Journal of Molecular Catalysis A: Chemical 415 (2016) 144–150

Contents lists available at ScienceDirect

Journal of Molecular Catalysis A: Chemical

journal homepage: www.elsevier.com/locate/molcata

Catalytic application of 1-(carboxymethyl)pyridinium iodide on the synthesis of pyranopyrazole derivatives

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ARTICLE INFO

Article history:
Received 12 December 2015
Received in revised form 13 January 2016
Accepted 1 February 2016
Available online 3 February 2016

Keywords:
Pyranopyrazole
Tandem reaction
1-(Carboxymethyl)pyridinium iodide
Solvent-free

ABSTRACT

In this investigation, acetic acid functionalized pyridinium salt, namely 1-(carboxymethyl)pyridinium iodide {[cmpy]I}, has been introduced as reusable catalyst for green, simple and efficient synthesis of 6-amino-4-(4-methoxyphenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazoles by the one-pot tandem four-component condensation reaction of aryl aldehydes with ethyl acetoacetate, malononitrile and hydrazine hydrate at 100 °C under solvent-free conditions. Additionally, ^{1}H and ^{13}C NMR, mass, CHN analysis, Fourier transform infrared spectroscopy (FT-IR), scanning electron microscope (SEM), thermal gravimetric analysis (TGA), differential thermal gravimetric (DTG), X-ray diffraction analysis (XRD), and calculation of crystallite size and inter planer distance of the catalyst have been investigated.

1. Introduction

Tandem reaction, as a modern protocol in organic transformations, is a reaction in which several bonds are formed in some sequences without separating of any intermediates, changing reaction conditions and adding reagents. Clean reaction condition, high atomic economy and much complexity in one step are some important advantages of tandem reactions [1–5].

Pyranopyrazoles are interesting class of heterocyclic compounds; they have been used as fungicidal [6], bactericidal [7], vasodilatory [8] and anticancer [9]. They have also reported as pharmaceutical ingredients and biodegradable agrochemicals [10]. Additionally, pyrano[2,3-c]pyrazoles have been acted as potential insecticidal [11] and molluscicidal agents [12,13]. Several catalysts have been introduced for the synthesis of pyranopyrazoles, including imidazole [13], per-6-amino-b-cyclodextrin [14], phase transfer catalyst (HDBAC) [15], organocatalysts (MDOs) [16], D,L-Proline [17], hexa decyl tri methyl ammonium bromide (HTMAB) [18], disulfonic acid imidazolium chloroaluminate {[Dsim]$AlCl_4$} [19], gamma-alumina [20], magnetic Fe_3O_4 nanoparticles [21] and isonicotinic acid [22]. Therefore, considerable attention has been focused on the development of new protocols for the preparation of these compounds.

Recently, we have introduced a new category of ionic liquids and solid salts (with an organic cation), namely sulfonic acid functionalized imidazolium salts (SAFIS) [23–33]. In this class of salts, S—N bond formation in imidazole ring, as five member's heterocyclic compounds, was reported for the first time. These compounds have been successfully applied as catalysts or reagent for the synthesis of bis(indolyl) methanes [23], *N*-sulfonyl imines [24], 1-amidoalkyl-2-naphthols [25], various xanthene derivatives [26], 1-carbamatoalkyl-2-naphthols [27], 4,4′-(arylmethylene)-bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)s [28], *N*-boc protected amines [29], hexahydroquinolines [30], nitroaromatic compounds [31,32], 1,2,4,5-tetrasubstituted imidazoles [33]. In continuation of our previous projects involving the preparation and applications of acidic ionic liquids and solid salts in organic transformations, we have used 1-(carboxymethyl) pyridinium iodide {[cmpy]I} on the synthesis of 6-amino-4-(4-methoxyphenyl)-5-cyano-3-methyl-1-phenyl-1, 4-dihydropyrano[2,3-c]pyrazoles by the one-pot multi-component condensation reaction of arylaldehydes with ethyl acetoacetate, malononitrile and hydrazine hydrate (Scheme 1).

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http://dx.doi.org/10.1016/j.molcata.2016.02.003
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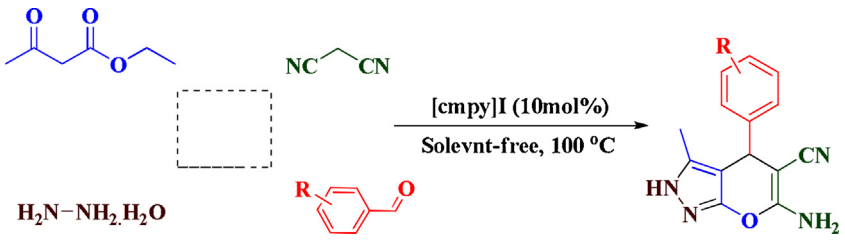
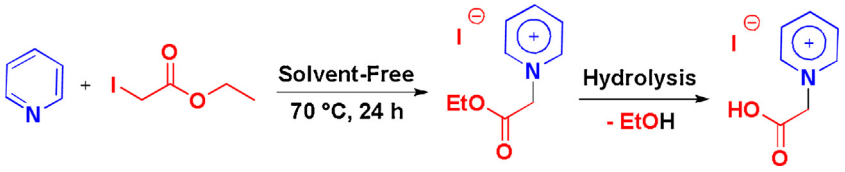


Scheme 1. The preparation of pyranopyrazole derivatives using [cmpy]I.



Scheme 2. The synthesis of 1-(carboxymethyl) pyridinium iodide {[cmpy]I}.

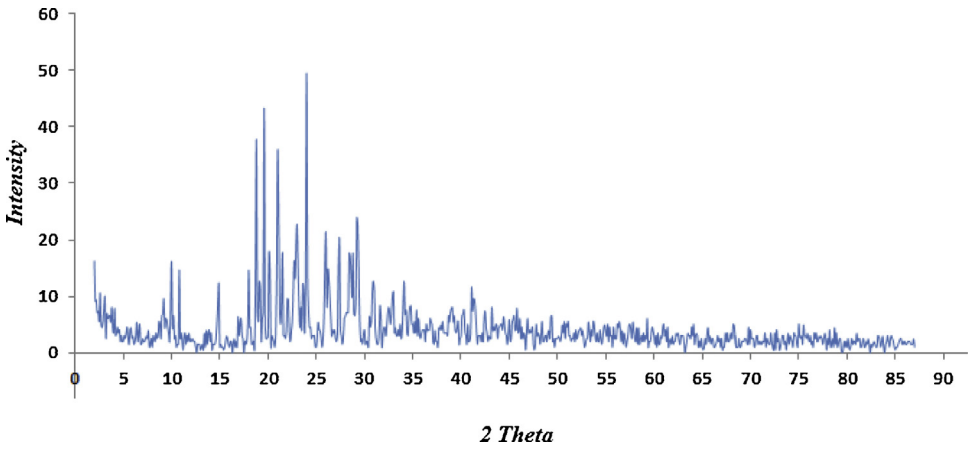


Fig. 1. The XRD pattern of 1-(carboxymethyl) pyridinium iodide [cmpy]I.

2. Experimental

2.1. General

All chemicals were purchased from Merck or Fluka Chemical Companies. The known products were identified by comparison of their melting points and spectral data with those reported in the literature. Progress of the reactions was monitored by TLC using silica gel SIL G/UV 254 plates. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a Bruker Avance DPX-250 FT-NMR spectrometer (δ in ppm). Infrared spectrum of products was recorded by PerkinElmer PE-1600-FTIR. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

2.2. Procedure for the synthesis of 1-(carboxymethyl) pyridinium iodide {[cmpy]I}

A mixture of pyridine (0.010 mol) and ethyl iodoacetate (0.010 mol) was stirred and heated at 70 °C for 24 h. After this time, the reaction mixture turned to a dark viscous liquid. The liquid was washed with diethyl ether (3 × 30 mL) and dried under vacuum for 2 h. Then, a solution of HCl 37% (0.011 mol) was added to prepare liquid and refluxed for 30 min. Finally, the solvent was removed under reduced pressure and the remaining solid was washed with diethyl ether to give the product as a yellowish powder.

2.3. General procedure for the synthesis of 6-amino-4-(4-methoxyphenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazoles

A mixture of aromatic aldehyde (2 mmol), malononitrile (0.132 g, 2 mmol), ethyl acetoacetate (0.26 g, 2 mmol) hydrazine hydrate (2.5 mmol) and {[cmpy]I (10 mol%) was added in a 10 mL round-bottomed flask connected to a reflux condenser, and stirred at 100 °C. After completion of the reaction, as monitored by TLC, H_2O (10 mL) was added to the reaction mixture, stirred and refluxed for 5 min. Then the reaction mixture was filtered and the solvent of the filtrate (H_2O) was removed under reduced pressure to separate the catalyst from crude product. The solid residue (crude product) was triturated by a mixture of ethanol and water (9/1) to obtain the pure product.

3. Results and discussion

1-(Carboxymethyl)pyridinium iodide {[cmpy]I} was synthesized by the reaction of pyridine with ethyl iodoacetate at 70 °C. Then, the product was hydrolysed to give [cmpy]I. The structure of [cmpy]I was confirmed by ^{1}HNMR, ^{13}CNMR, IR and mass as well as CHN analysis (Scheme 2).

The IR spectrum of [cmpy]I has been shown in Fig. S1. The broad peak at 2493–3050 cm^{-1} can be related to O—H stretching of the COOH group. Also, the peak observed at 1734 cm^{-1} correspond to vibrational modes of C=O bond of the COOH group. Also, the C—H

stretching vibrations of pyridine ring in 1-(carboxymethyl) pyridinium iodide observed at 3050 cm^{-1} and C—H bending vibrations of pyridine ring in [cmpy]I appeared at 692 and 888 cm^{-1}. These mentioned peaks clearly confirmed the structure of [cmpy]I.

The structure of [cmpy]I was also studied by NMR studies. The important peak in ^{1}H NMR spectra of the [cmpy]I was related to the acidic hydrogen of COOH which was observed at 14.06 ppm (Fig. S2). Moreover, in ^{13}C NMR spectra of [cmpy]I, the peaks related to methylene group and carbonyl group were observed at 60.56 and 167.66 ppm respectively. The peaks related to pyridine ring were seen at 127.12, 146.15 and 146.74 ppm (Fig. S3).

X-ray diffraction analysis (XRD) pattern of 1-(carboxymethyl) pyridinium iodide {[cmpy]I} was studied in a domain of 0–90° (Fig. 4). As it is shown at Fig. 1, indicates that XRD pattern exhibited diffraction lines of a high crystalline nature at about $2\theta \approx 18.8°, 19.6°, 23.0°, 24.0°, 26.0°, 27.4°$ and 28.8°. Crystallite size was calculated by Debye–Scherrer's formula given by equation: $D = K\lambda/(\beta \cos\theta)$. The crystallite size obtained using this formula was at about 32.49 nm (for the highest diffraction line at 24.0°) and inter planer distance was calculated *via* the Bragg equation: $dhkl = \lambda/(2\sin\theta)$, which obtained 0.3703 nm (λ:Cu radiation 0.154178 nm).

In another investigation, the scanning electron microscope (SEM) micrographs of the catalyst were studied. The SEM images showed that the particles have not completely agglomerated. Moreover, particles of the catalyst were observed in nano size which is in good agreement with calculated size by Debye–Scherrer's equation (Fig. 2) provided the presence of the expected elements in the structure of the catalyst, namely carbon, oxygen, nitrogen and iodide. Therefore, the structure of the catalyst was completely confirmed by EDX analyze.

Thermal gravimetric analysis (TGA) of the 1-(carboxymethyl) pyridinium iodide {[cmpy]I} was also studied. The corresponding diagrams are shown in Fig. 4. The thermogravimetry (TG) and differential thermal gravimetric (DTG) of the catalyst showed weight losses in two steps. [cmpy]I was decomposed after 286 °C.

To optimize the reaction conditions, the condensation between hydrazine hydrate (2.5 mmol) ethyl acetoacetate (2 mmol), malononitrile (2 mmol) and 4-chlorobenzaldehyde (2 mmol), as a model reaction, was investigated in the presence of different amounts of [cmpy]I at range of 60–120 °C in the absence of solvent (Table 1). Energy-dispersive X-ray spectroscopy (EDX) from

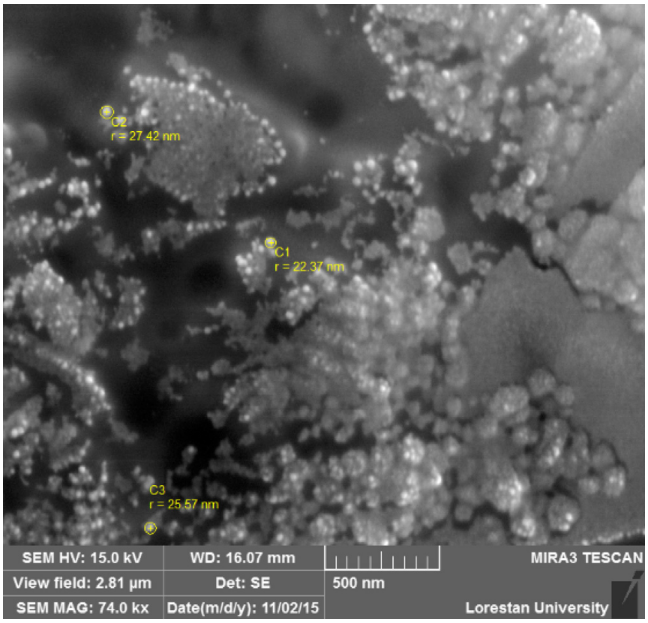


Fig. 2. The SEM images of 1-(carboxymethyl) pyridinium iodide [cmpy]I.

Table 1
Effect of different amounts of the catalyst and temperature on the reaction of hydrazine hydrate (2.5 mmol) with ethyl acetoacetate (2 mmol), malononitrile (2 mmol) and 4-chlorobenzaldehyde (2 mmol) in the absence of solvent.

Entry	Mol% of catalyst	Temp. (°C)	Time (min)	Yield[a] (%)
1	10	60	10	65
2	10	80	5	78
3	10	100	3	93
4	10	120	3	92
5	–	100	45	Trace
6	5	100	10	72
7	7	100	10	72
8	10	100	4	93
9	15	100	5	93

[a] Isolated yield.

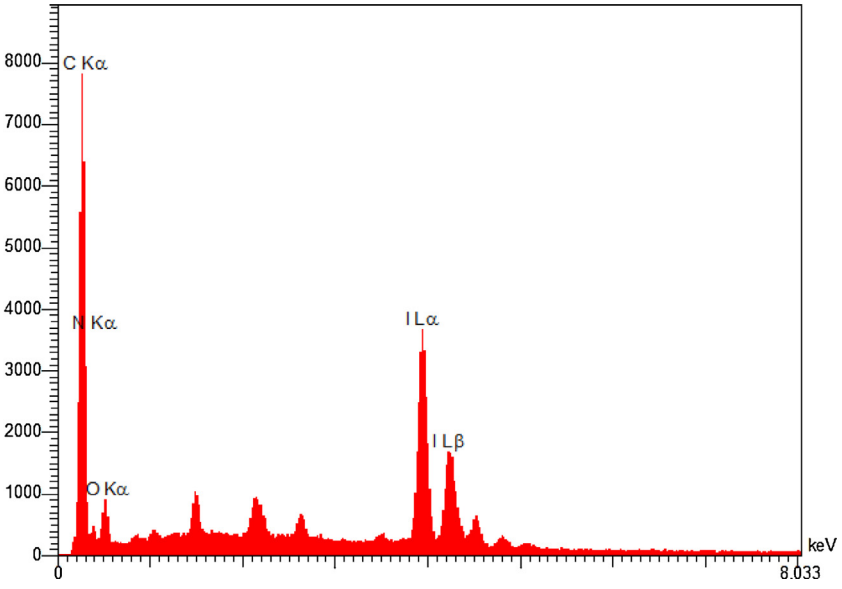


Fig. 3. Energy-dispersive X-ray spectroscopy (EDX) of 1-(carboxymethyl) pyridinium iodide [cmpy]I.

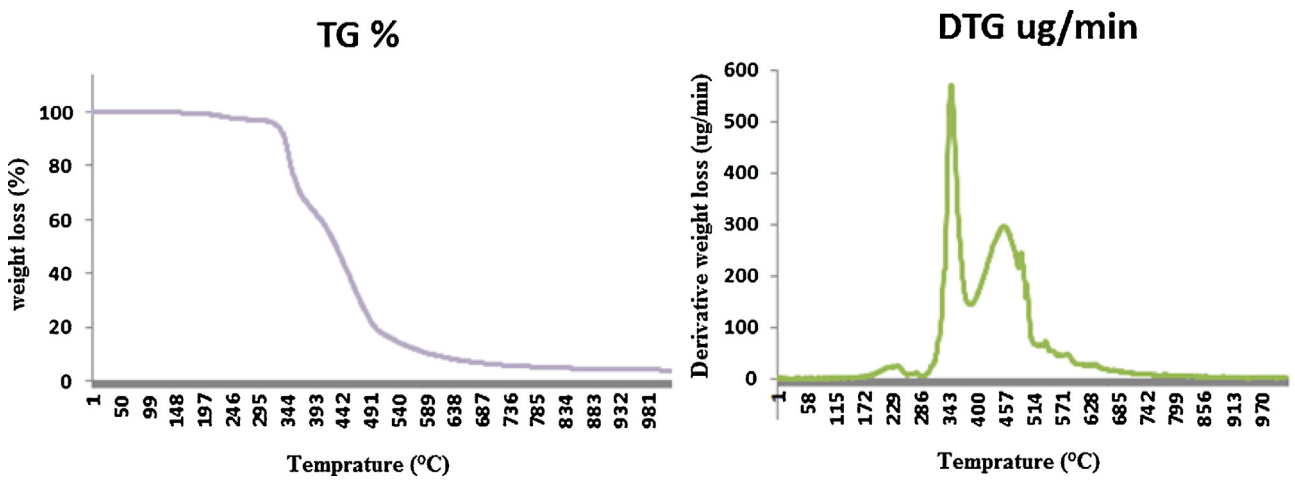
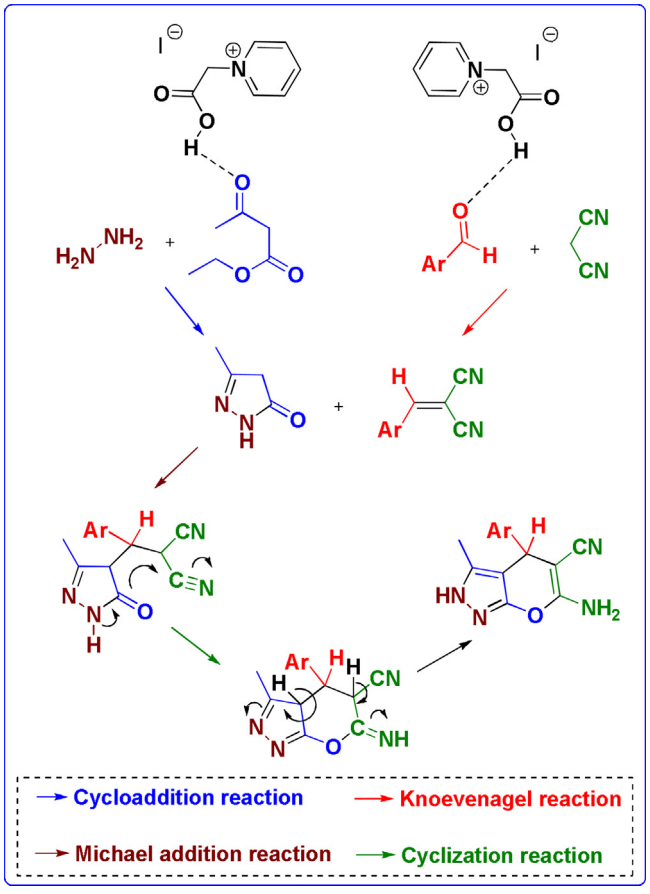


Fig. 4. TG/DTG diagrams of 1-(carboxymethyl) pyridinium iodide [cmpy]I.



Scheme 3. The plausible mechanism for the synthesis of pyranopyrazoles.

the obtained nanoparticles (Fig. 3). As it is shown in Table 1, the reaction was efficiently performed using 10 mol% of the catalyst at 100 °C to give the desired product in high yield within short reaction time (Table 1, entry 3). The reaction was also tested at 100 °C without catalyst under solvent-free conditions in which the reaction did not significantly progress even after long reaction time (Table 1, entry 5).

In the next step, the model reaction was examined in several solvents using 10 mol% of [cmpy]I under reflux conditions. The results are depicted in Table 2. As it is shown in Table 2, indicates that the solvent-free conditions are more effective than solvent conditions.

Table 2
The reaction of hydrazine hydrate (2.5 mmol) with ethyl acetoacetate (2 mmol), malononitrile (2 mmol) and 4-chlorobenzaldehyde (2 mmol) using [cmpy]I (10 mol%) in different solvents (5 mL) under reflux conditions.

Entry	Solvent	Time (min)	Yield[a] (%)
1	–	3	93
2	H_2O	5	72
3	Acetinitrile	60	40
4	Ethanol	60	45
5	CH_2Cl_2	30	23

[a] Isolated yield.

To investigate the efficacy and generality of [cmpy]I in the synthesis of 6-amino-4-(4-methoxyphenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazoles, various arylaldehydes (including benzaldehyde, and arylaldehydes aldehydes possessing electron-releasing substituents, electron-withdrawing substituents and halogens on their aromatic ring) were reacted with hydrazine hydrate, ethyl acetoacetate and malononitrile under the optimal reaction conditions to obtain the desired products in high yields and in short reaction times. The results are displayed in Table 3.

In a plausible mechanism, initially, ethyl acetoacetate was activated by [cmpy]I and hydrazine attacked to the carbonyl group of the activated ethyl acetoacetate. Then, loss of H_2O, and intramolecular nucleophillic attack by another NH_2 group of hydrazine to the next carbonyl group of ethyl acetoacetate afforded 5-methyl-2, 4-dihydro-pyrazol-3-one and removed EtOH. In the next step, by the reaction of aromatic aldehyde, which was activated by [cmpy]I, with malononitrile, cyanoolefin compound was prepared. Finally, by the tandem Michael addition–cyclization reaction of 5-methyl-2,4-dihydro-pyrazol-3-one with cyanoolefin compound the desired pyranopyrazole was prepared (Scheme 3).

In another investigation, recyclability of the catalyst was examined upon the reaction of hydrazine hydrate (2.5 mmol) with ethyl acetoacetate (2 mmol), malononitrile (2 mmol) and 4-chlorobenzaldehyde (2 mmol). After completion of the reaction, H_2O was added to the reaction mixture, stirred and refluxed for 5 min. Then the reaction mixture was filtered and the solvent of the filtrate (H_2O) was removed under reduced pressure to separate the catalyst from crude product. Finally, the reused catalyst was used for another reaction. We observed that the catalytic activity of the catalyst was restored within the limits of the experimental errors for eight successive runs (Fig. 5). In this method, in order to reuse of the catalyst, unreacted hydrazine hydrate is miscible in water and is separated with catalyst.

Table 3
The preparation of 6-amino-4-(4-methoxyphenyl)-5-cyano-3-methyl-1-phenyl-1,4- dihydropyrano[2,3-c]pyrazoles using [cmpy]I as catalyst at 100 °C.

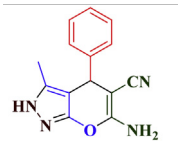
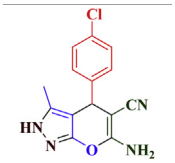
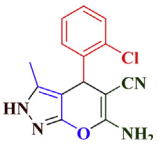
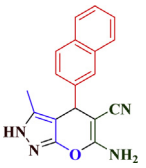
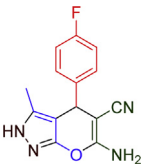
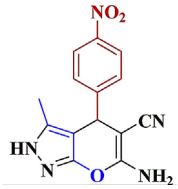
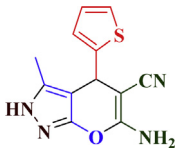
Entry	Product	Time (min)	Yield[a] (%)	Mp. °C (Lit.)
1		3	90	261–263 (264–266 [19])
2		4	94	226–228 (234–236 [20])
3		3	86	253–255 (261–263 [19])
4		3	92	198–200 (206–208 [15])
5		3	91	220–222 (250–252 [9])
6		3	83	229–230
7		3	95	216–218 (244–245 [9])
8		3	86	198–199 (208–210 [21])
9		3	84	258–259 (262–264 [19])
10		3	84	212–214 (208–210 [18])
11		4	89	242–244 (251–253 [15])

Table 3 (*Continued*)

Entry	Product	Time (min)	Yield[a] (%)	Mp. °C (Lit.)
12		3	86	219–220 (223–225 [19])
13		3	87	194–196 (210–211 [9])
14		3	85	242–244 (248–250 [9])

[a] Isolated yield.

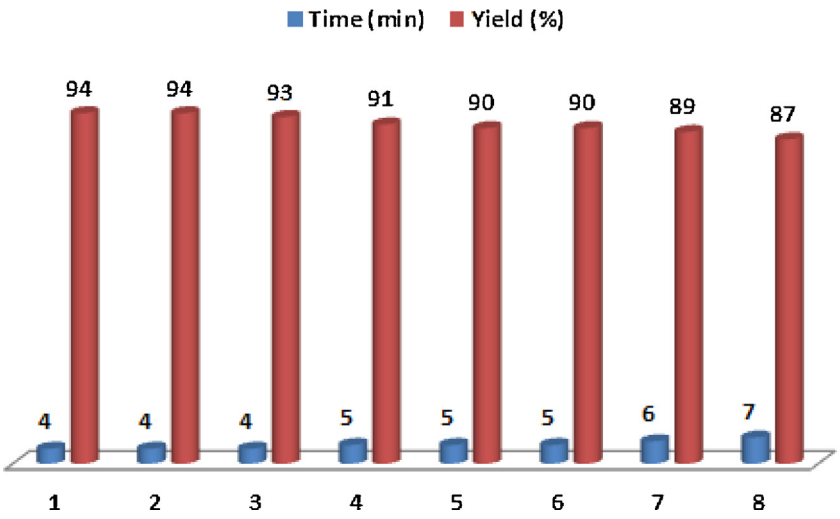


Fig. 5. The reaction of hydrazine hydrate with ethyl acetoacetate, malononitrile and 4-chlorobenzaldehyde in the presence of reused [cmpy]I at 100 °C under solvent-free conditions.

Table 4
Comparison of the results of the condensation reaction of hydrazine hydrate with ethyl acetoacetate, malononitrile and 4-chlorobenzaldehyde catalyzed by [cmpy]I with those obtained by the recently reported catalysts.

Reaction condition	Catalyst loading	Time (min)	Yield[a] (%)	TOF[b] (min^{-1})	Ref.
SiO_2TMG, solvent-free, 100 °C	10 mol%	20	98	0.49	[9]
Gamma-alumina, H_2O, reflux	30 mol%	35	90	0.085	[20]
HDBAC, EtOH, reflux	30 mol%	45	81	0.06	[15]
Imidazole, H_2O, 80 °C	50 mol%	20	90	0.09	[13]
[cmpy]I, solvent-free, 100 °C	10 mol%	3	86	2.86	–[c]

[a] Isolated yield.
[b] Turn over frequency.
[c] Our work.

To compare the efficiency of our catalyst with the previous reported catalysts for the preparation of 6-amino-4-(4-methoxyphenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazoles, we have depicted the results of these catalysts to perform the reaction of hydrazine hydrate with ethyl acetoacetate, malononitrile and 4-chlorobenzaldehyde in Table 4. As Table 4 indicates that [cmpy]I has remarkably improved the synthesis of pyranopyrazoles. The reaction times were shorter, and the yields were higher when our catalyst was utilized.

4. Conclusions

In summary, we have reported the efficient synthesis of 6-amino-4-(4-methoxyphenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazoles in the presence of 1-(carboxymethyl) pyridinium iodide {[cmpy]I} as an acetic

acid functionalized pyridinium salt and reusable catalyst. The promising points for the presented methodology are efficiency, generality, high yield, relatively short reaction time, low cost, cleaner reaction profile, ease of product isolation, simplicity, and finally compliance with the green chemistry protocols.

Acknowledgements

The authors gratefully acknowledge the Bu-Ali Sina University, Iran National Science Foundation (INSF) for financial support (The Grant of Allameh Tabataba'i's Award) to our research group and Sayyed Jamaleddin Asadabadi University for providing support to this work.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molcata.2016.02.003.

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