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One-pot three-component synthesis of dialkyl 3-(alkylamino)-1-aryl-1*H*-pyrazole-4,5-dicarboxylates using α-Fe_2O_3 nanoparticles and phenylisocyanate in solvent-free conditions

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Abstract

A simple and efficient synthesis of dialkyl 3-(alkylamino)-1-aryl-1*H*-pyrazole-4,5-dicarboxylates was described in this work *via* a three component reaction between arylhydrazine, alkylisocyanide and dialkylacetylenedicarboxylates in the presence of phenylisocyanate and α-Fe_2O_3 nanoparticles. Eco friendly, solvent-free conditions, excellent yields, and short reaction times, inexpensive and readily available catalysts were the main advantages of this method.In this work, phenylisocyanateand α-Fe_2O_3 nanoparticles were used as a potent mixed catalyst for promoting the reaction and taking it in a special way to obtain the titled compounds in good to excellent yields. This reaction was not carried out without any of the components of this mixed catalyst. It means that, for performance of this reaction, both of the mixed catalyst components are required.

Keywords: Pyrazole; α-Fe_2O_3; phenylisocyanate; nanocatalyst; solvent-free.

Introduction

Multicomponent reaction (MCR) is a chemical process through which three or more compounds reacts to produce a single product. By definition, MCRs are those reactions whereby more than two reactants

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combine in a sequential manner to form highly selective products that retain majority of the atoms of the starting material. Recently, multicomponent formats involving condensation of three or more reactants either in tandem or in single step have become an integral section of drug discovery plan [1-20]. Pyrazoles are one of the most interesting heterocyclic organic compounds that possess chemical and pharmacological interest such asantihyperglycemic, hypoglycemic, antibacterial, analgesic, anti-inflammatory, antipyretic and sedative-hypnotic activities [21-26]. They are also found in many natural products and synthetic intermediates [27]. Recently, some 5-aminopyrazoles have been reported as cyclin dependent kinase and glycogen synthase kinase inhibitors [28]. Fipronil is a new 5-aminopyrazole with high insecticide activity [29].

Magnetic nanoparticles (MNPs) such as α-Fe_2O_3 could catalyze organic reactions in a mild and environment friendly manner. The use of minimum of reagent and energy, high yield of products, easy reaction, simple work-up procedure and the minimize byproduct are the main advantages of this catalyst [30,31]. Over the last decades, there have been reported numerous articles on organic synthesis using MNPs because of its low cost and efficiency [32-36]. The *α*-Fe_2O_3 magnetic nanoparticles were synthesized *via* Pechini sol-gel method using citric acid and polyethylene glycol-6000 as chelating agents [37].To confirm nano*α*-$Fe_2O_3$the FT-IR srectrum, XRD pattern and SEM image of nano*α*-Fe_2O_3 were carried out in Figure 1.

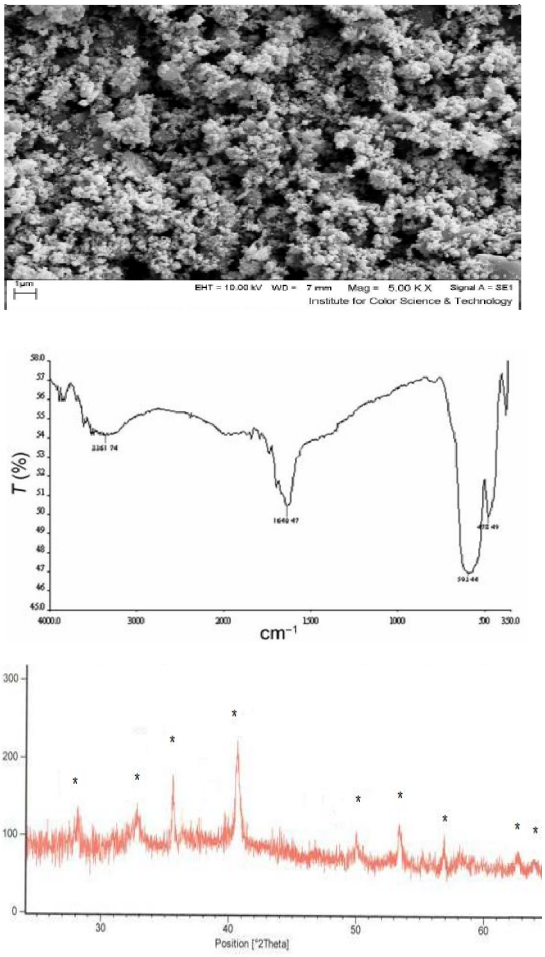
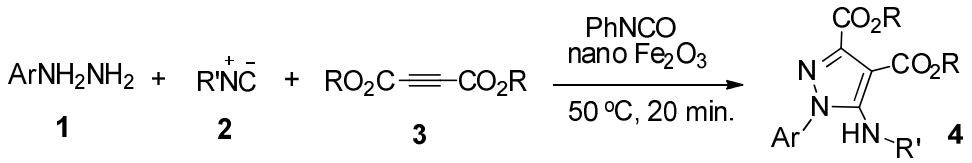


Figure 1. SEM image (A), FT-IR (B) andXRD pattern (C) of nano*α*-Fe_2O_3, the average particle size was 75 nm

As part of our studies on the development of efficient and straightforward methods to prepare organic compounds from readily available building blocks and also simple organic catalyst [4, 38-43], herein we

report a simple and efficient method for the synthesis of highly substituted pyrazoles by three simple component reactions of arylhydrazine, alkylisocyanide and arylaldehydes using an efficient mixed catalyst of phenylisocyanate and α-Fe_2O_3 nanoparticles under solvent-free conditions to afford the titled compound 3 in good to excellent yields (Scheme 1, Table 1).



Scheme 1. Synthesis of dialkyl 3-(alkylamino)-1-aryl-1*H*-pyrazole-4,5-dicarboxylates using PhNCO and nanoα-Fe_2O_3

Experimental

General materials and devices

All starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. *α*-Fe_2O_3 magnetic nanoparticles were synthesized *via* Pechini sol-gel method using citric acid and polyethylene glycol-6000 as chelating agents and then calcinating at 600 ^oC[37]. The progress of the reaction was monitored by TLC. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. ^1H NMRand^{13}C NMR spectra ($CDCl_3$) were recorded on a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz respectively. Elemental analyses for C, H and N were performed using a CHN-O-Rapid analyzerand the instrument model was Eager 300 for EA11112. Chromatography columns were prepared from Merck silica gel 60 mesh.

General procedure for the preparation of 4a-h

The reaction was carried out by first mixing thephenylhydrazine **1** (1 mmol, 0.107 g), cyclohexylisocyanide **2** (1mmol, 0.109 g) and phenylisocyanate (1 mmol, 0.119 g) in the presence of α-Fe_2O_3 nanoparticles (0.12 mmol, 0.019 g), adding dimethylacetylenedicaboxylate **3** (1mmol, 0.144 g) to the reaction mixture and then heating at 50^oC for 20 minutes under solvent free condition. Reaction monitoring by TLC clearly indicated formation of the corresponding dimethyl 5-(cyclohexylamino)-1-phenyl-1*H*-pyrazole-3,4-dicarboxylate **4a**. Upon completion, the reaction mixture was cooled to room temperature andα-Fe_2O_3 nanoparticles were

separated by dissolvingthe reaction mixture in dichloromethane (CH_2Cl_2) and then it was centrifuged. After that the product was separated by column chromatography using *n*-hexane: EtOAc, 6:1 as eluent. The solvent was removed and the product was recrystallized from 1:1 n-hexane-EtOAc. The isolated yield was 85 % (Table 1). ^{1}HNMR and ^{13}C NMR analysis of the pure product confirmed the structure of the product **4a**.

The structures of the isolated products **4a-h** were confirmed by their melting points values and their high-field ^{1}H and ^{13}C NMR spectral data [38].

Characterization data of some of the compounds

Dimethyl 5-(cyclohexylamino)-1-phenyl-1*H*-pyrazole-3,4-dicarboxylate4a:^{1}H NMR(500.1 MHz, $CDCl_3$): δ = 1.29 (m, 3 H, 3 CH), 1.39 (m, 2 H, 2 CH), 1.61 (m, 1 H, CH), 1.74 (m, 2 H, 2 CH), 2.10 (m, 2 H, 2 CH), 3.64 (m, 1 H, CH), 3.81 and 3.83 (2s, 6 H, 2 OCH_3), 5.44 (d, *J* = 7.6 Hz, 1H, NH), 7.33 (t, *J* = 7.3 Hz, *J* = 7.2 Hz, 1 H, CH), 7.41 (t, *J* = 7.4 Hz, *J* = 7.7 Hz, 2 H, 2 CH), 7.47 (d, *J* = 7.7 Hz, 2H, 2 CH).^{13}C NMR(125.8 MHz, $CDCl_3$): δ = 24.74, 25.87 and 33.22 (3 CH_2), 51.23 (NCH), 51.37 and 53.08 (2 CH_3), 99.32 (C=CNN), 123.23, 127.97 and 129.15 (3 CH), 135.95 (C=N), 139.24 (=CNN), 156.34 (CH), 161.89 and 163.98 (2 C=O).

Dimethyl 5-(*tert*-butylamino)-1-phenyl-1*H*-pyrazole-3,4-dicarboxylate4e: ^{1}H NMR (500.1 MHz, $CDCl_3$): *δ* 1.46 [9 H, s, $C(CH_3)_3$], 3.81 and 3.86 (6 H, 2 s, 2 OCH_3), 5.63 (1 H, br. s, NH), 7.33 (1 H, t, *J* = 7.5 Hz, CH), 7.42 (2 H, dd, *J* = 8.2 Hz and *J* = 7.5 Hz, 2 CH), 7.49 (2 H, d, *J* = 8.2 Hz, 2 CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): *δ* 29.06 [$C(CH_3)_3$], 51.37 [$NC(CH_3)_3$], 51.42 and 53.17 (2 OCH_3), 100.25 (C), 122.76, 127.71 and 129.14 (3 CH), 135.25, 139.41 and 155.73 (3 C), 162.34 and 164.18 (2 C=O).IR (KBr) (ν_{max}/cm^{-1}): 3423 (NH), 1745 and 1697 (C=O), 1597, 1557, 1543, 1510, 1483, 1443, 1420, 1391, 1364, 1271, 1221, 1132, 1094, 1072, 1047, 941, 791, 758, 692. EI-MS, *m/z* (%): 331 (M^+, 18), 316 (56), 300 (6), 284 (100), 275 (7), 252 (8), 243 (17), 214 (4), 185 (4), 143 (6), 77 (28), 57 (8), 41 (8). Anal. Calcd for $C_{17}H_{21}N_3O_4$ (331.37): C, 61.62; H, 6.39; N, 12.68%. Found: C, 61.6; H, 6.5; N, 12.6%.

Table 1. Synthesis of dialkyl 3-(alkylamino)-1-aryl-1H-pyrazole-4,5-dicarboxylates 4a-h using PhNCO and nano α-Fe_2O_3 **4a-h**

4	Ar	R	R'	Yield[a]/ %
a	Ph	Me	Cyclohexyl	85
b	Ph	Et	Cyclohexyl	82
c	Tolyle	Me	Cyclohexyl	86
d	Tolyle	Et	Cyclohexyl	80
e	Ph	Me	t-Bu	89
f	Ph	Et	t-Bu	88
g	Ph	Me	1,1,3,3-TMB[b]	78
h	Ph	Et	1,1,3,3-TMB	75

[a] Isolated yields
[b] 1,1,3,3-tetramethylbutyl

Results and discussion

Arylhydrazine, alkylisocyanide and dialkylacetylenedicarboxylates, in the presence of phenylisocyanate and α-Fe_2O_3 nanoparticles, produced dialkyl 3-(alkylamino)-1-aryl-1*H*-pyrazole-4,5-dicarboxylates **4a-h** in 75-89% yields (Table 1). This reaction was carried out as a three-component reaction under solvent-free conditions by simultaneously using of a protective agent (PhNCO) and nanoα-Fe_2O_3 as catalyst.

To optimize this reaction, the **4a** preparation was selected as a model, then the effects of nano α-Fe_2O_3 and phenylisocyanate amounts and also the effects of the other Lewis acidssuch as ZnO and γ-MnO_2 nanoparticles to the reaction yields were tested. Finally, the reaction temperature was optimized. The results of these experiments were displayed in the Tables 2, 3 and 4. All of these tests were done in solvent-free condition. Optimal quantity of nano α-Fe_2O_3 was examined by carrying the reaction out in the presence of the optimum quantity of phenylisocyanate and vice versa. The effect of temperature to the reaction yields was tested and indicated in table 4. As can be seen from Table 4, at low and high temperatures, the reaction yields were low and it may be because of low reaction rate and being incomplete at low temperatures and formation of the other byproducts at high temperatures. According to the Tables 2, 3 and 4, the highest yield was obtained in the presence of 12 mol % of nano α-Fe_2O_3 and 100 mol % of PhNCO at 50 ^oC (Table 2, 3 and 4). However, arylhydrazines are very strong and reactive nucleophiles that are able to react with dialkylacetylenedicarboxylates to afford corresponding alkyl 5-hydroxy-1-aryl-1*H*-pyrazole-3-carboxylates [44].

Table 2. Synthesis of **4a** in the presence of various amounts of α-Fe_2O_3 nanoparticles

Entry	ZnO/mol %	γ-MnO_2/mol %	α-Fe_2O_3/mol %	Yeild[a]/ %
1	0	0	2	15
2	0	0	4	28
3	0	0	6	45
4	0	0	8	67
5	0	0	10	80
6	0	0	12	85
7	0	0	14	85
8	0	0	12[b]	35
9	0	0	0	8
10	12	0	0	65
11	0	12	0	55

[a]Isolated yields
[b]Commercial Fe_2O_3

Table 3. Synthesis of **4a** in the presence of α-Fe_2O_3 nanoparticles (0.12 mol %) and various amounts of PhNCO at 50 °C

Entry	PhNCO/mol %	Yeild[a]/ %
1	0	0
2	20	8
3	40	15
4	60	17
5	80	22
6	100	85
7	120	83
8	140	75

[a]Isolated yields

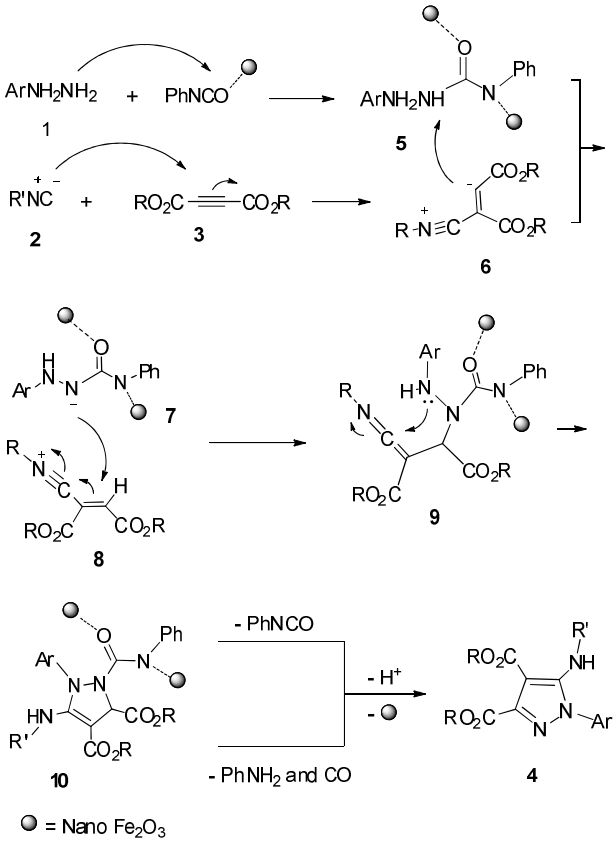
In this reaction, phenylisocyanate was used as a protective agent to reduce nucleuphilic effect of arylhydrazine and increase N-H acidity due to the resonance of non-shared electron pairs of terminal Nitrogen atom with the adjacent carbonyl group. Because of these reasons, phenylhydrazine plays a different role as a protective agent in this reaction.

Table 4. Synthesis of **4a** at various temperaturesin the presence of α-Fe_2O_3 nanoparticles (0.12 mol %) and PhNCO (100 mol %)

Entry	Temperature/ °C	Yeild[a]/ %
1	25	68
2	35	75
3	45	79
4	50	85
5	55	80
6	65	77
7	75	62
8	85	55
9	95	34
10	120	30

[a]Isolated yields.

Mechanistically, it is reasonable to assume that the first step may involve nucleuphilic addition of arylhydrazine **1** to nano catalyst activated phenylisocyanate to form nano catalyst linked hydrazinecarboxamide **5**. Michael additions of alkylisocyanide **2** to the acetylenic ester **3** leads to 1:1 zwitterionic adduct **6**. Protonation of adduct6 by hydrazinecarboxamide5 and thenaddition of conjugate base **7** to positively charged ion **8** gives ketenimine intermediate **9**. Intramolecular cyclization ofketenimine intermediate **9** forms 2,3-dihydro-1*H*-pyrazole-3,4-diwcarboxylate **10**. Elimination of a proton, nanoα-Fe_2O_3, CO, $PhNH_2$and PhNCO[45] gives the final product **4** (Scheme 2).



Scheme 2. A possible path for the synthesis of dialkyl 3-(alkylamino)-1-aryl-1*H*-pyrazole-4,5-dicarboxylates **4a-h**

TLC tracking of the reaction mixture clearly indicated consumption and production of phenylisocyanate during the reaction. GC-MS analyses of the reaction mixture, at the end of the reaction time, confirmed producing of phenylisocyanate and aniline at the final step of the proposed mechanism.

Because of these results, two paths have been proposed for the conversion of intermediate **10** to the product **4** (Scheme 2).

The mp values, elemental analyses, and spectral data of these compounds were also in good agreement with those of authentic samples [38].

Conclusion

In conclusion, We have developed a simple and efficient synthesis of dialkyl 3-(alkylamino)-1-aryl-1*H*-pyrazole-4,5-dicarboxylates using α-Fe_2O_3 nanoparticles and phenylisocyanatein solvent-free conditions. Excellent yields of products, short reaction times and mild reaction conditions, use of simple chemicals, Eco friendly, inexpensive and readily available catalyst and high atomic economy are the main advantages of this method.

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