ICC
Iranian Chemical Communication
Original Research Article
Payame Noor University http://icc.journals.pnu.ac.ir

Guanidine hydrochloride: An efficient catalyst for the synthesis of 2-hydrazolyl-4-thiazolidinone derivatives under solvent free conditions

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Received: 29 February 2016, Accepted: 4 January 2017, Published: 1 April 2017

Abstract

A highly efficient protocol has been developed for the synthesis of 2-hydrazolyl-4-thiazolidinone derivatives installing one pot three component reaction of an aromatic aldehyde, thiosemicarbazide and maleic anhydride using guanidine hydrochloride as an inexpensive and environmentally friendly catalyst under solvent free condition with good to excellent yields, it offers short reaction time, good to excellent yields and simple and easy workup procedure as compared to the traditional methods. The products are characterized by spectroscopic methods like IR, ^{1}H NMR and ^{13}C NMR. In the present protocol, we reports heterocyclic and unsaturated aldehydes first time using guanidine hydrochloride with excellent yields.

Keywords: 2-hydrazolyl-4-thiazolidinones; thiosemicarbazide; maleic anhydride; guanidine hydrochloride; Solvent free.

Introduction

4-Thiazolidinones derivatives are heterocyclic and biologically important compounds [1]. 2-Hydrazolyl-4-thiazolidinones are compounds that combine thiosemicarbazones with 4-thiazolidinones, two building blocks with interesting biological properties. For example, *Trypanosoma crizi*, [2], *Plasmodium falciparum* [3], and antitumor [4], hypnotic activity [5], antitubercular [6], anticonvulsant [7], and COX-2 inhibition [8], anti HIV [9], and antibacterial [10], anti-inflammatory [11], as well as human chondrocyte antidegenerative [12], properties have been found for 4-thiazolidinones derivatives. In addition, the combination of these two has been used to exhibit anti-Toxoplasma Gondii [13], antimicrobial [14], antiviral [15], and antifungal [16] properties.

In the literature [17] the reported methods for the synthesis of 2-hydrazolyl-4-thiazlidinone is a two-step, first step involves the reaction between aromatic aldehydes and thiosemicarbazide to form corresponding thiosemicarbazones, step second involves a thia-Michael addition of thiosemicarbazones with maleic anhydride in dry toluene and N, N-dimethyl formamide at reflux conditions to produce 2-hydrazolyl-4-

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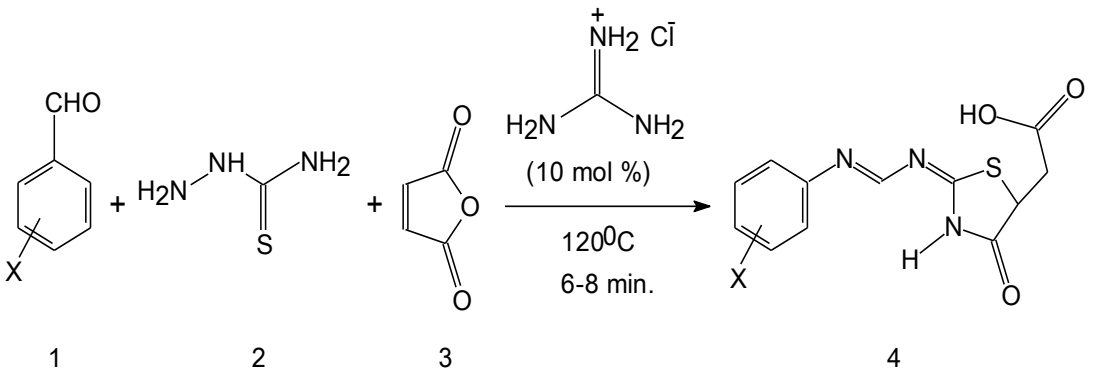
thiazlidinones. Derivatives of 4-thiazolidinone were synthesized by various methods. However, a conventional method for such synthesis was frequently used. It involves the cyclo-condensation reaction and one-pot method was convenient for the synthesis of 4-thiazolidinone. This method includes the reaction of enaminones with ethyl-2-bromopropionate [18]. A common synthetic route for the preparation of iminothiazolidinones is the cyclization of thiourea or thiosemicarbazide derivatives with α-haloesters or thioglycolic acids using inorganic base catalyst in polar solvents. These cyclization reactions were carried out by conventional heating [19] or microwave irradiation [20]. Guanidine hydrochloride [21] is used for preparation of biologically important heterocyclic compounds. Guanidinium hydrochloride has been found to be a highly efficient and environmentally friendly catalyst [22]. In continuation of an interest in developing methodologies for one pot multicomponent reaction [23], herein we disclose an efficient and yielding protocol for the synthesis of 2-hydrazolyl-4-thiazolidinone scaffolds installing a one pot three component coupling reaction of an aldehyde, thiosemicarbazide and maleic anhydride using guanidine hydrochloride as catalyst under solvent free condition. (Scheme 1).



Scheme 1. Synthesis of 2-hydrazolyl-4-thiazolinone derivatives

Experimental

General

All the melting points were determined by open capillary method. The purity of compounds was checked by Blaker-Flex silica gel 1B-F (1.55 cm) TLC plates, and the spots were detected by UV light absorption. ^{1}H NMR spectral data was registered on Brucker avance II-400 NMR spectrometer (400 MHz) in DMSO using tetramethylsilane as an internal standard. The IR spectra were recorded using KBr disc on Shimadzu FTIR spectrophotometer. The chemicals used are of AR grade from Sd fine and Loba chemicals.

General Procedure

To a 50 mL two necked round bottom flask was added aromatic aldehydes (5 mmol), thiosemicarbazide (5 mmol) maleic anhydride (5 mmol) and guanidine hydrochloride (10 mol %) was heated at 120 ^{0}C. Upon the completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature. To the reaction mixture water (20 mL) was added. The obtained solid product was

filtered and recrystallized from pure alcohol.

Spectroscopic data for the 2-Hydrazolyl-4-Thiazolidinone derivatives.

4a: IR (KBr) (cm^{-1}): 3065 (OH). 1707 (C=O), 1621 (N-C=O), 1582 &1555 (C=N), 1334 (N-S) and 1252 (N-N-C). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.8 (s, 1H, COOH); 10.4(s, 1H, NH); 8.3 (s, 1H, CH=N); 7.3-7.5 (m, 5H, Ar-H); 4.5 (t, 1H, J=6Hz, CH); 3.1 (d, 2H, CH_2).^{13}C NMR (75.4 MHz, DMSO-d_6): 173.6 (COOH); 171.8 (C=O); 164.5 (C=N); 157.6 (CH=N); 135.1 (Cq Ar); 130.7 (CH Ar); 128.7 (CH Ar); 128.1 (CH Ar); 42.5 (CH); 36.6 (CH_2).

4b: IR (KBr) (cm^{-1}): 3064 (OH), 1728 (C=O); 1618 (N-C=O); 1587 &1550 (C=N); 1343 (N-C-S); 1226 (N-N=C); 1040 (C-S) ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 12.8 (s, 1H, COOH); 10.4 (s, 1H, NH), 8.3 (s,1H, CH=N); 7.8 (d, 2H, J= 8.4Hz, Ar-H); 7.2 (d, 2H, J=8.4 Hz, Ar-H); 4.5 (t, 1H, J=6Hz, C-H); 3.1 (d, 2H, J= 6Hz, CH_2); ^{13}C NMR (75.4 MHz, DMSO-d_6): 173.5 (COOH); 171.3 (C=O); 161.5 (C=N); 155.8 (CH=N); 136.2 (Cq Ar); 135.8 (Cq Ar); 128.7 (CH Ar); 127.3 (CH Ar); 41.9 (CH); 36.6 (CH_2).

4c: IR (KBr) (cm^{-1}): 3045 (OH), 1721(C=O); 1623 (N-C=O); 1575 and 1548 (C=N); 1341 (N-C-S); 1248 (N-N=C); 1034 (C-S) ^{1}H NMR: (400 MHz, DMSO-d_6) δ(ppm): 12.8 (s, COOH); 10.4 (s, 1H, NH), 8.3 (s,1H, CH=N); 7.7(d,2H, Ar-H); 7.4-7.5 (d, 2H, Ar-H), 4.5 (t, 1H, J=5.7 Hz, C-H); 3.1 (d, 2H, J=5.7 Hz, CH_2); ^{13}C NMR (75.4 MHz, DMSO-d_6): 173.6 (COOH); 171.6 (C=O); 165.4 (C=N); 154.8 (CH=N); 135.3 (Cq Ar); 132.9 (CH Ar); 129.3 (CH Ar); 128.9 (CH Ar); 42.5 (CH); 36.7 (CH_2).

4d: IR (KBr) (cm^{-1}): 3065 (OH), 1724 (C=O), 1606 (N-C=O); 1529 (C=N); 1360 (N-C-S); 1239 (N-N=C); 1030 (C-S) ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 12.8 (br, s, 1H, COOH); 10.4 (s, 1H,NH); 9.6 (s, 1H, Ar-OH); 8.1 (s,1H, CH=N); 7.3-7.5 (d, 2H, Ar-H), 6.7 (d, 2H, J= 8.7 Hz, Ar-H), 4.5 (t, 1H, J= 5.7 Hz, C-H); 3.1 (d, 2H, J=5.7 Hz, CH_2).

4e: IR (KBr) (cm^{-1}): 3065 (OH), 1720 (C=O); 1618 (N-C=O); 1590 & 1560 (C=N); 1347 (N-C-S); 1249 (N-N=C); 1330 3.1 (d, 2H, J=5.7 Hz, CH_2). (C-S). $^{1}HNMR$ (400 MHz, DMSO-d_6) δ(ppm): 12.8 (s, 1H, COOH); 10.4 (s, 1H, NH); 9.6 (s, 1H, Ar-OH); 8.1 (s, 1H, CH=N); 7.6 (dd, 1H, J=8.4 Hz and 1.2 Hz, Ar-H); 7.4 (m, 1H, Ar-H); 7.2 (m, 1H, Ar-H); 7.0 (dd, 1H, J=8.4 Hz and 1.2 Hz, Ar-H); 4.5 (t, 1H, J=5.7 Hz, C-H); 3.1 (d, 2H, J=5.7 Hz, CH_2). ^{13}C NMR (75.4 MHz, DMSO-d_6): 173.6 (COOH); 171.8 (C=O); 162.9 (C=N); 157.9 (CH=N); 149.6 (Cq Ar) 135.3 (Cq Ar); 122.7 (CH Ar); 115.5 (CH Ar); 110.1 (CH Ar); 42.4 (CH); 36.8 (CH_2).

4f: IR (KBr) (cm^{-1}): 3060 (OH), 1720 (C=O); 1612 (N-C=O); 1580 &1545 (C=N); 1340 (N-C-S); 1220 (N-N=C); 1042 (C-S) ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 12.8 (s, 1H, COOH); 10.4 (s, 1H, NH), 9.8 (s, 1H, Ar-OH); 8.3 (s,1H, CH=N); 7.8 (s, 1H, Ar-H); 7.4 (m, 1H, Ar-H); 7.2 (m, 2H, Ar-H); 4.5 (t, 1H, J=6Hz, C-H); 3.1 (d, 2H, J= 6Hz, CH_2). ^{13}C NMR (75.4 MHz, DMSO-d_6): 173.5 (COOH); 171.5 (C=O); 162.9 (C=N); 157.5 (CH=N); 149.1 (Cq Ar) 135.1 (Cq Ar); 122.7 (CH Ar); 115.5 (CH Ar); 110.1 (CH Ar); 108.6 (CH Ar) 42.3 (CH); 36.5 (CH_2).

4g: IR (KBr) (cm^{-1}): 3058 (OH), 1711(C=O), 1615 (N-C=O), 1579 and 1552 (C=N), 1344 (N-C-S), 1245 (N-N=C), ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 12.7 (s, 1H, -COOH), 10.4 (s, 1H, NH), 8.2 (s, 1H, CH=N), 7.66 (d,

2H, J= 8.4 Hz, Ar-H), 7.1 (d, 2H, J= 8.4 Hz, Ar-H), 4.5 (t, 1H, J= 5.4 Hz, CH), 3.8 (s, 3H, OCH_3), 3.1 (d, 2H, J= 5.4 Hz, CH_2). ^{13}C NMR (75.4 MHz, DMSO-d_6): 173.6 (COOH); 171.8 (C=O); 161.6 (C=N); 157.9 (CH=N); 151.9 (Cq Ar); 135.3 (Cq Ar); 129.3 (CH Ar); 128.6 (CH Ar); 42.4 (CH); 39.7 $(CH_3)_2$; 36.7 (CH_2)

4h: IR (KBr) (cm^{-1}): 3060 (OH), 1728 (C=O); 1618 (N-C=O); 1580 & 1555 (C=N); 1342 (N-C-S); 1240 (N-N=C); 1040 (C-S). ^{1}HNMR (400 MHz, DMSO-d_6) δ(ppm): 12.8 (s, 1H, COOH); 10.4 (s, 1H, NH); 8.2 (s, 1H, CH=N); 7.2-7.4 (d, 2H, Ar-H); 7.0 (d, 2H, Ar-H); 4.5 (t, 1H, J=5.7 Hz, C-H); 3.0 (d, 2H, J=5.7 Hz, CH_2); 2.4 (s, 3H,CH_3). ^{13}C NMR (75.4 MHz, DMSO-d_6): 173.5 (COOH); 171.5 (C=O); 163.2 (C=N); 157.2 (CH=N); 161.3 (Cq Ar); 135.1 (Cq Ar); 129.3 (CH Ar); 128.5 (CH Ar); 55.2 (OCH_3); 42.3 (CH); 36.7 (CH_2).

4i: IR (KBr) (cm^{-1}): 3059 (OH), 1724 (C=O), 1617 (N-C=O), 1580 and 1560 (C=N), 1350 (N-C-S), 1240 (N-N=C); ^{1}H NMR (400 MHz, DMSO-d6) δ(ppm): 12.8 (s, 1H, COOH); 10.4 (s, 1H, NH); 8.2 (s, 1H, HC=N); 6.9 (s, 2H, Ar-H); 4.4 (dd, 1H, J= 3.6 and 8.1 Hz, CH); 3.8 (s, 9H, OCH_3); 3.1 (dd, 1H, J= 8.1 and 17Hz, CH_2). ^{13}C NMR (75.4 MHz, DMSO-d_6): 173.1 (COOH); 171.3 (C=O); 161.9 (C=N); 157.3 (CH=N); 143.1 (Cq Ar) 139.7 (CH Ar); 104.1 (CH Ar); 104.1 (CH Ar); 41.6 (CH); 36.1 (CH_2).

4j: IR (KBr) (cm^{-1}): 3064 (OH), 1664 (C=O), 1595 (N-C=O), 1525 (C=N), 1448 (N-C-S), 1369 (N-N=C), 1325 (C-S); ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 11.3 (s, 1H, COOH); 9.6 (s, 1H, NH); 8.2 (s, 1H, CH=N); 7.9 (d, 1H, J=1.8 Hz, Ar-H); 7.7 (dd, 1H, J = 1.8 Hz and 8 Hz, Ar-H); 6.6 (d, 1H, J=8 Hz, Ar-H); 3.3 (t, J= 5.7 Hz, CH); 3.0 (s, 3H, OCH_3); 2.5 (d, 2H, J= 5.7Hz, CH_2); ^{13}C NMR (75.4 MHz, DMSO-d_6): 173.3 (COOH); 171.4 (C=O); 163 (C=N); 157.4 (CH=N); 138.1 (CH C=C) 135.1 (Cq Ar); 128.7 (CH Ar); 128 (CH Ar); 126.1 (CH Ar); 119 (CH C=C); 43.3 (CH); 36.2 (CH_2).

Results and discussion

Initially, we focused on systematic evaluation of different catalysts for the model reaction of *p*-nitrobenzaldehyde, thiosemicarbazide and maleic anhydride under solvent free condition heated at 120 ^{0}C (Scheme1). We have applied a range of catalyst including guanidine, guanidine hydrochloride, guanidine carbonate, guanidine sulphate, guanidine nitrate to improve the yield for the specific synthesis of 2-hydrazolyl-4-thiazolidinone scaffolds. As shown in Table 1, the reaction did not take place without any catalyst (Table 1, Entry 1). As mentioned in Table 1, most interesting result was obtained with guanidine hydrochloride as the catalyst and the yield of the desired was maximized.

Table 1. Optimization of reaction condition using different catalyst[a]

Entry	Catalyst	Time (Min)	Yield[b] (%)
1	----------	120	00
2	Guanidine	60	34
3	Guanidine sulfate (10 mol %)	60	41
4	Guanidine carbonate (10 mol %)	60	53
5	Guanidine nitrate (10 mol %)	60	48
6	Guanidine hydrochloride (10 mol %)	06	92

[a]*p*-Nitrobenzaldehyde (5 mmol), thiosemicarbazide (5 mmol), maleic anhydride 5 mmol) and guanidine hydrochloride (10 mol %) at 120 ^{0}C
[b]Isolated yields of pure products

We then tried to screen the reaction in various organic solvents in order to optimise the reaction conditions using guanidine hydrochloride as the catalyst (Table 2). The results revealed that solvent shows great effect on the catalytic activity of guanidine hydrochloride. The highest yield was obtained with solvent free condition at 120 ^{0}C.

Guanidine hydrochloride had emerged as the most suitable catalyst for the model reaction of *p*-nitrobenzaldehyde, thiosemicarbazide and maleic anhydride under solvent free condition at 120 ^{0}C. We then tried to optimise the catalyst load for the reaction leading to the rapid formation of 2-hydrazolyl-4-thiazolidinone scaffold. Our optimisation studies revealed that the yield increased smoothly with catalyst load up to 10 mol % and then remained unaltered up to 14 mol % after that there was sharp drop in the yield. This drop may be attributed to the coagulation of guanidine hydrochloride which decreases the effective surface area of the catalyst.

Table 2. Solvent screening for the model reaction

Entry	Solvent	Yield[a,b] (%)
1	Toluene	34
2	Dimethyl sulfoxide	38
3	N,N-Dimethyl formamide	52
4	Toluene + N,N-Dimethyl formamide	61[17]
5	Water	--
6	Ethanol + Water	Trace
7	No solvent	92

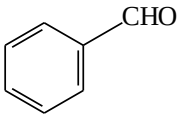
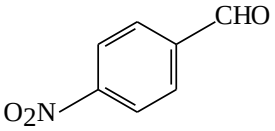
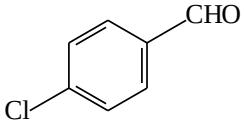
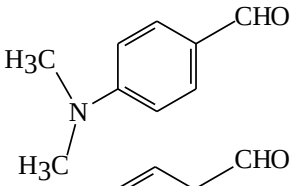
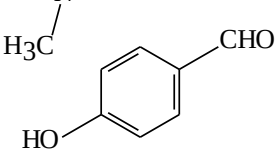
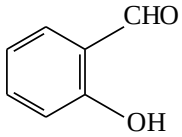
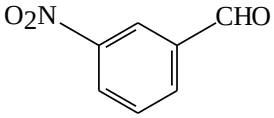
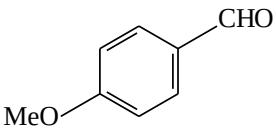
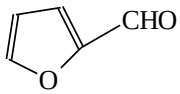
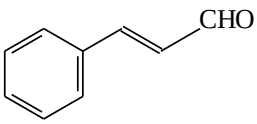
[a]*p*-Nitrobenzaldehyde (5 mmol), thiosemicarbazide (5 mmol), maleic anhydride 5 mmol) and guanidine hydrochloride (10 mol %) at 120 ^{0}C
[b]Isolated yields of pure products

The reaction of various aldehydes, thiosemicarbazide and maleic anhydride in presence of catalytic amount of guanidine hydrochloride was carried out at 120 ^{0}C without solvent. Rapid reaction rates and high conversions were achieved and the results were also summarised. (Table 3). In our study, the guanidine hydrochloride has been employed as an efficient catalyst for 2-hydrazolyl-4-thiazolidinone scaffold.

Both electron rich and electron deficient aldehydes worked well giving high yields of products. Electron deficient aldehydes furnished excellent yields of the corresponding 2-hydrazolyl-4-thiazolidinones in short reaction time, whereas electron rich aldehydes resulted in comparatively low yields and required longer reaction time. The heterocyclic aldehydes and unsaturated aldehydes reacts with thiosemicarbazide and maleic anhydride in presence of guanidine hydrochloride at 120 ^{0}C under solvent free condition produce in good to excellent yields of corresponding 2-hydrazolyl-4-thiazolidinone scaffold.

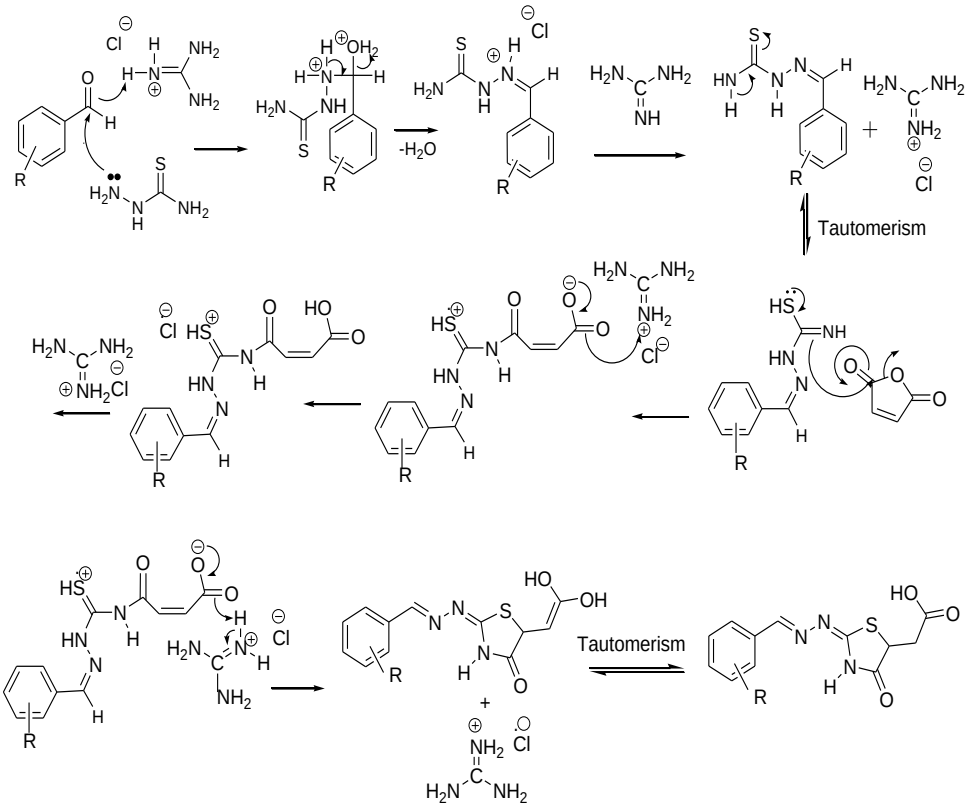
In a plausible mechanism (Scheme 2), at first, the nucleophilic attack of thisemicarbazide tooks place to aldehydes using guanidine hydrochloride to form thiosemicarbazone intermediate (A). Thiosemicarbazone intermediate undergoes tautomerism to produce sulfur as nucleophile (B). Nucleophilic attack of sulfur on maleic anhydride by ring opening and formation of new ring produce corresponding 2-hydrazolyl-4-thiazolidinone scaffold.

Table 3 : Synthesis of 2-hydrazolyl-4-thiazolidone derivatives using guanidine hydrochloride

Entry	Aldehyde (1)	Product (4)	Yield [a,b] (%)	Time (min)	MP ^0C	Ref.
a		**4a**	89	8	240- 241	17
b		**4b**	92	6	278-280	17
c		**4c**	88	6	245-248	17
d		**4d**	86	8	276-278	17
e		**4e**	79	8	240-242	c
f		**4f**	82	8	258-260	c
g		**4g**	84	7	278-280	c
h		**4h**	87	7	272-274	17
i		**4i**	86	7	286-288	c
j		**4k**	68	8	199-200	c

[a] Yield of isolated product.[b] Products characterised by IR, ^{1}HNMR, ^{13}CNMR.

[c] Newly Synthesized.



Scheme 2. Plausible mechanism for the reaction and the role of guanidine hydrochloride

Conclusion

A simple methodology for an efficient synthesis of 2-hydrazolyl-4-thiazolidinone derivatives has been reported by using guanidine hydrochloride as catalyst. It offers short reaction time, good to excellent yields and simple and easy workup procedure as compared to the traditional methods of synthesis.

Acknowledgments

SSP thanks BCUD, Savitribai Phule Pune University, Pune for the financial assistance 14SCI001801. SAIF Panjab University Chandigarh, KTHM College Nasik for spectral analysis and Principal, Padmashri Vikhe Patil College Pravaranagar for providing all laboratory facilities during the completion of project work.

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