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Atom efficient grinding technique for the synthesis of hydrazones catalyzed by citric acid

Mohammed Zamir Ahmed[1,*], NT Patel[1], KA Shaikh[2], MA Baseer[1], Shaikh Shahid[1] and Vishal A Patil[2]

[1]Organic Chemistry Research Laboratory, Yeshwant Mahavidyalaya, Nanded, India.

[2]Department of Chemistry, Sir Sayyad College of Arts, Commerce and Science, Aurangabad, India.

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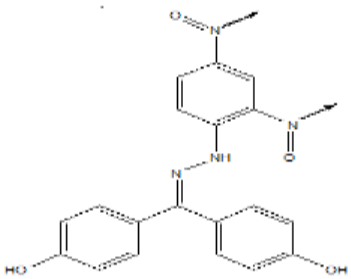
ABSTRACT

A highly efficient and expedient protocol for the synthesis of hydrazones catalyzed by citric acid is investigated via reaction of hydrazine hydrate with different carbonyl compounds. The use of inexpensive, non-hazardous easily available citric acid as a catalyst for the synthesis hydrazones employing grinding technique is reported. The structures of the synthesized compounds are established on the basis of physical, chemical and spectral data.

Introduction

In recent decades various diseases threatened the world with their hazardous effects like Cancer, Malaria, AIDS and Tuberculosis. More than 50 million peoples are affected by malaria causing approximately 2 million deaths per year. Tuberculosis claims over 2 million lives worldwide each year. Researchers are involved in the business to synthesize the molecules of biological interest which can provide relief to the world from these hazardous diseases. Hydrazones have been emerged as one of the fruitful product of their efforts.

L.R. Morgan *et al.* explored the studies of anticancer agent 4,4`-dihydroxybenzophenone-2,4-dinitrophenylhydrazone (a) by preparing its stable double salts showing improved in vitro anticancer activity than its precursor alone [1].



(a)

In addition to this, various substituted hydrazones exhibit antimicrobial [2], antimalarial [3], anti-inflammatory [4], anti-HIV [5], anticonvulsant [6], anti-hyperalgesic [7] and other pharmacological potencies [8-10]. On the other fold, hydrazones have been utilized in synthetic chemistry for protection of carbonyl compounds [11] and as chemical intermediate which can act as electrophile and as nucleophile in mannich type reaction, asymmetric syncyanation and allylation reactions [12]. Variety of hydrazones has been employed as ligands for preparing various bioactive complexes [13-16]. Apart from these we must discuss the use of hydrazones in medical biotechnology in coupling methods. They are used to couple with certain drugs. The hydrazones based bond is stable at neutral pH (in the blood) but it is rapidly destroyed in acidic environment of lysosomes and the drug become free for its action [17].

Classical method for the synthesis of hydrazones is the reaction of hydrazine with slight excess of carbonyl compounds in refluxing conditions using ethanol or toluene as a solvent. Recently RS Varma utilized the polystyrene sulphonic acid as a catalyst for the synthesis of hydrazones under microwave conditions [18]. DJ Brondani reported the synthesis of some aryl hydrazones in aqueous media under ultrasound irradiation [19]. And the very recent development in the synthetic methods is the use of Ball-Mill for the solvent free synthesis of hydrazones by F Lamaty [12].

These days, variety of acid catalysts has been employed in synthetic chemistry. Competing with the huge range of catalyst citric acid played a vital role in organic synthesis [20-21] due to its non toxic nature, easy availability and for simple work up procedure. Efficiency and selectivity of solid state reactions are more fruitful than solution reaction [22], the reason lies in the regular and tight arrangement of molecules in a crystal.

In persuasion to develop neat methodologies and exploring the green chemistry goals [23] we offer the synthesis of hydrazones by reacting various halo substituted aldehydes and ketones with hydrazine hydrate catalyzed by citric acid via grinding technique.

Experimental:

Methods and Analysis:

All chemicals were purchased from S. D. fine Chemicals (India). Melting points were recorded using open capillary method and are uncorrected. The progress of the reaction was monitored by thin layer chromatography technique. IR spectra were recorded on Perkin-Elmer 237 spectrometer. ^{1}H NMR spectra on Bruker Avance DPX400 MHz spectrometer with

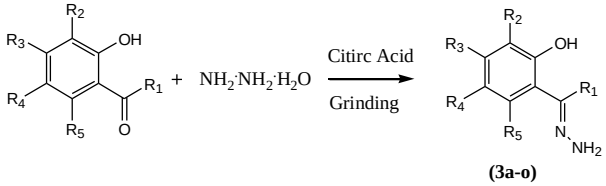
Tele:

E-mail addresses: mohammedzameer_chem@rediffmail.com

$CDCl_3$/ DMSO as solvent and TMS internal standard. The chemical shift values are expressed in part per million (ppm).

General procedure for the synthesis of hydrazones

A mixture of o-hydroxy acetophenone (0.01 mole) and hydrazine hydrate (0.02 mole) in 1:2 molar ratios were taken in a mortar. Citric acid was added to the reaction mixture in catalytic amount and grinded with a pestle. Accomplishment of the reaction was judged by thin layer chromatography (accomplished within a couple of minute). Ice cold water was added to the reaction mixture and stirred for few minutes for separation of molecules. The separated solid filtered, dried and recrystallized with suitable solvent. (Scheme-1)



Scheme 1. Synthesis of hydrazones via grinding technique

The physical data of the synthesized compounds is mentioned in Table-1.

Spectral analysis of representative molecules

2, 4-Dibromo-6-hydrazonomethyl-phenol (3c): IR (KBr) ν cm^{-1}: 3396 (O-H), 3287 (N-H), 3073 (Ar C-H), 1625 (C=N), 1369, 1213 (C-O) cm^{-1}. ^1H NMR (400 MHz, δ ppm): 12.45 (s, 1H, OH), 7.7 (s, 1H, CH=N), 7.1-7.4 (m, 2H, Ar-H), 6.90 (s, 2H, NH_2). Mass (ESI) m/z: 294

2-(1-Hydrazono-ethyl)-4, 6-diiodo-phenol (3f): IR (KBr) ν cm^{-1}: 3379 (O-H), 3290 (N-H), 2940 (Ar C-H), 1590 (C=N), 1382, 1185 (C-O) cm^{-1}. ^1H NMR (400 MHz, δ ppm): 14.06 (s, 1H, OH), 7.5-7.9 (m, 2H, Ar C-H), 6.39 (s, 2H, NH_2), 2.20 (s, 3H, CH_3), 2.21 (s, 3H, CH_3). Mass (ESI) m/z: 402

2-Bromo-6-(1-hydrazono-ethyl)-4-methyl-phenol (3o): IR (KBr) ν cm^{-1}: 3385 (O-H), 3310 (N-H), 2948 (Ar C-H), 1604 (C=N), 1370, 1213 (C-O) cm^{-1}. ^1H NMR (400 MHz, δ ppm): 14.07 (s, 1H, OH), 7.1-7.18 (m, 2H, Ar C-H), 6.47 (s, 2H, NH_2), 2.24 (s, 3H, CH_3), 2.15 (s, 3H, CH_3). Mass (ESI) m/z: 243

Results and Discussion:

In present report, we have investigated the green synthesis of hydrazones by the reaction of various carbonyl compounds with hydrazine hydrate catalyzed by citric acid via grinding technique. The present protocol is adopted by overcoming the reported time consuming methods, use of perilous solvents and expensive catalytic systems. We have also evaluated the applicability of this methodology by the reaction of variety of halo substituted salicylic aldehydes and halo, methyl substituted ortho hydroxy ketones and we are glad to say that all the substituted aldehydes and ketones responded well with equal ease producing excellent yield with high purity.

For the optimization and evaluation of efficiency of the catalyst we studied the reaction with different mole ratios. We observed that only 0.1 mmol of catalyst was ample evidence for the fruitful completion of reaction. On escalating up the quantity of catalyst we did not observed any remarkable effect on the reaction parameters. The data for the catalytic evolution is summarized in Table-2.

Conclusion: The rationale behind our investigation is two folded,

1. Development of neat methodology for the synthesis of hydrazones by reacting hydrazine hydrate with various carbonyl compounds.
2. Exploration of citric acid as an efficient catalyst in synthetic chemistry.

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Table-1. Physical data of synthesized compound (3a-o)

Sr.No.	Product	Molecular Formulae	Yield (%)	M.P. (^{0}C)
1	3a	$C_8H_{10}N_2O$	95	65-68
2	3b	$C_9H_{11}ClN_2O$	88	99-104
3	3c	$C_7H_6Br_2N_2O$	87	160-162
4	3d	$C_7H_6I_2N_2O$	90	210-213
5	3e	$C_8H_8BrClN_2O$	83	156-158
6	3f	$C_8H_8I_2N_2O$	92	119-122
7	3g	$C_8H_9ClN_2O$	90	84-86
8	3h	$C_9H_{11}IN_2O$	85	124-126
9	3i	$C_9H_9BrN_2O$	98	75-78
10	3j	$C_7H_8N_2O$	80	89-91
11	3k	$C_8H_{10}N_2O_2$	86	>250
12	3l	$C_8H_8Br_2N_2O_2$	89	140-142
13	3m	$C_9H_{10}BrClN_2O$	92	200-203
14	3n	$C_8H_8ClIN_2O$	94	145-148
15	30	$C_9H_{11}BrN_2O$	96	142-145

Table-2. Catalytic study for the synthesis of hydrazones

Entry	Citric acid (mmol)	Time (Min)	Yield (%)
1	0.1	2	98
2	0.2	2	96
3	0.4	2	94
4	0.6	2	94
5	0.8	2	94

	R_1	R_2	R_3	R_4	R_5
3a	CH_3	H	H	H	H
3b	CH_3	H	CH_3	Cl	H
3c	H	Br	H	Br	H
3d	H	I	H	I	H
3e	CH_3	Br	H	Cl	H
3f	CH_3	I	H	I	H
3g	CH_3	H	H	Cl	H
3h	CH_3	I	H	CH_3	H
3i	CH_3	H	H	Br	H
3j	H	H	H	H	H
3k	CH_3	H	OH	H	H
3l	CH_3	Br	H	Br	H
3m	CH_3	Br	CH_3	Cl	H
3n	CH_3	I	H	Cl	H
3o	CH_3	Br	H	CH_3	H