Amberlyst A21: a reusable solid catalyst for green synthesis of pyran annulated heterocycles at room temperature. C R Chim

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Amberlyst A21 Catalyzed Chromatography-Free Method for Multicomponent Synthesis of Dihydropyrano[2,3-*c*]pyrazoles in Ethanol

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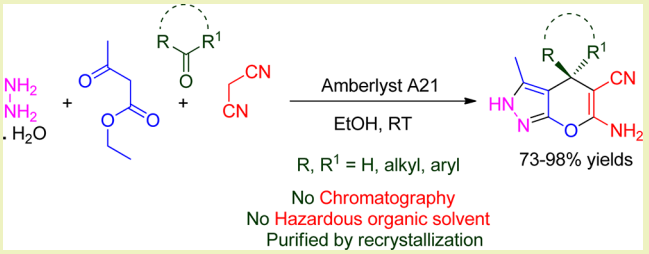
Supporting Information

ABSTRACT: Amberlyst A21 was found to be an extremely efficient catalyst for synthesis of a series of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-carbonitriles by a four-component reaction of a mixture of ethyl acetoacetate, hydrazine hydrate, aldehyde, and malononitrile in ethanol at room temperature. The catalytic efficiency of Amberlyst A21 was compared with some other resin-bound free and anionic bases in order to ascertain the best catalyst for the said conversion. The catalyst was found to work extremely well also for acyclic/cyclic ketones to give corresponding dihydropyrano[2,3-*c*]pyrazoles or their spirocyclic variants. Easy recovery of the catalyst and its reusability, room temperature reaction conditions, short reaction time, excellent yields, no chromatographic purification, and evasion of environmentally hazardous solvents in the entire reaction process may make this protocol very useful for academia and industry.



KEYWORDS: *Dihydropyrano[2,3-c]pyrazole, MCRs, Amberlyst A21, Green synthesis, Spiro compounds*

INTRODUCTION

Development of efficient and practical catalysts for organic transformation to synthesize valuable target compounds is one of the most important research areas in academia and industry.[1,2] Although homogeneous catalysts are finding applications in diverse aspects of synthetic chemistry[3] in recent years, the environmental concerns associated with their toxicity and disposal and catalyst/product separation are limiting their applications in general. Therefore, resin-bound catalysts are becoming increasingly important in organic synthesis, primarily due to their easy removal from reactions by filtration. They offer additional engineering advantages in the form of increased manufacturing flexibility and reduced operating costs. Unlike commonly used acid−base catalysts, resin-bound catalysts offer easy recovery of the catalyst and also enhance safety features for potentially explosive reagents. Therefore, resin-bound catalysts can be used in excess to drive a reaction into completion without introducing any difficulty in purification.

Synthesis of focused libraries for easy access of biologically important scaffolds for their SAR studies have made multicomponent reactions (MCRs) a very useful tool in synthetic organic chemistry as well as in drug discovery programs. Additionally, the emergence of combinatorial synthesis by MCRs has brought about a paradigm shift in synthetic reaction designs that address the issues of atom economy, economy of steps, and environmental safety. If such MCRs can perform in environmentally benign solvents in the presence of reusable resin-bound catalysts at room temperature, it is possible to accomplish the reactions without percolating anything to the environment during the reaction process. Given the huge environmental awareness among the scientific community, designing environmentally compatible protocols devoid of hazardous chemical ingredients to eliminate toxic waste and byproducts is the utmost priority for synthetic chemists. As organic solvents are considered to be the highest contributors toward environmental waste, the use of environmentally compatible solvents such as ethanol or water is gaining considerable significance. As a result, the discovery of novel synthetic methodologies to facilitate the preparation of compound libraries using MCRs without the use of hazardous solvents and reusable catalysts are the pivotal focal points in industry and academia.[4,5]

The dihydropyrano[2,3-*c*]pyrazole compounds are versatile synthetic building blocks and the structural unit of a variety of therapeutic agents. The synthesis of dihydropyrano[2,3-*c*]-pyrazole derivatives is getting tremendous attention among synthetic chemists for their diverse bioactivity profiles,[6−9] which include anticancer, anti-inflammatory, insecticidal, antimicrobial, and analgesic properties and Chk1 kinase[10] inhibitory activity. Most of the synthetic endeavors to synthesize this bioactive core involve the multicomponent reaction of a mixture of aldehyde, malononitrile, ethyl acetoacetate, and hydrazine hydrate in the presence of environmentally noncompatible base catalysts[11−17] at elevated temperature. The use of a base catalyst at elevated temperature for such reactions has the potential to accomplish various side

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reactions such as Aldol condensation and the Cannizzaro reaction to generate unwanted byproducts. Although development of a new base-catalyzed methodology at ambient temperature can reduce the formation of side products, the synthesis of dihydropyrano[2,3-*c*]-pyrazole at room temperature is not finding enough attention yet. Recently, Zhao et al.[18,19] accomplished stereoselective synthesis of dihydropyrano[2,3-*c*]pyrazole in both three- and four-component reaction strategies using a cinchona-derived organocatalyst at room temperature, but the use of environmentally hazardous dichloromethane as a solvent and the nonrecyclability of the catalyst were some of the drawbacks associated with those methods. Major improvement along this direction were reported by Pitchumoni et al.,[20] where they used per-6-amino-β-cyclodextrin in a catalytic amount to achieve dihydropyrano[2,3-*c*]pyrazoles in excellent yield at room temperature. Very recently, Shi et al. also reported the synthesis of pyrano[2,3-*c*]pyrazoles with[21] or without[22] base under ultrasound irradiation at room temperature. However, we have not come across any literature on the use of resin-bound catalysts, which can be an easy yet efficient tool for large-scale industrial synthesis of this highly versatile biologically active core.

Tertiary amine-substituted macroreticular ion exchange polystyrene resins such as Amberlyst, Amberlite, and Dowex have found a lot of applications in recent years because they are widely available at very low cost, carry a variety of functionalities, and have high loading capacities. Amberlyst A21 is finding a lot application for its high catalytic activity[23−26] and selectivity,[27,28] long lifetime, superior resistance to thermal, mechanical, and osmotic shock, excellent stability, and low leaching. In addition, it works with equal efficiency in both aqueous and organic solvents. In continuation of our recent efforts to develop an environmentally benign catalyst system for various chemical transformations,[29−32] we report the synthesis of a range of pharmaceutically important dihydropyrano[2,3-*c*]pyrazoles employing the MCR strategy in the presence of a highly reusable resin-bound catalyst, Amberlyst A21 in ethanolic media. Here, we have successfully demonstrated the synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-carbonitriles by stirring a mixture of ethyl acetoacetate, hydrazine hydrate, aldehyde, and malononitrile in ethanol at room temperature in the presence of a catalytic amount of Amberlyst A21 as a highly reusable base catalyst (Scheme 1).

Scheme 1. Synthesis of Dihydropyrano [2,3-c]pyrazole

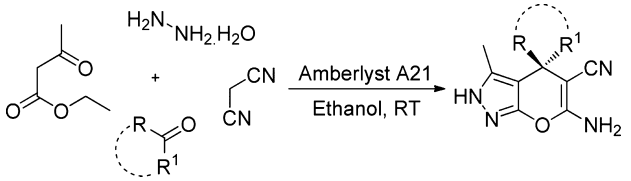
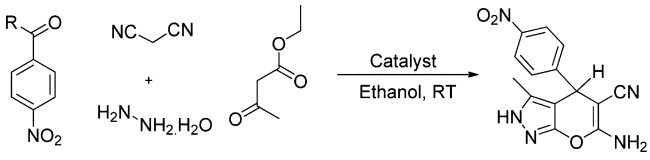


Table 1. Screening of Catalysts[a]



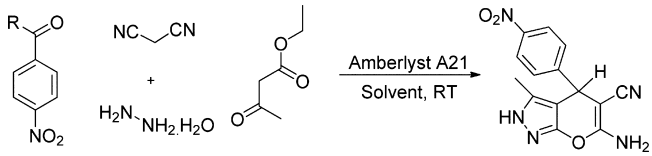
entry	catalyst	isolated yield (%)
1	Amberlyst A21	98
2	Amberlite IRA-67	82
3	Amberlyst A26 OH	55
4	Amberlite IRA-400 OH	60

[a]Reaction conditions: Stoichiometric ratio of all the reactants with base (50 mg/mmol) in ethanol at RT for 20 min.

RESULTS AND DISCUSSION

Initially, ethyl acetoacetate (1 mmol) and hydrazine hydrate (1 equiv) were mixed to observe instantaneous formation of 3-methyl-1*H*-pyrazol-5(4*H*)-one as a white solid. The solid was then dissolved in ethanol (10 mL), and *p*-nitrobenzaldehyde (1 equiv) and malononitrile (1 equiv) were added into it. Then the solution was allowed to stir at room temperature with Amberlyst A21 (50 mg). After 15 min, all the starting materials were found to be consumed to form a single product without any side product. Because the product as well as the Amberlyst A21 is solid, we added warm ethanol to dissolve the product and then filtered to get back the

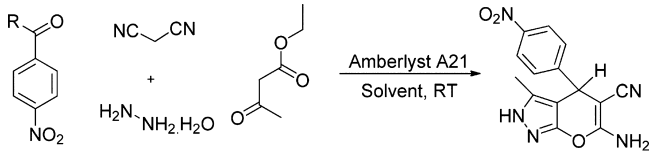
Table 2. Screening of Solvents[a]



entry	solvent	isolated yield (%)
1	no solvent	30
2	dichloromethane	<10
3	chloroform	<10
4	THF	50
5	DMF	40
6	ethanol	98
7	water	20

[a]Reaction conditions: Stoichiometric ratio of all the reactants with base (30 mg/mmol) in ethanol at RT for 10 min.

Table 3. Optimization of Catalyst Loading[a]



entry	catalyst (mg/mmol)	time (min)	isolated yield (%)
1	10	90	57[b]
2	20	20	96
3	30	10	98
4	40	10	97
5	50	10	98

[a]Reaction conditions: Stoichiometric ratio of all the reactants with base in ethanol at RT. [b]Incomplete conversion.

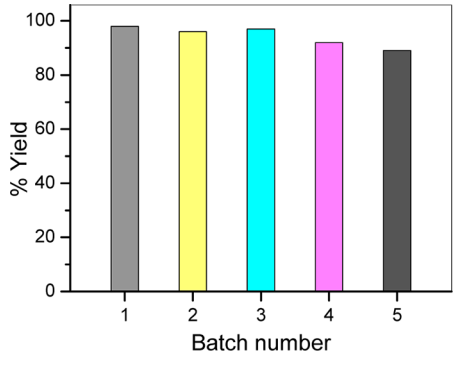


Figure 1. Study of catalyst reusability.

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catalyst, Amberlyst A21. The catalyst was further washed with warm ethanol to achieve it in pure form. The combined ethanolic solution was concentrated under vacuuo, and the super saturated solution was kept in a refrigerator to get the pure crystalline product.

Table 4. Synthesis of Dihydropyrano[2,3-*c*]pyrazole from Aromatic Aldehydes via Scheme 1[a,b]

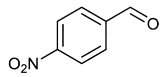
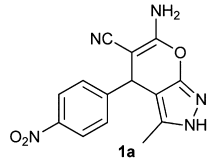
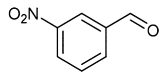
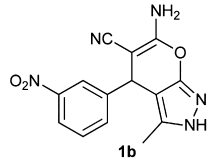
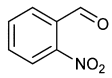
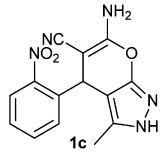
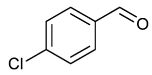
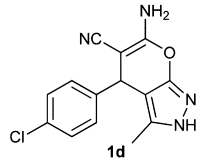
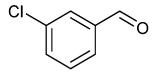
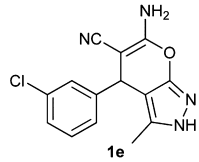
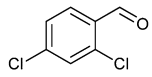
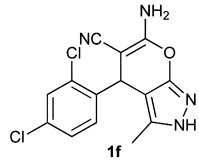
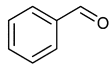
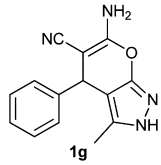
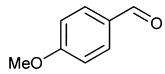
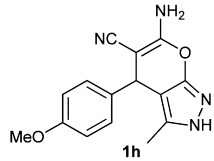
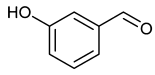
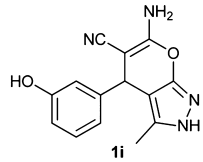
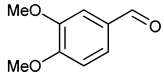
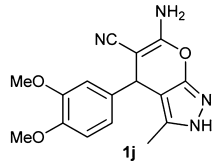
Entry	Aldehyde	Product	Time/min	% Yield[c]	m.p. /°C
1		 1a	10	98	195 -196
2		 1b	10	96	190-192
3		 1c	10	95	222-224
4		 1d	15	98	175-176
5		 1e	15	94	176-177
6		 1f	25	97	209-210
7		 1g	25	90	169 -170
8		 1h	35	94	174 -175
9		 1i	30	92	220-223
10		 1j	60	87	195-196

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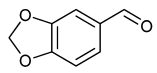
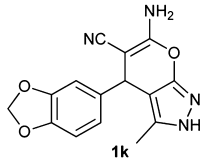
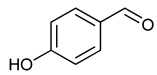
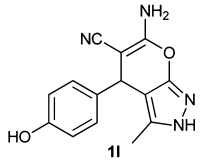
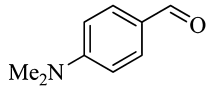
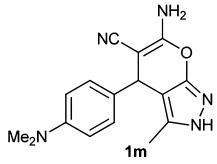
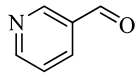
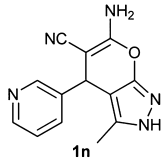
Table 4. continued

Entry	Aldehyde	Product	Time/min	% Yield[c]	m.p. /°C
11		 1k	65	85	204-206
12		 1l	20	87	224-227
13		 1m	50	82	166-168
14		 1n	15	95	214-215

[a]All reactions were carried out at room temperature. [b]Equimolar ratio of all the reactants with 30 mg Amberlyst A21/mmol of aldehyde. [c]Isolated yields.

Having been inspired by the observation, we wanted to explore other resin-bound base catalysts at our disposal, viz. Amberlite IRA-67 (free base), Amberlyst A26 OH, and Amberlite IRA-400 OH, to screen their efficiency for this conversion (Table 1). As Amberlyst A21 and Amberlite IRA-67 are tertiary amines, they were expected to behave like tertiary amine-containing organic bases. When a equimolar mixture of *p*-nitrobenzaldehyde, malononitrile, ethylacetoacetate, and hydrazine hydrate were stirred with Amberlite IRA-67 (50 mg) in ethanol for 20 min, the reaction was almost complete to give an 82% isolated yield of the desired product. However, the strong ion exchange resins such as Amberlyst A21 OH and Amberlite IRA-400 were found to be relatively less efficient. They were found to generate *p*-nitrobenzyl alcohol and *p*-nitrobenzoic acid (probably via the Cannizzaro reaction) besides forming the desired products in 55% and 60% isolated yield, respectively, under identical reaction conditions.

As Amberlyst A21 has unusually high porosity and surface area to expose more ionic groups in a nonaqueous system, we wanted to study the effect of various solvents on catalytic efficiency of the catalyst for the same reaction. The results shown in the Table 2 revealed that the swelling action of the solvent on the anion exchange resin is not the only factor that governs the catalytic efficiency of the catalyst. The solubility of all the reactants has definitely played an important role on the overall efficacy of the system. For example, Amberlyst A21 swells better in chlorofom and methylene chloride than in ethanol, but the reaction gave very poor yield (<10%) of the desired product in those solvents during the same reaction time. As the solubility of hydrazine hydrate in ethanol is much better than chloroform and methylene chloride, the former might have helped to make a homogeneous solution of reactants that resulted in nearly quantitative yield of the desired dihydropyrano[2,3-*c*]pyrazole in the presence of Amberlyst A21. Similarly, catalytic activity of Amberlyst A21 in THF and DMF was found inferior for the said reaction, in spite of being more swelled than in ethanol.

As ethanol is coincidently a better solvent from an environmental perspective, we set out to optimize the amount of Amberlyst A21 required to catalyze the reaction in ethanol (Table 3). It was observed that 30 mg of the catalyst for 1 mmol of aldehyde is sufficient to catalyze the reaction in optimum time. Addition of a higher amount, viz. 40 mg/mmol and 50 mg/mmol, gave similar yield but did not reduce the reaction time appreciably. On the other hand, reduction of the amount of catalyst to 20 mg/mmol of the aldehyde doubled the reaction time. When catalyst loading was further reduced to 10 mg against each mmol of aldehyde, the reaction gave a 57% isolated yield along with 3-methyl-1*H*-pyrazol-5(4*H*)-one and the Knoevenagel product after stirring for 90 min.

Then we studied reusability of the catalyst, i.e., Amberlyst A21, for the same reactants (Figure 1). It was observed that the recovered catalyst works with the same efficiency up to the fourth run, while in the fifth run, it takes almost half an hour to complete the reaction. In the sixth run, the partly broken catalyst beads could not complete the reaction even after 4 h.

Having optimized the reaction parameters, we generalized the applicability of this method for synthesis of a series of dihydropyrano[2,3-*c*]pyrazoles starting from various aromatic and aliphatic aldehydes. In case of aromatic aldehydes, the nature of substituent on the phenyl rings did not have any effect on overall yields of the product (Table 4). The aldehydes having both the electron-donating and electron-withdrawing substituents on the phenyl ring gave excellent yields at room temperature (entries 1−14, Table 4). Likewise, the position (*o*-, *m*-, and *p*-) of the substituent on the phenyl ring did not have any noticeable effect on either the reaction time or the yield (entries 1−5, Table 4). It has also been established that many sensitive functional groups, such as phenolic hydroxy, *N*,*N*- dimethylamino, methoxy, and

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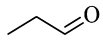
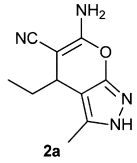
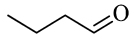
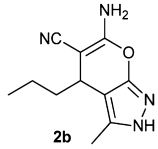
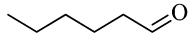
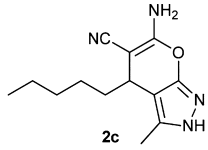
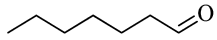
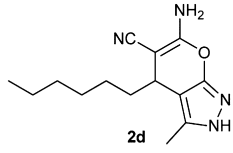
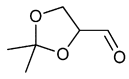
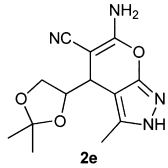
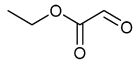
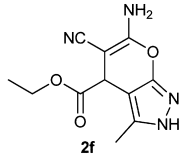
Table 5. Synthesis of Dihydropyrano[2,3-*c*]pyrazole from Aliphatic Aldehydes via Scheme 1[a,b]

Entry	Aldehyde	Product	Time/min	% Yield[c]	m.p./°C
1		 2a	90	73	131-133
2		 2b	120	82	146-148
3		 2c	90	75	150-153
4		 2d	90	79	153-154
5		 2e	30	85	190-192
6		 2f	25	90	187-189

[a]All reactions were carried out at room temperature. [b]Equimolar ratio of all the reactants with 30 mg Amberlyst A21/mmol of aldehyde. [c]Isolated yields.

methylenedioxy are very much compatible to our reaction conditions, as evidenced from their exceedingly good yields.

It is worthwhile to mention that many reported procedures did not give good yield for aliphatic aldehydes. Upon thorough scrutiny, we observed that the formation of Knoevenagel products from the reaction of aliphatic aldehydes with malononitrile were very sluggish at room temperature. When the temperature was increased, the formation of aldol products of aliphatic aldehyde was observed in addition to the desired Knoevenagel product. The poor yield of dihydropyrano[2,3-*c*]pyrazoles in the case of aliphatic aldehydes might be attributed to the formation of unwanted aldol products at elevated temperature. However, the reaction worked extremely well for the aliphatic aldehydes under our reaction conditions (Table 5). Best results were achieved when the aldehyde and malononitrile were added after formation of 3-methyl-1*H*-pyrazol-5(4*H*)-one from the reaction of ethyl acetoacetate and hydrazine hydrate and the catalyst, i.e., Amberlyst A21 was added at the end.

In spite of having a considerable number of methods to synthesize dihydropyrano[2,3-*c*]pyrazoles from aldehyde, studies on synthesis of the similar heterocyclic core using ketone is finding scant attention[20] partly due to the low reactivity of ketones toward condensation with malononitrile to form the Knoevenagel product. To test the efficacy of our method for the said synthesis, condensation of acetophenone, malononitrile, ethyl acetoacetate, and hydrazine hydrate were carried out under similar reaction conditions. We were excited to see the formation of the desired product (entry 1, Table 6) in very good yields at room temperature, albeit in longer time duration. When the methodology was tested for other ketones having electron-donating (entries 2−3, Table 6) and electron-withdrawing (entries 4−5, Table 6) substituents, reaction times for complete conversion were found to be substantially lower in the later cases. Irrespective of substituent patterns in the phenyl ring, all the ketones gave very good yield. Even aliphatic ketone (entry 6) without having any additional field effect worked under our reaction conditions to generate the corresponding dihydropyrano[2,3-*c*]pyrazoles in very good yield. Having been inspired by these observations, we set out to study the same reaction for cyclic ketones (entries 7−9, Table 6) to generate spiro-substituted dihydropyrano[2,3-*c*]pyrazoles. As a matter of fact, many naturally occurring spiro compounds are characterized by their highly pronounced biological properties.[33,34] Because of their interesting conformational features, spiro compounds fused at a carbon carry important structural implications on biological systems.[35] Recently, spiro-substituted nitrogen-containing heterocycles have found applications in the treatment of certain pathologies of the central nervous system,[36,37] rheumatoid arthritis, atherosclerosis,[38] and type II diabetes mellitus.[39] In our bid

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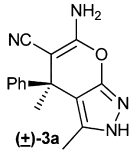
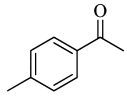
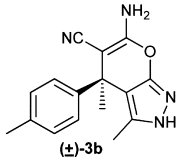
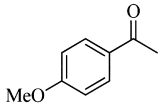
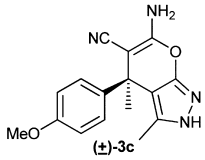
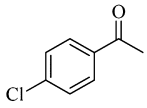
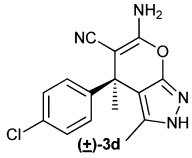
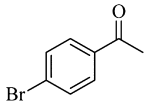
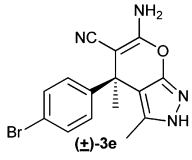
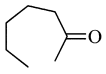
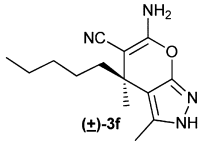
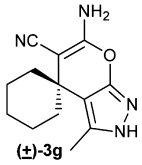
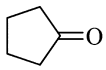
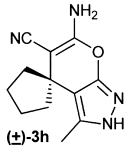
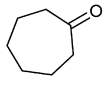
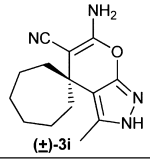
Table 6. Synthesis of Dihydropyrano[2,3-*c*]pyrazole from Ketones via Scheme 1[a,b]

Entry	Ketone	Product	Time/h	% Yield[c]	m.p./°C
1		 (±)-3a	8	85	177-178
2		 (±)-3b	8	84	183-184
3		 (±)-3c	8	82	194-195
4		 (±)-3d	5	90	181-182
5		 (±)-3e	5	88	178-179
6		 (±)-3f	12	78	135-137
7		 (±)-3g	12	85	147-148
8		 (±)-3h	10	90	164-165
9		 (±)-3i	12	77	145-146

[a]All reactions were carried out at room temperature. [b]Equimolar ratio of all the reactants with 30 mg Amberlyst A21/mmol of aldehyde. [c]Isolated yields.

to synthesize spiro-substituted dihydropyrano[2,3-*c*]pyrazole using our protocol, we found that all cyclic ketones took an almost similar time (12 h) for complete conversion of the starting materials and to generate their spiro-substituted dihydropyrano[2,3-*c*]pyrazole counterparts in good yields.

As for the mechanism, the 3-methyl-1*H*-pyrazol-5(4*H*)-one, **1**, resulted from the condensation of ethyl acetoacetate and hydrazine hydrate reacted with Amberlyst A21 to form the enolate **4**, which undergoes a Michael type addition with the Knoevenagel product, **3**. The intermediate, **5**, generated from condensation of **3** and **4** might have undergone intramolecular cyclization to generate the dihydropyrano[2,3-*c*]pyrazole derivatives, **6** (Scheme 2).

In summary, we have developed a completely green method for the synthesis of a diverse range of pyran annulated heterocyclic systems using Amberlyst A21 as a reusable catalyst. No chromatography, no hazardous organic solvents, no elevated

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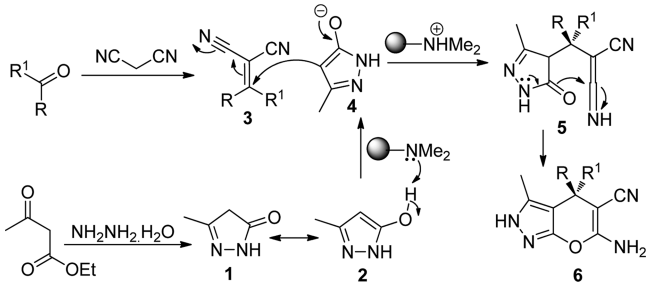
Scheme 2. Probable Mechanism of the Role of Amberlyst A21



temperature, and very good to excellent yield of the products are some of the major achievements of this reaction protocol, which has potential to be extremely useful for synthetic applications. The method was found to be useful for synthesis of ketone-derived dihydropyrano[2,3-*c*]pyrazoles, including spiro-substituted dihydropyrano[2,3-*c*]pyrazoles.

■ ASSOCIATED CONTENT

Supporting Information

General method, experimental procedure, spectral data of new compounds, and copies of ^{1}H and ^{13}CNMR spectra of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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