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SBA-Pr-NH_2 CATALYZED PREPARATION OF PYRANO[2,3-c]PYRAZOLES UNDER SOLVENT-FREE CONDITIONS

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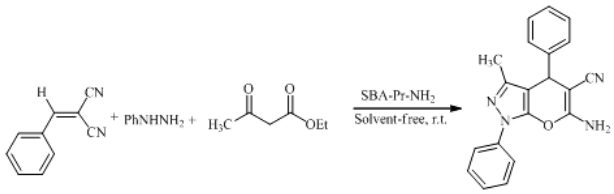
This report provides a description of an efficient and simple procedure for the synthesis of pyrano[2,3-c]pyrazole derivatives via a one-pot three-component reaction of arylmethylidene malononitrile, ethylacetoacetate and phenylhydrazine in the presence of amino-functionalized SBA-15 as a highly effective heterogeneous solid basic catalyst under solvent-free conditions. The remarkable advantages are the simplicity of the experimental procedures, high yields, short reaction times, and reusability of the catalyst.



INTRODUCTION

It is well known that pyrano[2,3-c]pyrazole and its derivatives are very useful heterocyclic compounds because of their synthetic as well as biological applications.[1-4] Pyrano [2,3-c]pyrazoles have also been used as antimicrobial,[5] insecticidal[6] and herbicidal[7] agents. A variety of methods have been reported for the synthesis of pyrano[2,3-c]pyrazoles in the literatures. [8-17] However, these methods for preparing pyrano[2,3-c]pyrazole derivatives have not been entirely satisfactory and involve some disadvantages such as long reaction times, use of organic solvents and generally need expensive or non-available reagents. Thus, the introduction of new methods and /or further work on technical improvements to overcome these limitations is still needed. SBA-15, a mesoporous silica based on uniform hexagonal pores, can be modified with different functional groups such as organic acids and amines.[18–20] Propyl amino-functionalized SBA-15 (SBA-Pr-NH_2) synthesized by the reaction of free silanol groups on the SBA-15 surface with 3-aminopropyl trimethoxysilane, is used as a catalyst in chemical transformations.[21, 22] In continuation of our research on organic synthesis[23, 24] and according to the wide applications of pyrano[2,3-c]pyrazoles in pharmaceutical and biological industries, we report the synthesis of these heterocyclic compounds in the mild and non-toxic conditions with high yields in the presence of SBA-Pr-NH_2 as a heterogeneous solid basic catalyst.

RESULTS AND DISCUSSION

Characterization of the catalyst

To confirm that 3-aminopropyltrimethoxysilan has supported on the surface of SBA-15, FT-IR and SEM techniques were used. The FT-IR spectra of SBA-15 and SBA-Pr-NH_2 are shown in Fig. 1. For SBA-15 and SBA-Pr-NH_2, the peaks at 791 and 1072 cm^{-1} were attributed to the symmetric and asymmetric stretching modes of Si–O–Si. The

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broad peak around 3475 cm^{-1} was assigned to the O–H stretching vibration of the SiO–H and HO–H of adsorbed water. In the spectra of SBA-Pr-NH_2, the bands at 1491 cm^{-1} were assigning to the (–CH_2) bending vibration, whereas the peaks at 2885 and 2933 cm^{-1} are attributed to C-H stretching vibrations in the methylene groups of the aliphatic chain, indicating the presence of the anchoring 3-aminopropyltrimethoxysilan on the silica surface. Moreover, the absorption band at 1567 cm^{-1} which almost overlapped with the bending vibration of the adsorbed H_2O, corresponded to the bending vibration of NH_2 groups (Fig. 1). Therefore, the FT-IR results confirmed the anchoring of the amine groups on the SBA-15 silica surface.

In order to obtain the morphology of the catalyst, SEM images of SBA-15 and SBA-Pr-NH_2 were obtained and are presented in Fig. 2. The SEM image showed the parallel channels, which resembled the configuration of the pores in SBA-15. This indicated that the pores in SBA-Pr-NH_2 had not collapsed during the functionalization reaction.

The XRD pattern of SBA-15 showed the (100), (110), and (200) reflections typical of an ordered mesoscopic structured silica [25] which exhibit a two-dimensional hexagonal symmetrical array of nano-channels. SBA-Pr-NH_2 was also characterized by the same pattern, indicating that the grafting of 3-aminopropyltrimethoxysilan did not affect the structural integrity of SBA-15.[26]

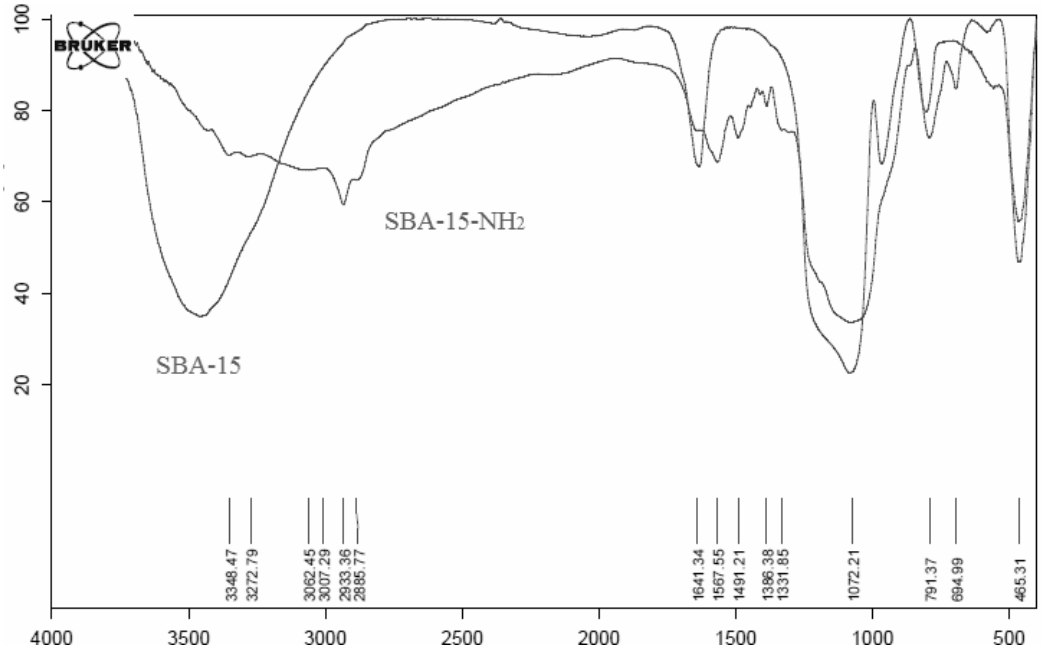


Fig. 1 – FT-IR spectra of SBA-15 and SBA-Pr-NH_2.

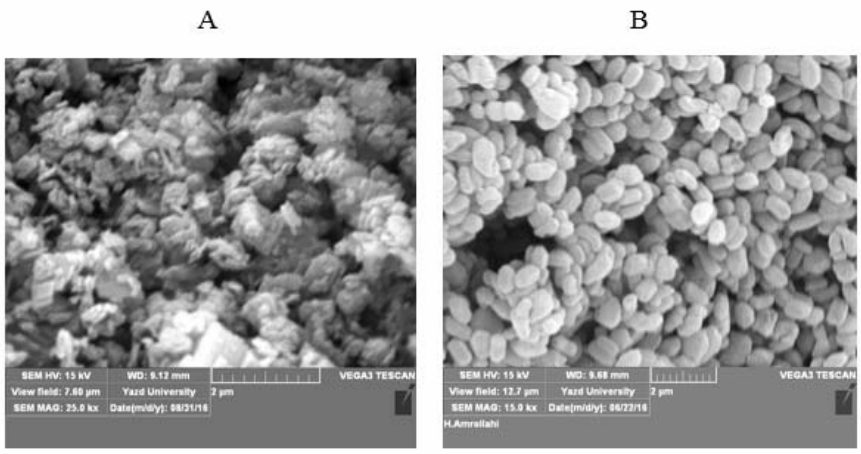


Fig. 2 – SEM images of SBA-15 (A) and SBA-Pr-NH_2 (B).

Catalyst activity

Catalytic activity of SBA-Pr-NH_2 in the synthesis of pyrano[2,3-c]pyrazole was investigated by a one-pot three-component reaction of arylmethlidene malononitrile, ethyl acetoacetate and phenylhydrazine. Initially in order to perform optimization experiments, the reaction of 2-benzylidenemalononitrile (1 mmol), phenylhydrazine (1 mmol) and ethyl acetoacetate (1 mmol) in the presence of SBA-Pr-NH_2 was selected as the model reaction. To investigate the effect of the solvent on the reaction, the model reaction was performed in various solvents and also under solvent-free conditions. The results show that the highest yield in shortest time was achieved under solvent-free conditions. To optimize the amount of the catalyst, the model reaction was carried out in the presence of various amount of the catalyst under solvent-free condition at room temperature for 5 minutes and the results are reported in Table 1. The results show that in terms of time and yield the best amount of the catalyst is 0.05 g (Table 1, Entry 7).

Following the obtained results, the reaction of arylmethlidene maloninitrile, ethyl acetoacetate and phenylhydrazine was carried out in the presence of SBA-Pr-NH_2 under solvent-free conditions and the corresponding pyrano[2,3-c]pyrazoles were obtained in high yields (Table 2, Entries 1-7). The results show that the arylmethlidene malononitriles with both electron-donating and electron-withdrawing substituent have little effect on the reaction times and yields.

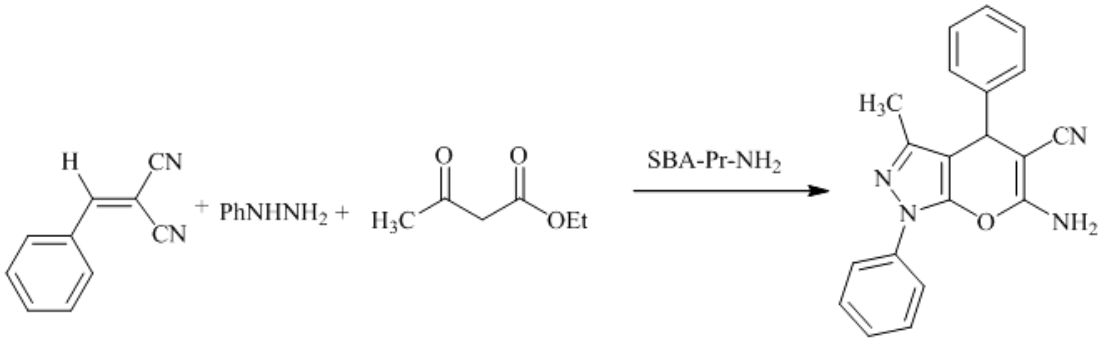
Reuse test of SBA-Pr-NH_2

The reuse of SBA-Pr-NH_2 in the model reaction was investigated. SBA-Pr-NH_2 could be easily recovered through by filtration and washed, then new substrates were added for the next cycle. This procedure was repeated two more times. Results show no changes in reaction times and yields of the products which indicated stability of the catalyst due to the covalent bond of amino group with the surface of SBA-15.

Finally, we compared SBA-Pr-NH_2 with other catalysts recently used in the synthesis of pyrano[2,3-c]pyrazole derivatives. According to the results shown in Table 3, SBA-Pr-NH_2 has better activity in terms of higher yields, shorter times of reaction and reusability of the catalyst.

Table 1

Optimization of the reaction conditions [a)]



Entry	Solvent	SBA-Pr-NH_2(g)	Time(min)	Yield(%) [b)]
1	EtOH	0.02	100	40
2	H_2O	0.02	100	55
3	H_2O:EtOH (1:1)	0.02	100	45
4	MeCN	0.02	100	15
5	Solvent-free	0.02	10	65
6	Solvent-free	0.04	5	85
7	Solvent-free	0.05	5	95
8	Solvent-free	0	100	0
9	Solvent-free	SBA-15 (0.05)	100	0

[a)] Reaction conditions: 2-benzylidenemalononitrile (1 mmol), phenylhydrazine (1 mmol) and ethyl acetoacetate (1 mmol).
[b)] Isolated yields

Table 2

Synthesis of pyrano[2,3-c]pyrazole derivatives in the presence of SBA-Pr-NH_2 [a)]

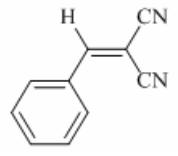
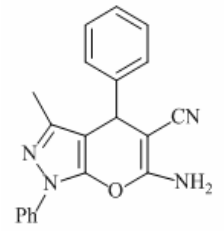
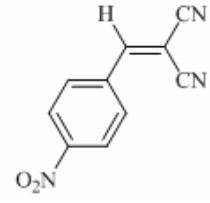
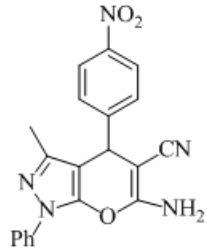
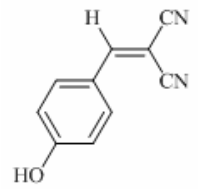
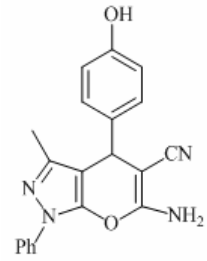
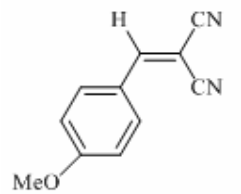
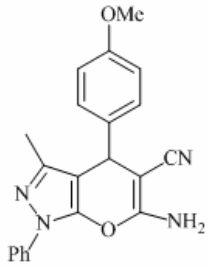
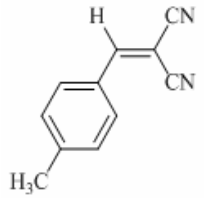
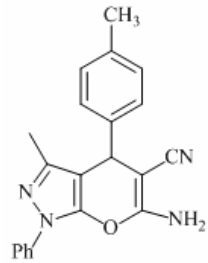
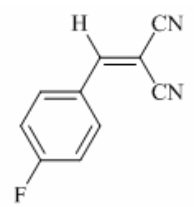
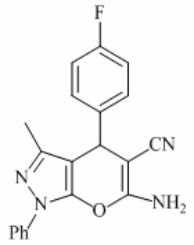
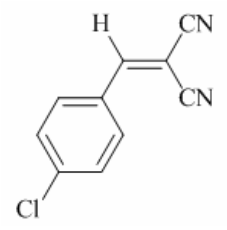
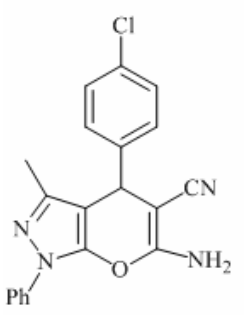
Entry	Arylmethylidene malononitrile	Product	Time (min)	Yield (%)	M.P. (˚C)	Ref.
1			5	95	168-169	[27]
2			5	95	194-196	[27]
3			5	80	211-212	[27]
4			8	85	175-176	[27]
5			5	82	177-178	[27]
6			7	93	166-168	[28]

Table 2 (continued)

7			5	95	173- 174	[27]

[a] Reaction conditions: arylmethlidene malononitrile (1mmol), phenylhydrazine (1 mmol) and ethyl acetoacetate (1mmol), r.t., solvent-free

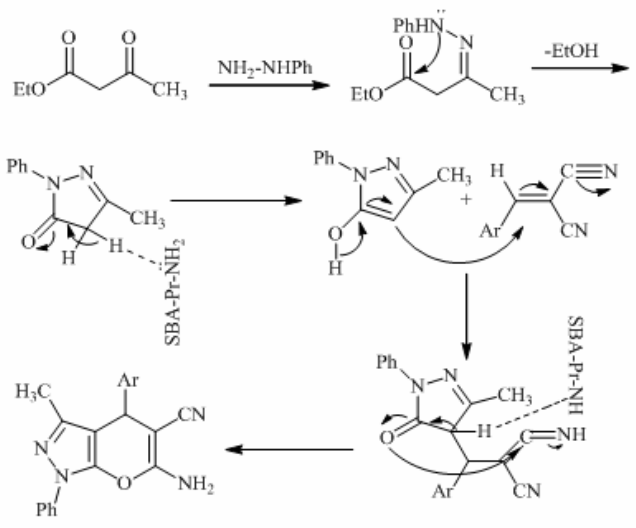
Table 3

Comparison of the efficiency of SBA-Pr-NH_2 with that of the reported catalysts for the synthesis of pyrano[2,3-c]pyrazoles

Entry	Catalyst	Reaction conditions	Time (min)	Yield (%)	Ref.
1	SBA-15-NH_2	Solvent-free, r.t.	5	95	this work
2	PVPy	Solvent-free, 80 °C	18	92	[14]
3	Sodium bezoate	H_2O, r.t.	60	85	[29]
4	Meglumine	H_2O/EtOH, r.t.	15	95	[13]

Mechanistic aspects

A probable mechanism for the reaction has been illustrated in Scheme 1.[29] The synthesis of pyrano[2,3-c]pyrazole derivatives involves an amination, Michael addition, cyclization and isomerization steps respectively. SBA-Pr-NH_2 catalyzed Michael and cyclization reactions by activation of the C-H bond of pyrazolone derivatives (Scheme 1).



Scheme 1 – Reaction pathway for the synthesis of pyrano[2,3-c]pyrazoles.

EXPERIMENTAL

Materials and methods

All reactants and solvents used in this work were purchased from Merck and Aldrich Company and were used without further purification. SBA-15 was purchased from Scientific and Industrial Research Organization of Iran. Progress of the reactions was monitored using Silica gel TLC plates containing active fluorescence with Kiselgel 60 F_{254} detector which also purchased from Merck Company. Synthesized compounds were characterized by ^{1}H- and ^{13}C NMR and FT-IR spectral analysis. ^{1}H– and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker (DRX-400 Avance) 400 MHz spectrometer. Infrared spectra of the catalysts and reaction products were recorded on a Bruker FT-IR Equinax-55 spectrophotometer in KBr with absorption in cm^{-1}. Morphology of the SBA-Pr-NH_2 was investigated with SEM technique.

Preparation of SBA-Pr-NH_2 [26]

SBA-15 (1g) was activated at 200 °C under vacuum for 4 h to remove any surface humidity and subsequently refluxed in dry toluene (30 mL) for 1 h. After this, 3-amino-propyltrimethoxysilan (6 mmol) was slowly added to the reaction mixture and the reaction was refluxed for a further 24 h. The mixture was then filtered and washed with toluene. The residual organosilane was removed by soxhlet extraction in ethanol over a 24 h period. The resulting material was denoted as SBA-Pr-NH_2.

General procedure for preparation of arylmethlidene malononitriles [30]

Mixture of aromatic aldehyde (2 mmol) and malononitrile (2 mmol) in EtOH (5 mL) was stirred for appropriate period of

time at room temperature. After completion of the reaction cold water was added to the mixture and then the precipitated product was filtered and dried. Further purification was achieved by recrystallization in EtOH (Scheme 2).

Typical procedure for the synthesis of pyrano[2,3-c]pyrazoles

Phenylhydrazine (1 mmol) and ethyl acetoacetate (1 mmol) was grinded in a mortar for 2 minutes and then arylmethlidene malononitrile (1 mmol) and SBA-Pr-NH_2 (0.05 g) was added and grinding was continued for 5-8 minutes at room temperature. After completion of the reaction as indicated by TLC ($CHCl_3$:n-hexane, 1:1), in order to separate the catalyst from crude product the mixture was dissolved in EtOH and then filtered. The solvent of resulted filtrate was evaporated and the pure product was obtained by recrystalization from EtOH.

Physical and spectroscopic data of synthesized pyrano[2,3-c]pyrazoles

6-Amino-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (Table 2, Entry 1).
Yield: 95 %, orange crystals, mp 168-169 °C. IR (KBr, cm^{-1}): 3410, 3325, 3106, 2178, 1650, 1596, 1262, 1061. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.87 (s, 3H), 4.37 (s, 1H), 5.17 (br, s, 2H), 7.31-7.40 (m, 5H), 7.62-7.85 (m, 5H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.0, 31.2, 65.9, 104.8, 114.6, 119.9, 125.9, 128.1, 129.8, 130.1, 133.7, 138.5, 142.9, 144.1 149.9, 152.0.

6-Amino-3-methyl-4-(4-nitrophenyl)-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (Table 2, Entry 2).
Yield: 95 %, yellow crystals, mp 194-196 °C. IR (KBr, cm^{-1}): 3441, 3305, 3037, 2201, 1649, 1581, 1146. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.76 (s, 3H), 4.73 (s, 1H), 5.05 (br, s, 2H) 7.42-7.51 (m, 3H), 7.62-7.75 (m, 2H), 7.81 (d, 2H, *J* = 8.2 Hz), 7.87 (d, 2H, *J* = 8.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.5, 37.5, 68.1, 110.8, 119.6, 119.9, 120.9, 129.9, 129.8, 130.1, 133.7, 138.5, 145.9, 149.3, 153.0, 159.4.

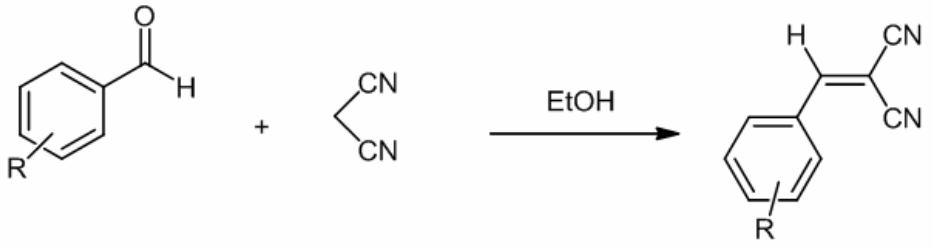
6-Amino-4-(4-hydroxyphenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (Table 2, Entry 3).
Yield: 80 %, yellow crystals, mp 211-212 °C. IR (KBr. cm^{-1}): 3450, 3325, 2204, 1607, 1580, 1293, 1034. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.76 (s, 3H), 4.64 (s, 1H), 6.51 (br, s, 2H) 6.83 (d, 2H, J = 7.8 Hz), 6.91(d, 2H, J = 7.7 Hz), 745-7.56 (m, 2H), 7.78-7.95 (m, 4H), 8.19 (br, s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.6, 33.1, 72.7, 108.2, 113.4, 121.1, 127.8, 129.2, 132.0, 136.6, 138.1, 141.8, 145.3, 148.0, 150.3, 150.9.

6-Amino-4-(4-methoxyphenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (Table 2, Entry 4).
Yield: 85 %, yellow crystals, mp 175-176 °C. IR (KBr, cm^{-1}): 3466, 3350, 3165, 2214, 1620 1590, 1293, 1034. ^{1}H NMR (400 HMz, DMSO-d_6): δ 1.72 (s, 3H), 3.66 (s, 3H), 4.45 (s, 1H), 4.70 (br, s, 2H), 6.83 (d, 2H, *J* = 7.4 Hz), 6.91 (d, 2H, *J* = 7.4 Hz), 7.33-750 (m, 2H), 7.78-7.90 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.6, 35.7, 55.6, 77.7, 102.3, 113.4, 118.1, 121.1, 127.8, 129.2, 132.0, 136.6, 139.5, 140.5, 146.8, 149.3, 151.0.

6-Amino-3-methyl-1-phenyl-4-(p-tolyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (Table 2, Entry 5).
Yield: 82 %, yellow crystals, mp 177-179 °C. IR (KBr, cm^{-1}): 3444, 3320, 2189, 1647, 1588, 1221.
^{1}H NMR (400 MHz, DMSO-d6): δ 1.70 (s, 3H), 2.07 (s, 3H), 4.55 (s, 1H), 4.90 (br, s, 2H). 6.87 (d, 2H, *J* = 7.8 Hz), 7.32-7.41 (m, 3H), 7.48-7.56 (m, 2H), 7.22 (d, 2H, *J* = 7.8 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.8, 35.2, 38.1 69.6, 109.6, 125.1, 118.7, 120.1, 124.7, 127.8, 129.6, 132.8, 136.5, 143.8, 145.1, 149.1, 152.2.

6-Amino-4-(4-fluorophenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (Table 2, Entry 6).
Yield: 93 %, light yellow crystals, mp 166-168 °C. IR (KBr, cm^{-1}): 3465, 3310, 3065, 2215, 1605, 1585, 1230, 1120. ^{1}H NMR (400 MHz, DMSO-d6): δ 1.75 (s, 3H), 4.81 (s, 1H), 4.95 (br, s, 2H), 7.32-7.41 (m, 3H), 7.48-7.56 (m, 2H), 7.88 (d, 2H, *J* = 8.4 Hz), 7.91 (d, 2H, *J* = 8.5 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.0, 37.1, 57.9, 111.5, 118.8, 120.8, 121.1, 128.1, 129.8, 130.4, 133.2, 138.5, 145.6, 149.1, 156.1, 161.1.

6-Amino-4-(4-chlorophenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (Table 2, Entry 7).
Yield: 95 %, white crystals, mp 173-174 °C. IR (KBr, cm^{-1}): 3450, 3340, 3125, 2190, 1625, 1580, 1175, 765. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.75 (s, 3H), 4.71 (s, 1H), 4.95 (br, s, 2H), 7.25-7.31 (m, 3H), 7.46-7.52 (m, 2H), 7.75 (d, 2H, *J* = 8.5 Hz), 7.82 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.4, 34.5, 61.5, 100.8, 115.1, 118.9, 120.9, 127.1, 129.7, 130.1, 133.5, 137.9, 144.8, 146.1, 150.1, 159.2.



R = 4–H, 4–NO_2, 4–OH, 4–MeO, 4–CH_3, 4–F, 4–Cl

Scheme 2 – Synthesis of arylmethlidene malononitriles.

CONCLUSIONS

This paper reports the development of an efficient procedure for the synthesis of pyrano[2,3-c]pyrazoles using SBA-Pr-NH_2 as a catalyst at room temperature under solvent-free conditions. We have established SBA-Pr-NH_2 as an efficient heterogeneous solid basic catalyst that can be easily handled and removed from the reaction mixture by simple filtration. Short reaction times and high product yields under our reaction conditions clearly demonstrate the advantages of using SBA-Pr-NH_2 as a catalyst for this reaction. SBA-Pr-NH_2 can be reused at least 3 times without significant decrease of its catalytic activity.

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