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RESEARCH LETTER

Greener and facile aqueous synthesis of pyrazoles using Amberlyst-70 as a recyclable catalyst

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An environmentally benign, room temperature aqueous synthesis of pyrazoles by the condensation of hydrazines/ hydrazides with 1,3-diketones using Amberlyst-70 as a recyclable catalyst is described. The use of resinous, non-toxic, thermally stable and inexpensive Amberlyst-70 as a heterogeneous catalyst and simple reaction workup are the additional eco-friendly attributes of this synthetic protocol.

Keywords: pyrazoles; Amberlyst-70; aqueous synthesis; green synthesis; heterogeneous catalysis

Introduction

It has been proved that corrosive mineral acids are not environmentally friendly. They are not safe to handle and easy to dispose. This is the reason why safer and eco-friendly alternative solid acid catalysts like acidic zeolites, clays, sulfated zirconia and ion exchange resins are being developed for their applications in catalysis (*1*). There are various advantages for using these solid catalysts instead of a liquid catalyst. These advantages include reduced equipment corrosion, easy experimental and product isolation procedures, less contamination in waste streams and recyclability (*2, 3*). Recent decades have witnessed an exponential growth in the application of heterogeneous catalysis to carry out chemical transformations as a consequence of its significance in terms of environmental, economical and practical aspects (*4, 5*). Polystyrene sulfonic acid (PSSA) resin catalysts like Amberlyst-15, Amberlyst-70, Nafion, etc., are adding to the ever-growing portfolio of highly active solid acid catalysts. They have been used commercially as solid acid catalysts for hydration and etherification of olefins, dehydration of alcohol, alkylation of phenol, hydrolysis of ester and other acid catalyzed reactions (*1, 6–9*).

Among the many five-membered heterocycles, considerable interest has been focused on the pyrazole nucleus, which is known to possess a broad spectrum of biological properties such as hypoglycemic, cytotoxic, anti-malarial and antidepressant activities (*10–14*). Pyrazoles also possess important properties such as antitumor (*15*), cyclin-dependent kinase inhibitors (*16*), monoamine oxidase-B inhibitors and as atypical antipsychotic (*17*). In addition to these, pyrazole nucleus is a core structure of numerous biologically active compounds and highly popular drugs like Celebrex (*18*) and Viagra (*19*).

Synthetically pyrazole derivatives can be obtained by the action of hydrazine/hydrazides on 1,3-dicarbonyls (*20, 21*). Other synthetic routes that do not involve 1,3-dicarbonyls have also been developed (*22–27*). A few efficient routes have been reported. However, most of these utilize circuitous route, require longer reaction time and are often carried out in organic solvents (*28, 29*). Use of toxic organic solvents, expensive catalysts, harsh reaction conditions and disposal of catalyst/ reaction waste leaves scope for further development of new environmentally clean syntheses. Water as a solvent, is inexpensive, environmentally benign and often give better yields with completely new reactivity (*30, 31*). Non-toxic, non-corrosive and non-flammable nature and relatively high vapor pressure as compared to organic solvents are favorable individuality to render water as a sustainable alternative (*32, 33*).

Many researchers have explored the utility of various heterogeneous catalysts such as Nafion (NR-50), Scolecite, Montmorillonite K-10, etc., for different chemical transformations (*34–37*). Despite of having high thermal stability over other ion exchange resin catalysts, Amberlyst-70 is still under-explored for the synthesis of heterocycles. Furthermore, relatively few reports have been published on the use of heterogeneous catalyst for the synthesis of pyrazoles (*38–41*). Recently, Polshettiwar and Varma evaluated the catalytic efficiency of PSSA in the synthesis of pyrazoles (*21*). Moreover, the same group reported the use of nano-organocatalyst for the synthesis of

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pyrazoles (*42*). We have recently reported the utility of Amberlyst-70 for aqueous Biginelli reaction (*43*). In our quest for greener synthetic pathway, we herein report, the use of Amberlyst-70 as a recyclable catalyst for a simple, facile and environmentally benign aqueous synthesis of pyrazoles. This is the first report on the use of Amberlyst-70 for the synthesis of pyrazoles.
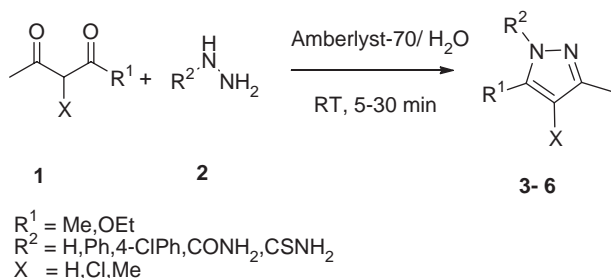
Results and discussion

Pyrazoles were synthesized in aqueous medium by the action of hydrazines/hydrazides on 1,3-dicarbonyls using Amberlyst-70 as a solid heterogeneous catalyst at room temperature (Scheme 1).

During initial exploratory reaction, condensation of acetylacetone and phenyl hydrazine was investigated to establish the feasibility of our strategy and to optimize reaction conditions using various solid acid catalyst like zeolites (H-Y, H-ZSM5, H-beta), Nafion resin (SAC-13) and Amberlyst-70. Figure 1 represents the effect of different catalysts on the condensation of acetylacetone and phenylhydrazine to pyrazole. The catalyst Amberlyst-70 gave an exclusively 94% selectivity for pyrazole at 94% conversion of acetylacetone within 15 minute of reaction time. Completion of reaction was monitored by thin layer chromatography (TLC) and the further quantitative analysis was done by gas chromatography (GC). The yield and the rate of reaction were superior in the case of Amberlyst-70 as compared to that of other catalysts.

The zeolites gave lower yield for pyrazole in comparison with Amberlyst-70. For zeolites, we have got the selectivity for pyrazole in the range of 25–30%. In the case of Nafion resin (SAC-13), yield was around 80%. This yield was lower than that obtained with Amberlyst-70.

We also studied the recyclability of Amberlyst-70 for the reaction of acetylacetone with phenyl hydrazine for five cycles (Figure 2). During filtration of the reaction mixture, the catalyst was easily separated, washed with ether, dried at 60 °C for 4 hr and used for recycle study. Each time, the used catalyst gave 2–3% lower yield than the previous one.
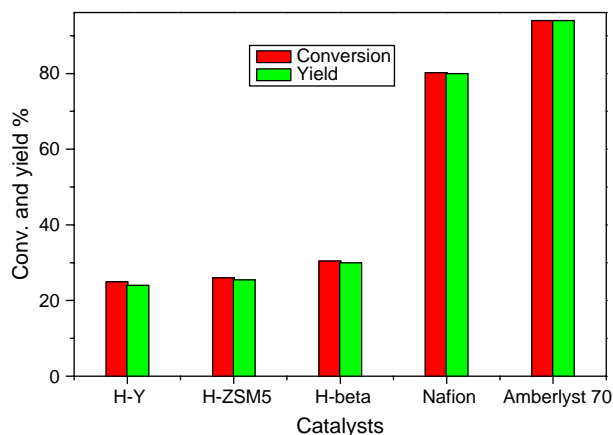

Figure 1. The effect of different catalyst on the condensation of acetylacetone and phenylhydrazine.

With the above optimized reaction condition, pyrazole synthesis using Amberlyst-70 in aqueous medium was probed for the synthesis of a wide variety of substituted pyrazoles (Table 1).

All aforementioned reactions (Table 1) proceeded expeditiously at room temperature and delivered good yields with range of 1,3-dicarbonyl compounds. In all the cases the pure product was isolated by simple filtration or extraction without use of any chromatography or cumbersome reaction workup. The recrystallization of solid products afforded pure compounds. The described protocol eliminates the use of organic solvent except for the extraction and recrystallization. It is noteworthy to mention that these reactions are working well in aqueous medium without using any phase transfer catalyst.

General procedure for the synthesis of pyrazoles

1,3-Dicarbonyl compound (1 mmol), hydrazine/ hydrazide (1.1 mmol) and catalytic amount of

Scheme 1. Amberlyst-70 catalysed synthesis of pyrazoles.

R^1 = Me, OEt
R^2 = H, Ph, 4-ClPh, CONH$_2$, CSNH$_2$
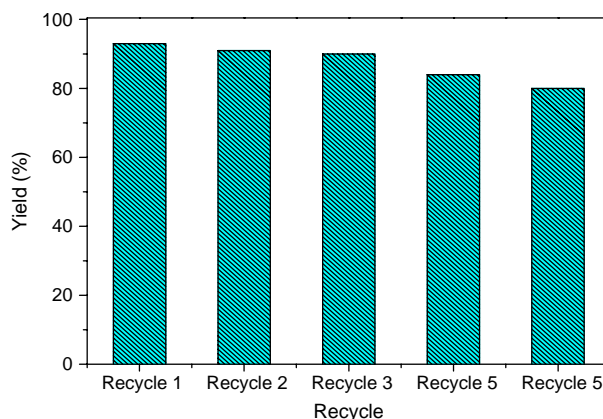X = H, Cl, Me

Figure 2. Recycle study of Amberlyst-70 for the reaction of acetylacetone with phenyl hydrazine.

Table 1. Amberlyst-70 catalyzed synthesis of pyrazoles at room temperature in aqueous medium.

Entry	R^1	X	R^2	Product	Yield[a] (%)
1	CH$_3$	H	Ph	3a	94
2	CH$_3$	H	H	3b	89
3	CH$_3$	H	4Cl-Ph	3c	97
4	CH$_3$	H	NH$_2$CO	3d	96
5	CH$_3$	H	NH$_2$CS	3e	97
6	OEt	CH$_3$	Ph	4a	85
7	OEt	CH$_3$	H	4b	91
8	OEt	CH$_3$	4Cl-Ph	4c	80
9	OEt	CH$_3$	NH$_2$CO	4d	94
10	OEt	CH$_3$	NH$_2$CS	4e	89
11	OEt	Cl	Ph	5a	97
12	OEt	Cl	H	5b	93
13	OEt	Cl	4Cl-Ph	5c	98
14	OEt	Cl	NH$_2$CO	5d	85
15	OEt	Cl	NH$_2$CS	5e	91
16	OEt	H	Ph	6a	80
17	OEt	H	H	6b	88
18	OEt	H	4Cl-Ph	6c	95
19	OEt	H	NH$_2$CO	6d	86
20	OEt	H	NH$_2$CS	6e	94

[a]Isolated yields.

Amberlyst-70 (0.050 g) were suspended in water (15 mL). The reaction mixture was stirred at 30 °C for 5–30 minute. The completion of the reaction was monitored by TLC. The reaction mixture was analysed for its contents by GC (Agilent, 6090N) equipped with flame ionization detector (FID) and capillary column (HP-5). Confirmation of the product has been done from GC-mass spectroscopy analysis and comparing with the retention times of the authentic samples. After confirmation, the reaction mixture was filtered, washed with excess of water. The product obtained was extracted with ethanol (the catalyst being separated at the same time) to afford almost pure pyrazoles in excellent yield.

Conclusion

Thus, we have demonstrated an elegant protocol for the synthesis of substituted pyrazoles using Amberlyst-70, which proceeds efficiently at room temperature in aqueous medium without use of any organic solvent. The adopted procedure is simple, rapid and eco-friendly due to the easy experimental and product isolation procedures; hence, it is a useful addition to the existing methods. The use of resinous, non-toxic, thermally stable and inexpensive Amberlyst-70 as a heterogeneous catalyst, simple

reaction workup are the additional eco-friendly attributes of this synthetic protocol.

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