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Succinimide-N-sulfonic acid Catalyzed One Pot, Efficient Synthesis of Substituted Pyrazoles

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ABSTRACT

A simple, facile and expeditious method to synthesis the pyrazoles carried out by using hydrazine/hydrazide and 1,3-dicarbonyl compounds in high yield. This eco-friendly protocol was catalyzed by succinimide-N-sulfonic acid and efficiently carried using water as a solvent within 15 minutes. The synthesized pyrazoles were characterized by ^{1}H, ^{13}C NMR and IR spectrums.

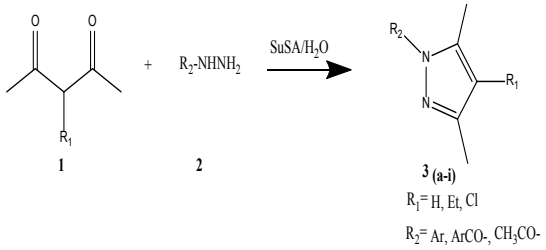
Keywords: Succinimide-N-sulfonic acid, 1,3-dicarbonyl, Aryl hydrazine, Condensation.

INTRODUCTION

Pyrazole is well known bio-active heterocyclic drug used in the chemical and pharma industry[1]. Several pharmaceutical drugs such as Fenpyroximate, Zometapine, Tebufenpyrad, Viagra and Celebrex include pyrazole derivatives as a building block[2-6]. Majority of pyrazoles possess several important pharmaceutical and biological activities like antimicrobial, antifungal, antiviral, antidepressant, antitumor, anticonvulsant, hypoglycemic, antiobesity, cholesterol lowering and anti-inflammatory activities[7-14]. There are several synthetic routes for the preparation of pyrazoles. The typical method includes the condensation of 1,3-dicarbonyl compounds or α, β unsaturated carbonyl with the aryl/alkyl hydrazine or the intramolecular cycloaddition of nitrile imine and diazoalkanes with alkynes and alkenes[15-17]. The most prominent route for the synthesis of substituted pyrazole derivatives is the condensation of 1,3-dicarbonyls with the hydrazine/hydrazide using various acids like sulfuric acid, acetic acid, p-Tolunesulfonic acid, polystyrene supported sulfonic acid, hydrochloric acid and phosphotungstic acid[18-21].

Most of the above pyrazole synthesis methods suffer from several drawbacks which include low yield, costly reagents, tedious experimental procedure and non recyclability[22]. Thus, there is still need of simple and a greener protocol for the synthesis of pyrazole derivatives. Reently, SuSA catalyst is used by many researchers for the various organic transformations[23-27]. In our continuous quest for the greener and useful protocol for the organic

transformations herein, we developed method for the synthesis of pyrazole derivatives by using the condensation of 1,3-dicarbonyl compounds and hydrazine/hydrazide using SuSA catalyst and water as a solvent.



Scheme 1. SuSA catalyzed pyrazole synthesis

EXPERIMENTAL

General

All the reagents used are of AR grade. All the solvents are distilled prior to use. 1,3-dicarbonyl compounds and hydrazine/hydrazide were purchased from Merck. TLC (Sigma Aldrich-silica gel 60F254 aluminium supported plates) was used to monitor the progress of reaction. Column chromatography was done using silica gel. An ^{1}H and ^{13}C NMR spectrum was obtained using Bruker Avance III HD (500 MHz) spectrometer. Perkin-Elmer 781 spectrometer was used to obtain the spectrum.

Preparation of the SuSA catalyst

The catalyst SuSA for the preparation 3,4-dihydropyrimidinones was synthesized using succinamide and chlorosulfonic acid[28]. In 25 mL suction flask the 1 g succinamide (10 mmol) and 5 mL dry dichloromethane were added. This suction flask further joined to constant pressure-dropping funnel. Further, 1.12 g chlorosulfonic acid (10 mmol) added to above reaction drop wise for the period of 15 min along with constant stirring on ice bath. This mixture further stirred for next 2.5 hours. The obtained cream colored solid residue was filtered as well as washed using diethyl ether solvent, afterwards it was dried under the vacuum.

Typical experimental procedure for the pyrazole synthesis

The hydrazine/hydrazide (0.55 mmol) and 1,3-dicarbonyl compound (0.50 mmol) were stirred in the small beaker. To this mixture 0.05 mL of 15% SuSA catalyst solution in water solvent is added drop wise. The above mixture further stirred for few minutes. The products were extracted into the ethyl acetate after completing the reaction. Further, the obtained products were purified over the column chromatography (silica gel: 20% ethyl acetate/hexane).

Table 1, entry 1

IR (KBr) cm^{-1}: 3116, 2761, 1640, 1417, 1134, 941, 764, 669, 575. ^{1}H NMR: 2.33 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 6.05 (s, 1H, CH), 7.29-7.43 (m, 5H, C_6H_5). ^{13}C: 12.49, 13.75, 106.96, 125.22, 128.42, 130.25, 140.33, 141.49, 150.32.

Table 1, entry 5

IR (KBr) cm^{-1}: 3085, 2905, 1610, 1575, 1450, 957, 765, 615, 556. ^{1}H NMR: 2.10 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.35 (s, 1H, CH_3), 7.30-7.32 (d, J = 8.7 Hz, 2H), 7.40-7.42 (d, J = 8.7 Hz, 2H). ^{13}C: 8.55, 12.40, 12.43, 112.59, 126.51, 130.75, 135.39, 142.48, 144.93, 152.66.

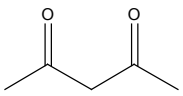
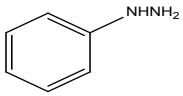
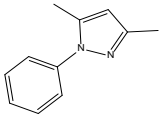
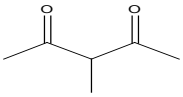
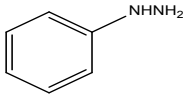
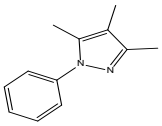
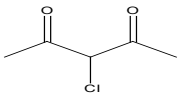
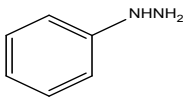
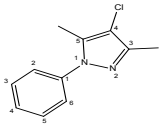
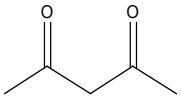
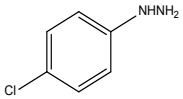
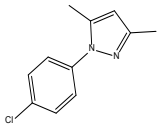
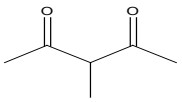
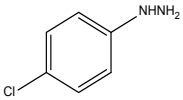
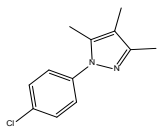
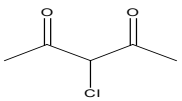
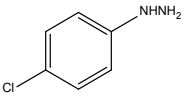
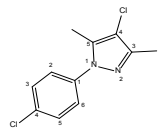
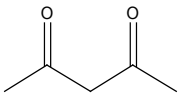
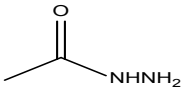
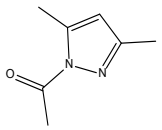
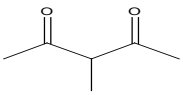
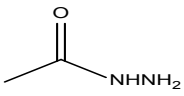
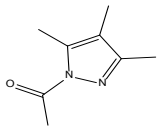
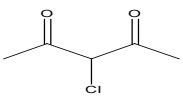
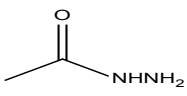
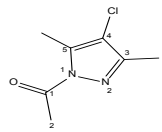
Table 1, entry 9

IR (KBr) cm^{-1}: 3077, 2933, 2882, 1715, 1695, 1587, 1414, 1343, 974, 821, 616, 563. ^{1}H NMR: 2.20 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.65 (s, 3H, CH_3). C13: 8.75, 14.39, 15.14, 26.73, 117.83, 144.38, 155.82, 159.32, 175.43.

RESULTS AND DISCUSSION

In our efforts to develop a simple, facile, greener and expeditious method, we have focused on the reusability of the catalyst and use of green solvent. Pyrazole derivatives were synthesized by using hydrazines/hydrazides and 1,3-dicarbonyls by using SuSA catalyst and efficiently carried out using water as a solvent. The results are summarized in Table 1. The effect of substituted 1,3-dicarbonyl compounds on the pyrazole synthesis was studied. Various hydrazines and hydrazides reacts effectively with substituted 1,3-dicarbonyl compounds within short reaction time to get excellent yields (87-95%). It is also observed that aryl hydrazines **4a-b** effectively reacts with 1,3-dicarbonyl compounds 1-3 affording the products **5a-f**. However, the hydrazide **4c** reacts moderately when compared to hydrazines **4a-b**. Acyl hydrazide **4c** was least reactive and required more time for the completion of reaction with low yields.

Table 1: SuSA catalyzed synthesis of substituted pyrazole derivativesa

Entry	1,3-Dicarbonyl compound (1)	Hydrazine/hydrazide (2)	Product(3 (a-i))	Time (min)	Yield (%)
1	 **1**	 **4a**	 **5a**	15	95
2	 **2**	 **4a**	 **5b**	19	90
3	 **3**	 **4a**	 **5c**	15	92
4	 **1**	 **4b**	 **5d**	20	92
5	 **2**	 **4b**	 **5e**	25	87
6	 **3**	 **4b**	 **5f**	20	88
7	 **1**	 **4c**	 **5g**	20	91
8	 **2**	 **4c**	 **5h**	25	87
9	 **3**	 **4c**	 **5i**	18	89

[a]Reaction condition: 1,3-dicarbonyl compound, (0.5 mmol), aryl/alkyl hydrazine (0.55 mmol), and SuSA catalyst (15 % solution in water)

Furthermore, the optimization of SuSA catalyst for the pyrazole synthesis was also studied (Table 2). The reaction shows traces of the product even after 150 min without catalyst. The enhancement in quantity of SuSA catalyst shows enhancement in the product yield up to 15 mol%. The highest yield and short reaction time was observed in case of 10 mol% SuSA catalyst. Accordingly, we decided to use this optimum quantity of SuSA catalyst i.e. 15 mol% for the further studies. As a model study, we selected the condensation reaction of phenyl hydrazine (0.55 mmol) and pentane-2,4-dione (0.5 mmol) with SuSA catalyst (15 mol%) in different solvents including CH_2Cl_2, THF, Ethanol, Water and CH_3CN. The condensation yield was excellent in water when compared with other solvents (Table 3).

Table 2: Optimization of SuSA catalyst

Entry	SuSAa (mol %)[a]	Time (min)	Yield (%)
1	without catalyst	150	Traces of the product
2	1	35	87
3	5	25	89
4	10	20	90
5	15	15	95
6	20	25	91

[a]Determined by TLC monitoring.

The recyclability of the recovered SuSA catalyst also studied to find the stability of catalyst. The recovered catalyst does not show the remarkable loss even after reuse. The catalyst was easily recovered and showed significant catalytic activity even after 3 runs (Table 4).

Table 3: Influence of different solvents

Solvent	Yield (%)
CH_2Cl_2	91
THF	82
Ethanol	89
Water	95
CH_3CN	90

Table 4: Recycling Experiments with SuSA catalyst

Run	Yield (%)[a]
1	95
2	93
3	89

[a]Isolated Yield

CONCLUSION

In summary, we developed the successful strategy to synthesize the of pyrazole derivatives by using hydrazine/hydrazide and 1,3-dicarbonyls by using SuSA catalyst and efficiently carried out using water as a solvent within 15 minutes. Simple experimental procedure, reusability of the catalyst and enhanced yield are the advantages of this green and efficient synthetic route.

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Conflict of interest

The author declare that we have no conflict of interest.

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