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Original Scientific Article

Novel one-pot Facile Synthesis of Thiopyranopyrazole Using [H mim]HSO_4 Catalyst

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Abstract. An efficient and easy protocol has been developed for synthesis of thiopyranopyrazole by using [H mim]HSO_4 as recyclable catalyst under solvent-free condition at room temperature. This environmentally benign method has advantages, such as high yield of products, simple work-up procedure, and avoidance of the organic solvents, which will contribute in serving as a green process greatly. The catalyst was easily recovered and reused without any considerable loss of activity.

Keywords: environmentally benign, solvent-free, cyclocondensation, ionic liquid, pyrazole-thione

INTRODUCTION

The present day industrialization has led to immense environmental worsening. One of the chief source of environmental pollution from the chemical industry is the organic solvents. The solvent vapours contaminate the atmosphere/ environment. The increasing awareness throughout the world has brought in a pressing need to develop an alternative synthetic approach for biologically and synthetically important compounds. This requires a new approach which will reduce the material and energy consumption, and eliminate or minimize the dispersion of harmful chemicals in the environment. Pollution free synthesis of organic compounds in presence of either non toxic solvents or in absence of solvent is an important challenge.[1–3]

One-pot sequential multi-step reactions are of increasing academic, economical and ecological interest because they address fundamental principles of synthetic efficiency and reaction design, so called multicomponent reactions (MCRs). It has an outstanding status in modern organic synthesis and medicinal chemistry because they are one-pot processes bringing together two or more than two components and exhibit high atom economy and high selectivity.[4] MCRs have great contribution in synthesis of complex organic molecules from simple and readily available starting materials, and have emerged as powerful tools for the development of new and more effective drug.[5]

In the last few years, one of the hot topics in the field of green chemistry is the introduction and application of ionic liquids (ILs) in organic synthesis. It has unique properties, such as wide liquid range, good solvating capability, negligible vapour pressure; they have gained considerable interest as environmentally benign reaction media, catalysts and reagents, and are easy to recycle.[6] Recently, the role of ILs to promote the selectivity of various organic reactions and to dramatically influence the outcome of chemical reactions, in the context of multicomponent ones, have also attracted much attention.

Recently a wide range of biological activities associated with the sulphur-heterocycles scaffolds have been identified.[7] Thiopyran and fused-thiopyran derivatives are known to exhibit anti-bacterials,[8] anti-inflammatory,[9] antipsychiatric,[10] anti-hyperplasia,[11] analgesic, and anti-cancer[12] activities and are widely present as key structural motifs in many natural products. Thiopyran derivatives can act as modulators of the estrogen receptors[13] and are found to possess a high dopamine receptor binding affinity.[14]

Thiopyrans are used as key units in medicinal chemistry and as versatile building blocks in organic synthesis.[15] For example, it has been reported that thiopyrans were widely used in the construction of analogues of natural products with various biological activities, such as tetrahydrodicranenone,[16] serricornin,[17] thromoboxanes,[18] and cyclopentanoids.[19] As a result, a great deal of efforts has been drawn to develop new and

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efficient synthetic routes to thiopyrans.[20] To match the increasingly synthetic and medicinal demands for thiopyran derivatives, it is still of significant interest to explore novel and efficient synthetic approaches for such thio-heterocycles.

Pyranopyrazoles are an important class of biologically active heterocycles. They are reported to possess a multiplicity of pharmacological properties including anticancer[21], antimicrobial,[22] anti-inflammatory,[23] insecticidal, and molluscicidal activities.[24] They are also potential inhibitors of human Chk1 kinase.[25] They also find applications as pharmaceutical ingredients and biodegradable agrochemicals.[26]

Prompted by the above reports and in continuation of our work on development of novel environmentally benign synthesis[27–30] herein we report a simple, efficient and green protocol for the synthesis of thiopyranopyrazole, catalysed by [H mim]HSO_4 under solvent-free condition with excellent yield. Short reaction time, simple reaction conditions, ease of the product isolation, use of cheap and readily available catalyst made this protocol very interesting from the environmental and economic perspective. The catalyst was easily recovered and reused without any considerable loss of activity.

EXPERIMENTAL SECTION

Melting points were determined by open glass capillary method and are uncorrected. All chemicals used were reagent grade and were used as received. IR spectra were recorded on a Shimadzu FTIR-420 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400^{o}C on a Bruker AVANCE DPX (400 MHz and 75 MHz) FT spectrometer in $CDCl_3$ using TMS as an internal reference (chemical shift in δ, ppm). Mass spectra were recorded on JEOL SX-303 (FAB) mass spectrophotometer at 70ev. Elemental analyses were carried out using a Coleman automatic C,H,N analyser.

6-Amino-4-aryl-3-methyl-2,4-dihydrothiopyrano[2,3-*c*]pyrazole-5-carbonitrile 4a–j:

At first, substituted/unsubstituted benzaldehyde (1 mmol) and [H mim]HSO_4 (5 mmol%) was mixed for 5 min and then O-ethyl 3-oxobutanethioate (1 mmol), hydrazine hydrate (1 mmol) and propanedinitrile (1 mmol) was added to this mixture and stirred at room temperature for 30 min. Completion of the reaction was monitored by TLC. After completion of the reaction, appropriate amounts of EtOH (96 %) were added and the mixture was stirred for 10 min then, the catalyst was separated by filtration. The precipitation was washed by cold ethanol and crystallized from hot ethanol to afford the pure products **4a-j**.

4a. *6-Amino-4-(4-chlorophenyl)-3-methyl-2,4-dihydrothiopyrano[2,3-c]pyrazole-5-carbonitrile:*
m.p. : 250ºC, *m/z*: 302; Mol. Wt: 302.78; FTIR (KBr) : ν/cm^{-1} = 3382, 3325, 3161 (NH), 2190 (CN), 1650 (δ NH_2), 1600 (δ C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ / ppm = 2.0 (s, 2H, NH_2), 2.79 (s, 3H, CH_3), 4.74 (s, 1H, C-4, thiopyran), 7.00 (d, 2H, *p*-tolyl), 7.15 (d, 2H, *p*-tolyl), 13.7 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 11.4, 24.1, 70.1, 117.3, 128.8, 130.5, 131.3, 133.3, 139.2; Anal. Calcd for $C_{14}H_{11}ClN_4S$: C, 55.53: H, 3.66: N, 18.50. Found: C, 55.45: H, 3.62; N, 18.45.

4b. *6-Amino-4-(3-chlorophenyl)-3-methyl-2,4-dihydrothiopyrano[2,3-c]pyrazole-5-carbonitrile:*
m.p. : 245ºC, *m/z*: 302; Mol. Wt: 302.78; FTIR (KBr): ν/cm^{-1} = 3389, 3330, 3167 (NH), 2194 (CN), 1654 (δ NH_2), 1604 (δ C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ / ppm = 2.0 (s, 2H, NH_2), 2.79 (s, 3H, CH_3), 4.74 (s, 1H, C-4, thiopyran), 6.94 (d, 1H, *p*-tolyl), 7.04 (s, 1H, *p*-tolyl), 7.08 (d, 2H, *p*-tolyl), 13.7 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 11.4, 23.6, 70.1, 117.3,125.9,127.2, 128.9, 130.1, 134.2, 136.5, 139.2, 167.1; Anal. Calcd for $C_{14}H_{11}ClN_4S$: C, 55.53: H, 3.66: N, 18.50. Found: C, 55.45: H, 3.62; N, 18.45.

4c. *6-Amino-4-(2-chlorophenyl)-3-methyl-2,4-dihydrothiopyrano[2,3-c]pyrazole-5-carbonitrile:*
m.p. : 242ºC, *m/z*: 302; Mol. Wt: 302.78; FTIR (KBr, cm^{-1}) : ν/cm^{-1} = 3389, 3330, 3167 (NH), 2194 (CN), 1654 (δ NH_2), 1604 (δ C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ / ppm = 2.0 (s, 2H, NH_2), 2.79 (s, 3H, CH_3), 4.74 (s, 1H, C-4, thiopyran),7.00 (d, 1H, *p*-tolyl), 7.01 (d, 1H, *p*-tolyl),7.02 (d, 1H, *p*-tolyl), 7.15 (d, 1H, *p*-tolyl), 13.7 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ / ppm = 11.4, 15.0, 70.1, 117.3,126.8, 127.2, 128.8, 130.5, 134.4, 139.2, 144.6, 167.1; Anal. Calcd for $C_{14}H_{11}ClN_4S$: C, 55.53: H, 3.66: N, 18.50. Found: C, 55.45: H, 3.62; N, 18.45.

4d. *6-Amino-4-(4-methoxyphenyl)-3-methyl-2,4-dihydrothiopyrano[2,3-c]pyrazole-5-carbonitrile:*
m.p. : 240ºC, *m/z*: 298; Mol. Wt: 298.36; FTIR (KBr) : ν/cm^{-1} = 3390, 3331, 3170 (NH), 2197 (CN), 1654 (δ NH_2), 1603 (δ C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ / ppm = 2.0 (s, 2H, NH_2), 2.79 (s, 3H, CH_3), 3.73 (s, 3H, −OCH_3), 4.74 (s, 1H, C-4, thiopyran), 6.65 (d, 2H, *p*-tolyl), 6.95 (d, 2H, *p*-tolyl), 13.7 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ / ppm = 11.4, 24.1, 55.9, 70.1, 114.2,117.3, 127.4, 130.1, 139.2, 157.7, 167.1; Anal. Calcd for $C_{15}H_{14}N_4OS$: C, 60.38: H, 4.73: N, 18.78. Found: C, 60.36: H, 4.70; N, 18.75.

4e. *6-Amino-3-methyl-4phenyl-2,4-dihydrothiopyrano[2,3-c]pyrazole-5-carbonitrile:*
m.p. : 225ºC, *m/z*: 268; Mol. Wt: 268.34; FTIR (KBr, cm^{-1}) : ν/cm^{-1} = 3372, 3320, 3164 (NH), 2192 (CN), 1652 (δ NH_2), 1600 (δ C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ / ppm = 2.0 (s, 2H, NH_2), 2.79 (s, 3H,

CH_3), 4.74 (s, 1H, C-4, thiopyran), 7.06 (d, 2H, *p*-tolyl), 7.07 (d, 1H, *p*-tolyl), 7.14 (d, 2H, *p*-tolyl), 13.7 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ / ppm = 11.4, 24.1, 70.1, 117.3,125.8, 128.7, 129.1, 135.1, 139.2, 167.1; Anal. Calcd for $C_{14}H_{12}N_4S$: C, 62.66: H, 4.51: N, 20.88. Found: C, 62.64: H, 4.48; N, 20.85.

4f. *6-Amino-4-(4-bromophenyl)-3-methyl-2,4-dihydrothiopyrano[2,3-c]pyrazole-5-carbonitrile:*
m.p. : 245ºC, *m*/*z*: 346; Mol. Wt: 347.23; FTIR (KBr, cm^{-1}) : ν/cm^{-1} = 3387, 3325, 3165 (NH), 2193 (CN), 1651 (δ NH_2), 1602 (δ C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ / ppm = 2.0 (s, 2H, NH_2), 2.79 (s, 3H, CH_3), 4.74 (s, 1H, C-4, thiopyran), 6.95 (d, 2H, *p*-tolyl), 7.31 (d, 2H, *p*-tolyl), 13.7 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ / ppm = 11.4, 24.1, 70.1, 117.3, 120.1,131.3, 131.6, 134.1, 139.2, 167.1; Anal. Calcd for $C_{14}H_{11}BrN_4S$: C, 48.43: H, 3.19: N, 16.14. Found: C, 48.40: H, 3.15; N, 16.10.

4g. *6-amino-4-(3-bromophenyl)-3-methyl-2,4-dihydrothiopyrano[2,3-c]pyrazole-5-carbonitrile:*
m.p. : 241ºC, *m*/*z*: 346; Mol. Wt: 347.23; FTIR (KBr, cm^{-1}) : ν/cm^{-1} = 3385, 3324, 3164 (NH), 2190 (CN), 1650 (δ NH_2), 1601 (δ C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ / ppm = 2.0 (s, 2H, NH_2), 2.79 (s, 3H, CH_3), 4.74 (s, 1H, C-4, thiopyran), 7.00 (d, 1H, *p*-tolyl), 7.03 (d, 1H, *p*-tolyl), 7.23 (s, 1H, *p*-tolyl), 7.24 (d, 1H, *p*-tolyl), 13.7 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ / ppm = 11.4, 23.4, 70.1, 117.3, 123.0,128.1, 128.7, 130.9, 133.8, 137.3, 139.2, 167.1; Anal. Calcd for $C_{14}H_{11}BrN_4S$: C, 48.43: H, 3.19: N, 16.14. Found: C, 48.40: H, 3.15; N, 16.10.

4h. *6-Amino-3-methyl-4-(4-nitrophenyl)-2,4-dihydrothiopyrano[2,3-c]pyrazole-5-carbonitrile:*
m.p. : 235ºC, *m*/*z*: 313; Mol. Wt: 313.33; FTIR (KBr, cm^{-1}) : ν/cm^{-1} = 3390, 3330, 3170 (NH), 2197 (CN), 1655 (δ NH_2), 1606 (δ C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ / ppm = 2.0 (s, 2H, NH_2), 2.79 (s, 3H, CH_3), 4.74 (s, 1H, C-4, thiopyran), 7.32 (d, 2H, *p*-tolyl), 8.07 (d, 2H, *p*-tolyl), 13.7 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ / ppm = 11.4, 23.4, 70.1, 117.3, 123.0,128.1, 128.7, 130.9, 133.8, 137.3, 139.2, 167.1; Anal. Calcd for $C_{14}H_{11}N_5O_2S$: C, 53.66: H, 3.54: N, 22.35. Found: C, 53.62: H, 3.50; N, 22.30.

4i. *6-Amino-3-methyl-4-(3-nitrophenyl)-2,4-dihydrothiopyrano[2,3-c]pyrazole-5-carbonitrile:*
m.p. : 230ºC, *m*/*z*: 313; Mol. Wt: 313.33; FTIR (KBr, cm^{-1}) : ν/cm^{-1} = 3393, 3333, 3173 (NH), 2198 (CN), 1656 (δ NH_2), 1608 (δ C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ / ppm = 2.0 (s, 2H, NH_2), 2.79 (s, 3H, CH_3), 4.74 (s, 1H, C-4, thiopyran), 7.40 (d, 1H, *p*-tolyl), 7.45 (d, 1H, *p*-tolyl), 7.99 (s, 1H, *p*-tolyl), 8.00 (d, 1H, *p*-tolyl), 13.7 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ / ppm = 11.4, 23.1, 70.1, 117.3, 118.1, 124.3, 129.6, 135.2, 136.0, 139.2, 148.3, 167.1; Anal. Calcd for $C_{14}H_{11}N_5O_2S$: C, 53.66: H, 3.54: N, 22.35. Found: C, 53.62: H, 3.50; N, 22.30.

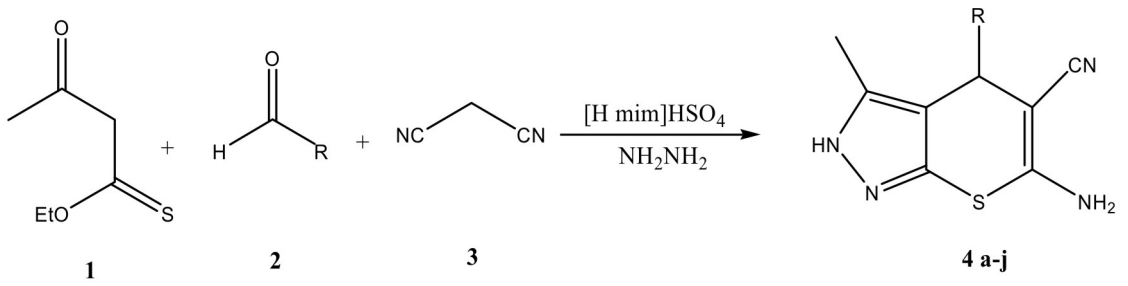
4j. *6-Amino-3-methyl-4-p-tolyl-2,4-dihydrothiopyrano[2,3-c]pyrazole-5-carbonitrile:*
m.p. : 233ºC, *m*/*z*: 282; Mol. Wt: 282.36; FTIR (KBr, cm^{-1}) : ν/cm^{-1} = 3374, 3324, 3160 (NH), 2191 (CN), 1652 (δ NH_2), 1602 (δ C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ / ppm = 2.0 (s, 2H, NH_2), 2.35 (s, 3H, CH_3, *p*-tolyl), 2.79 (s, 3H, CH_3), 4.74 (s, 1H, C-4, thiopyran), 6.94 (d, 4H, *p*-tolyl), 13.7 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ / ppm = 11.4, 24.1, 24.3,70.1, 117.3, 129.0, 132.1, 135.4, 139.2, 167.1; Anal. Calcd for $C_{15}H_{14}N_4S$: C, 63.80: H, 5.00: N, 19.84. Found: C, 63.78: H, 4.98; N, 19.80.

RESULTS AND DISCUSSION

In our initial study, reaction of benzaldehyde (1 mmol), O-ethyl 3-oxobutanethioate (1 mmol), hydrazine hydrate (1 mmol), propanedinitrile (1 mmol) and [H mim]HSO_4 (5 mmol%) as a catalyst was considered as a standard model reaction (Scheme 1).

During this investigation efforts were mainly focused on catalytic behaviour of [H mim]HSO_4 as well as their molar concentration. Further we have found that, there is significant decrease in time along with enhancement in yield using [H mim]HSO_4 as a catalyst at room temperature. However in the absence of catalyst, the reaction takes longer time for completion, which may reduce the rate of reaction.

To establish generality of the optimized reaction condition various aldehydes were allowed to undergo



Scheme 1. [H mim]HSO_4 catalyzed one pot synthesis of thiopyranopyrazole.

Table 1.

Products	R	Yields / %
4a	4-Cl-C_6H_4-	88
4b	3-Cl-C_6H_4-	87
4c	2-Cl-C_6H_4-	86
4d	4-MeO-C_6H_4-	85
4e	C_6H_5-	90
4f	4-Br-C_6H_4-	88
4g	3-Br-C_6H_4-	90
4h	4-NO_2-C_6H_4-	90
4i	3-NO_2-C_6H_4-	85
4j	4-Me-C_6H_4-	90

Table 2. Optimization of catalyst concentration[a]

Entry	Catalyst / mmol%	Time / min	Yield / %[(b)]
1	0	3.3 h	65
2	3	25	75
3[(c)]	5	30	90, 89, 87
4	10	30	90

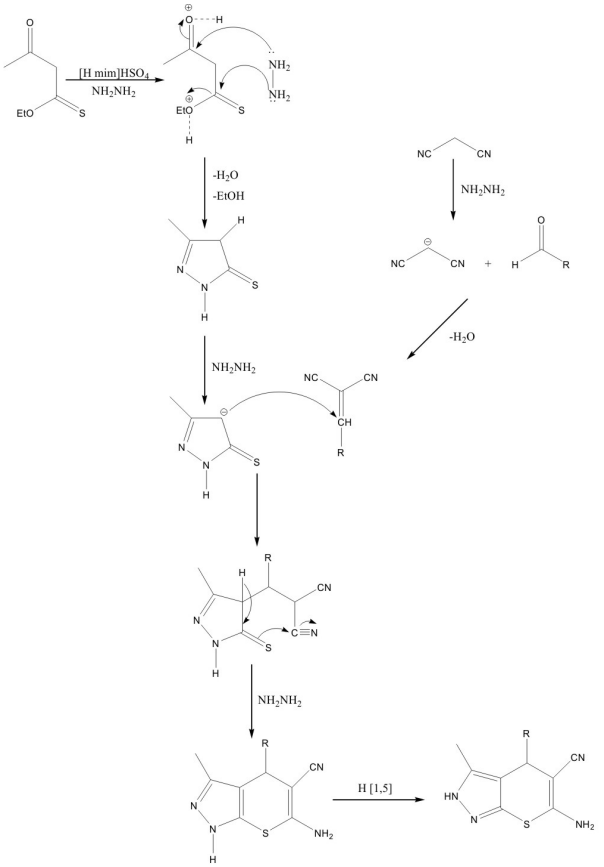
[(a)] Conditions: benzaldehyde (1 mmol), O-ethyl 3-oxobutanethioate (1 mmol), hydrazine hydrate (1 mmol), propanedinitrile (1 mmol) and [H mim]HSO_4 (5 mmol%) as a catalyst.

[(b)] isolated yields of the product **4a-j.**

[(c)] catalyst was used three times without any considerable loss of activity.

this cyclocondensation reaction, we found that aromatic aldehyde having electron withdrawing as well as electron releasing group both proved to be amenable to these reaction conditions. However no significant substituent effect was found in case of all aryl aldehydes (Table 1).

From the mechanistic point of view it is proposed that first step of the proposed mechanism (Scheme 2) was proceeded via cyclocondensation reaction of O-ethyl 3-oxobutanethioate with hydrazine hydrate followed by nucleophilic addition leading to the formation of the desired product (**4a-j**).



Scheme 2. Proposed mechanism for the synthesis of thiopyranopyrazole using [H mim]HSO_4 as a catalyst.

The synthetic pathways for preparation of the target compounds listed in Table 1 are shown in Scheme 1 and Scheme 2. The final compounds were easily obtained by cyclocondensation reaction of O-ethyl 3-oxobutanethioate with hydrazine hydrate followed by nucleophilic addition leading to the formation of the desired product (**4a-j**). All the synthesized compounds were identified by ^{1}H NMR, ^{13}C NMR, Mass spectra, IR and elemental analysis results are in agreement with the proposed structures. Encouraged by these results we further investigated effect of catalyst on the reaction (Table 2), we performed that the reaction using different molar concentration of catalyst and carefully studied its effect on isolated yield (Table 2), we found that on using 3, 5, 10 mmol% of [H mim]HSO_4 isolated yield was 75, 90, 90 % respectively. Since there was no enhancement in the yield on increasing the concentration of catalyst after 5 mmol% so we decided to use 5 mmol% of the catalyst for this reaction.

After completion of the reaction, activity of the recycled catalyst, [H mim]HSO_4 was also investigated with the optimized reaction conditions. After isolation of products, the ionic liquid [H mim]HSO_4 could be recycled for three times up to 72 % recovery and reused without any considerable loss of efficiency. It is found that the product was obtained 90, 89, 87 % yield after 1-3 runs, respectively in 30 min (Table 2).

CONCLUSION

Pyranopyrazoles exhibit greater biological activities and thiopyranes are important organic compounds with greater synthetic utility in medicinal chemistry. The use of ionic liquids in the field of green chemistry has brought a new revolution. Prompted by these reports and our work on development of environmentally benign synthesis we have developed, a new, easy and high

yielding protocol for synthesis of thiopyranopyrazole by using [H mim]HSO_4 as recyclable catalyst under solvent-free condition at room temperature.

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