among aldehydes, hydrazine hydrate, ethyl acetoacetate and ammonium acetate (Table 2).

According to the proposed mechanism for the synthesis of tetrahydrodipyrazolo-pyridine using the TEA:SA system, the sodium ion and hydroxyl groups of the catalyst activate the carbonyl groups of ethyl acetoacetate, accelerate the attack of hydrazine on ethyl acetoacetate and form pyrazolone (A). Then, pyrazolone (A) is converted to (B) by tautomerization. Then, the Knoevenagel condensation between (B) and activated aldehyde produces compound (C). By following the Michael addition reaction between (C) and (B), compound (D) is formed. Finally, the main product is formed by nucleophilic attack of NH_3 on compound (D) followed by intramolecular ring formation (Scheme 2).

For reusability investigation of the DES, TEA:SA (0.88:0.12) in tetrahydrodipyrazolopyridine synthesis, the model reaction was examined four times. After completion of any run, by adding water to reaction mixture, the product was isolated as solid and the catalyst was remained in water. By evaporation of water, the DES was obtained in high purity. As shown in Fig. 6, the reused catalyst did not show considerable decrease in its activity after four times. Meanwhile, the structure of recovered catalyst was studied by FTIR (Fig. 3b) which is comparable with fresh catalyst (Fig. 3a). The comparison of our catalyst, DES (TEA:SA (0.88:0.12)), and other reported catalyst in the synthesis of 5a is shown in Table 3. According to the obtained data, the high performance of our catalyst is shown considerably.

Table1 Optimization of the reaction conditions for the synthesis of 3,5-dimethyl-4-(4-methoxyphenyl)-1,4,7,8-tetrahydrodipyrazolo [3,4-b; 4′,3′-e] pyridine[a]

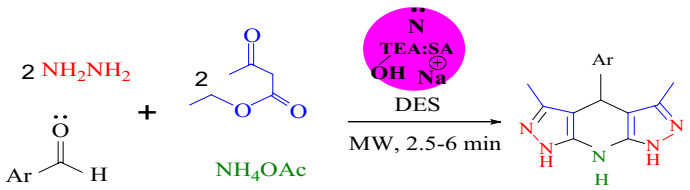


Entry	Catalyst (g)	Conditions	Time (min)	Yield (%)[b]
1	–	55 °C	40	70
2	–	110 °C	60	70
3	–	MW	3	60
4	$CH_3COO^-Na^+$ (0.1)	55 °C/ H_2O	315	70
5	$CH_3COO^-Na^+$ (0.1)	MW	3	98
6	$CH_3COO^-Na^+$ (0.01)	MW	3	96
7	TEA (0.13)	MW	3	96
8	DES (0.1)	25 °C	20	38
9	DES (0.1)	30 °C	10	32
10	DES (0.1)	50 °C	15	45
11	DES (0.1)	80 °C	45	40
12	DES (0.1)	Electrical mortar	30	98
13	DES (0.1)	MW	3	98
14	DES (0.06)	MW	3	98
15	DES (0.03)	MW	3	98
16	DES (0.01)	MW	3	98
17	DES (0.005)	MW	3	80

[a]Hydrazine hydrate (0.5 mmol), ethyl acetoacetate (0.5 mmol), 4-methoxybenzaldehyde (0.25 mmol), ammonium acetate (1 mmol) and deep eutectic, TEA:SA (0.88:0.12)

[b]Conversion yield

Table 2 Synthesis of tetrahydrodipyrazolo-pyridines in the presence of TEA:SA (0.88:0.12) under microwave irradiation[a]

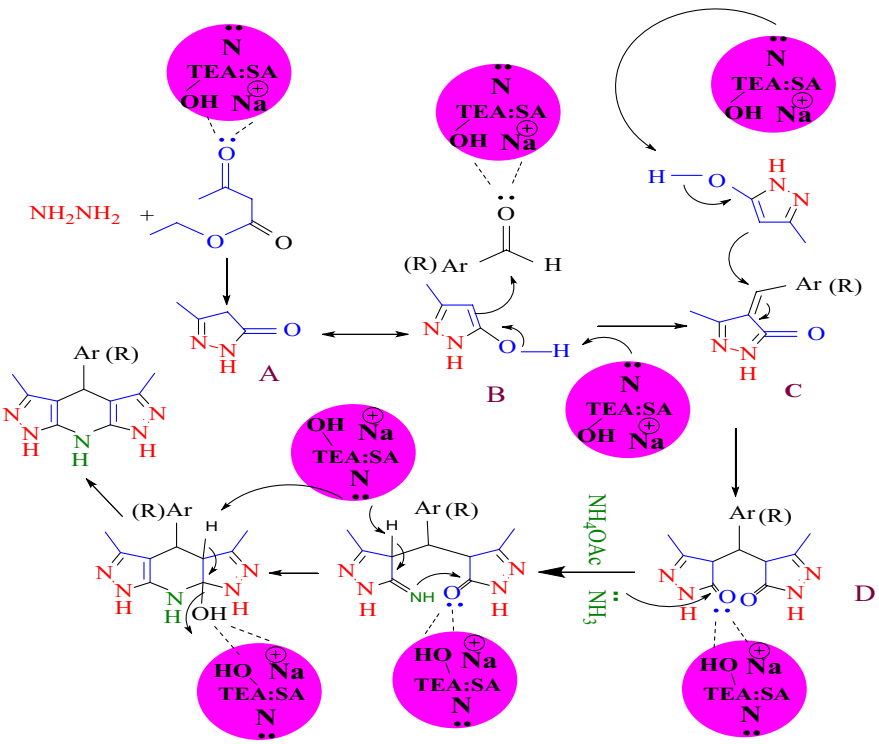


Ent	Ar	Prod	Time (min)	Yield[b] (%)	M.P. (°C) Obs.	Rep. References
1	C_6H_5	5a	4	95	233–236	244–246 [18]
2	2-Cl-C_6H_4	5b	6	95	175–178	170–172[18]
3	3-O_2N-C_6H_4	5c	5	98	244–247	282–284[18]
4	3-HO-C_6H_4	5d	3	99	225–228	220–222[18]
5	4-Br-C_6H_4	5e	3	97	221–224	165–166[19]
6	4-Me-C_6H_4	5f	3	92	213–216	241–243[18]
7	4-HO-C_6H_4	5 g	3	95	240–243	268–270[18]
8	4-MeO-C_6H_4	5 h	3	94	206–209	188–190[18]
9	4-O_2N-C_6H_4	5i	3	96	278–283	288–290[18]
10	4-Cl-C_6H_4	5j	5	98	215–218	256–258[18]
11	4-$(Me)_2$ N-C_6H_4	5 k	6	92	240–243	240–242[18]
12	3,4-$(HO)_2$-C_6H_3	5 l	4	99	204–207	208–210[18]
13	3-MeO-4-HO-C_6H_3	5 m	2.5	93	230–233	258–260[18]

[a]Aldehyde (hydrazine hydrate (0.5 mmol), ethyl acetoacetate (0.5 mmol), aldehyde (0.25 mmol), ammonium acetate (1 mmol) and deep eutectic, TEA:SA (0.88:0.12), (0.01 g)

[b]Isolated yield.

Scheme 2 A proposed mechanism for synthesis of tetrahydrodipyrazolo pyridine in the presence of TEA:SA



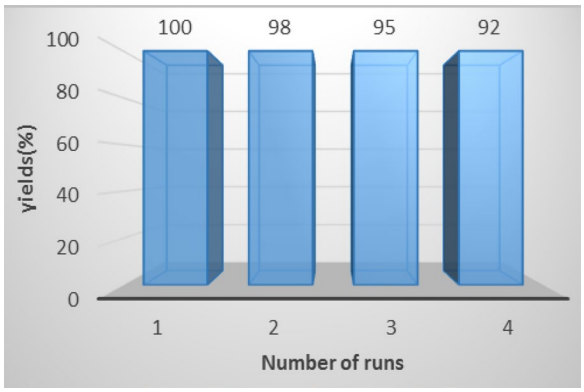


Fig. 6 Reusability of the catalyst TEA:SA (0.88:0.12)

Table 3 Efficiency comparison of TEA:SA (0.88:0.12) catalysts with other reported catalysts in the synthesis of **5a**

Entry	Catalyst	Conditions	Time (min)/ yield[a] (%) [References]
1	–	EtOH/reflux	300/79 [22]
2	Nano-$CdZr_4(PO_4)_6$, (0.6 mol %)	EtOH/reflux	40/94 [12]
3	Fe_3O_4/KCC-1/IL/HPW MNP, (0.0001 g)	H_2O/r.t	32/96 [13]
4	Fe_3O_4@SiO_2-SO_3H NPs, (0.004 g)	EtOH/MW	15/97 [17]
5	Nano-ovalbumin, (0.05 g)	H_2O/55 °C	45/93 [18]
6	Nano-$CuFe_2O_4$@HNTs, (0.0005 g)	EtOH/r.t	20/96 [20]
7	base@MWCNT-Fe_3O_4/SiO_2, (0.02 g)	–/r.t	90/85 [21]
8	TEA:SA (0.88:0.12) (0.01 g)	MW	3/98 [this work]

[a]Isolated yield

Conclusion

In conclusion, we have prepared and characterized a novel deep eutectic system from triethanolamine and sodium acetate as TEA:SA (0.88:0.12). This deep eutectic system was applied for the synthesis of dipyrazolopyridines under microwave condition. High yields, easy work-up and reusability of catalyst are the key advantages of this protocol.

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Compliance with ethical standards

Conflict of interest There are no conflicts to declare.

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