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Original article

Sulfamic acid as a green, reusable catalyst for stepwise, tandem & one-pot solvent-free synthesis of pyrazole derivatives

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ABSTRACT
Sulfamic acid (SA) is a bi-functional, cost-effective and reusable green catalyst for the synthesis of 4-(pyrazol-4-yl)methylenepyrazol-5(4*H*)-one derivatives by one-pot, three-component condensation of pyrazol-4-carbaxaldehydes, *β*-ketoesters and phenyl hydrazine (Route-I). In addition to this method, another simple condensation of pyrazol-4-carbaxaldehydes with pyrazolone in the presence of SA under the solvent-free condition in good yield is reported. The merits of these protocols are mild conditions, non-aqueous workup, high yields, easy availability of the catalyst, no chromatographic separation and inexpensive solid acid catalyst. Furthermore, SA could be recycled and reused for five times without losing its catalytic activity.

Keywords:
Pyrazol-4-carbaxaldehydes
Knoevenagel condensation
Sulfamic acid
Multicomponent reaction
Physical grinding.

1. Introduction

Pyrazole derivatives are well known for their broad range of biological properties [1-8]. Thus, it is attracting the scientists towards their preparation [9, 10]. Pyrazolones are structurally closed to pyrazoles, which are also associated with wide spectrum of biological activities [11-16]. Inspired by their importance, many research groups have reported different protocols for the synthesis of 4-pyrazolylmethylenepyrazol-5-(4*H*)-ones through two-component condensation of pyrazolone and pyrazole-4-carbaxaldehyde in the presence of different catalysts [17-20]. However, some of the above reported methods suffer from one or more drawbacks like use of unfavourable conditions, non-eco-friendly catalysts, solvents, prolonged reaction times, high catalyst loading and the use of expensive ionic liquids.

Literature survey reveals that, the multicomponent reactions (MCRs) have been recently discovered as a powerful tool in the field of medicinal chemistry and synthetic organic chemistry [21-24]. Moreover, MCRs are having huge applications like short reaction time, avoiding of intermediate isolation, diversity in reaction, atom- economy, environmental benign and substantial minimization of waste.

Organic transformations under the solvent-free conditions have also gained attention particularly from the view point of green strategy [25]. Physical grinding is one of the techniques which have increased in the use of organic synthesis rather than other traditional methods [26, 27]. This method offers many advantages interims of green protocol by avoiding of hazardous solvents, cost efficiency and product yields.

Sulfamic acid has been found to be a promising solid, proton donor catalyst. It is insoluble in almost all organic solvents, relatively stable, non-volatile, non-hygroscopic, non-corrosive and economically cheaper. This catalyst could be easily recycled and reused due to its very high immiscibility with most organic solvents. It acts as a solid acid catalyst for so many organic transformations as witnessed by many reports published in the past [28-34]. Mohan et al. reported the synthesis of pyrazolone with phenyl hydrazine and ethyl acetoacetate in the presence of sulfamic acid [35]. Thus, we decided to explore the capability of sulfamic acid to perform multi component reactions.

Here, we report a simple, convenient and eco-friendly method for the synthesis of 4-(pyrazol-4-yl)methylenepyrazol-5(4*H*)-one **6**(**a-n**) by using 3-diphenyl-1*H*-pyrazol-4-carboxaldehyde **4**(**a-h**) and pyrazolone **9**(**a**, **b**) (Scheme 1) and one-pot, three component reaction of 3-diphenyl-1*H*-pyrazol-4-carboxaldehyde **4**(**a-h**), *β*-ketoesters **5**(**a**, **b**) and phenyl hydrazine **2** in the presence of sulfamic acid and has not been reported elsewhere on its use for the synthesis of 4-(pyrazol-4-yl)methylenepyrazol-5(4*H*)-one.

2. Results and discussion

The starting materials consumed in the present study, 3-diphenylpyrazol-4-carboxaldehyde **4**(**a-h**) were prepared in accordance with literature procedure. The reaction of substituted acetophenones **1**(**a-h**) with phenyl hydrazine (**2**) in ethanol containing catalytic amount of acetic acid yields acetophenone phenyl hydrazones **3**(**a-h**). The latter undergoes Vilsmeier-Haack reaction to give 4-(1*H*-pyrazol-4-yl) methylenepyrazol-5(4*H*)-one **4**(**a-h**) in good yield (Scheme 1).

To optimise the reaction conditions, we have chosen 3-diphenyl-1*H*-pyrazol-4-carboxaldehyde (**4a)**, ethyl acetoacetate (**5a)** and phenyl hydrazine (**2)** as model substrates (Scheme 2). Initially, we have focused to find out the best catalyst for the synthesis of 4-(pyrazol-4-yl) methylenepyrazol-5(4*H*)-one **6**(**a-n**) by employing variety catalysts under different conditions (Table 1).

It is obvious from Table 1 that the best results were obtained in the presence of 20 mol% sulfamic acid under solvent-free grinding conditions (Table 1, entry 8). The other catalysts such as L-proline, $InCl_3$, montmorillonite-K10 and amberlyst-15 (Table 1, entries 2-5) afforded moderate to good yields. From the view of cost and performance of the catalyst SA was found as the best catalyst for the synthesis of **6a** through one-pot, three component reaction. The model reaction was also checked under catalyst-free conditions in which the reaction did not proceed even after 100 min (Table 1, entry 1). From these observations, it can be confirmed the crucial role played by SA to yield the desired product **6a**. The influence of various amounts of the catalyst was also examined on the model reaction. It is confirmed that, 20 mol% of sulfamic acid (Table 1, entry 8) is enough to get good yields in a shortest reaction time (35 min). Excess amount of sulfamic acid did not effect on reaction time and yields (Table 1, entry 9). Further, we thought of scrutinising with various solvents and the role played by them on the reaction time and yields. It was found that protic solvents like ethanol and methanol (Table 1, entries 11, 12) were effective than non-protic solvents (Table 1, entries 13-15). It is confirmed from Table 1, the best optimised reaction conditions are observed when the model reaction is carried out in the presence of 20 mol% sulfamic acid under solvent-free conditions.

After optimising the reaction conditions, formation of undesired side products was also examined under the similar conditions by carrying a set of reactions. Primarily, Knoevenagel condensation was carried out with 3-diphenyl-1*H*-pyrazol-4-carboxaldehyde (**4a**) and ethyl acetoacetate (**5a**) in the presence of sulfamic acid, under solvent-free grinding conditions. It does not yield condensation product even after 60 min (Scheme 3).

In another set of reactions, formation of hydrazones was tested by using **4a** and phenyl hydrazine **2** under the above similar conditions. It results in the formation of hydrazone **8a** in 50 min (Scheme 4).

Finally, pyrazolone **9a** was prepared as per literature procedure [35] (Scheme 4) by the condensation of ethyl acetoacetate **5a** with phenyl hydrazine **2** in the presence of sulfamic acid under solvent-free conditions for 30 min.

As it is clear from the above sets of reactions, in three-component reaction between **4a**, **5a** and **2** initially, it results in the formation of the pyrazolone as intermediate which further undergoes Knoevenagel condensation with **4a**. Hence, there is no side products formation in multicomponent reaction.

The compound **6a** can also be synthesized through tandem method as well as stepwise method. In stepwise manner, **9a** was prepared from **5a**, **2** and sulfamic acid were ground together for 30 min under solvent-free conditions [35]. Further, the compound **9a** was condensed with **4a** under the same conditions for 10 min. It results in the formation of **6a** in good yield (Scheme 5).

To compare the capability and efficiency of our methodology with respect to the reported catalysts for the preparation of **6a**, the results of these catalysts for the synthesis of **6a** were tabulated in Table 2.

It is clear from Table 2, our methodology is more efficient than previous reports because sulfamic acid is cheap when compared with other catalysts like Ionic liquids, B_2O_3-ZrO_2, easily handling eco-friendly nature.

The optimised reaction conditions were applied for the synthesis of other derivatives such as **6**(**b-h**)**.** Results of this study were presented in Table 3 and it concluded that the substitution on pyrazole ring does not exert any effect on the efficiency of the reaction.

Further, we have also examined recycling of the catalyst for model reaction (Scheme 2) under optimised conditions and the results are tabulated in Table 4. Sulfamic acid was insoluble in many organic solvents hence it can be easily separated from the reaction mixture. After completion of reaction, ethyl acetate was added to extract the product and the insoluble catalyst was separated by simple separating technique. The separated catalyst was reused for five times with fresh starting materials without losing its catalytic activity and slight reduction of products yields. This might be due to loss of small amount of catalyst during handling.

To find the structure of recovered catalyst, the IR spectra of fresh sulfamic acid were compared with 1st and 5th time recovered sulfamic acid (Fig.1). It is observed that there are no differences in the IR spectra. Hence, it can be concluded that the structure of recovered sulfamic acid is stable under the applied conditions even after 5th time recovery and reuse.

The plausible mechanism of this reaction is explained by the following sequence of reactions (Scheme 6). It consist two steps, in the first step ethylacetoacetate **5a** gets protonated in the presence of sulfamic acid. The protonated ethyl acetoacetate reacts with phenyl hydrazine **2** with subsequent cyclisation to form compound **9a**. Knoevenagel condensation involves in the second step of mechanism. In this step, **4a** undergoes protonation with sulfamic acid, which reacts with **9a** to form alcohol intermediate. The latter undergoes protonation followed by elimination of water molecule to yield desire product **6a**.

3. Conclusions

In summary, we have reported a bi-functional, efficient, and green methodology for the multi component reaction using sulfamic acid as solid acid catalyst. This method offers many advantages, like eco-friendly, economically cheaper, avoiding of hazardous organic solvents, short reaction time, without isolation of intermediates and high yields.

4. Experimental

4.1 Material and methods

All the chemicals sulfamic acid, derivatives of acetophenones, phenyl hydrazine and *β*-ketoesters were obtained from commercial sources & are used without purification. Melting points were determined in open capillary tubes on Cintex melting point apparatus and are uncorrected. Pre-coated TLC silica gel plates (Kieselgel 60 F254, Merck) were used for monitoring reactions and the spots are visualized under UV lamp (254 nm). IR spectra were recorded using Perkin-Elmer spectrum version 10.03.02 instrument in KBr Pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Bruker (400 MHz) or Varian Mercury 400 MHz spectrometer. Proton chemical shifts are presented in δ ppm with reference to TMS. Mass spectra were recorded on an Agilent LC-MS instrument giving only M^+ values.

*4.2. Synthesis of 4-((1, 3-diphenyl-1H-pyrazol-4-yl) methylene)-1-phenyl pyrazolin-5(4H)-one **6(a-n)***

One-pot synthesis of **6**(**a-n**): A mixture of appropriate 1,3-diphenylpyrazolin-5-(4*H*)-4-carbaldehyde **4**(**a-h**) (5 mmol), *β*-ketoesters **5**(**a, b**) (5 mmol), phenyl hydrazine **2** (5 mmol) and sulfamic acid (20 mol%) was thoroughly grind with pestle in an open mortar at room temperature. Reaction progress was monitored by TLC. Upon completion of the reaction ethyl acetate (5 mL×3) was added to the mixture, shaked well and insoluble catalyst was separated by simple separating methods. The combined organic layers were concentrated under reduced pressure to get the clean products **6**(**a-n**). Purification of the crude products was done by recrystallization from suitable solvent, which afforded respective 4-(1*H*-pyrazol-4-yl) methylene-1*H*-pyrazol-5(4*H*)-ones **6**(**a-n**). All the synthesized products are stable, coloured solids and authenticity of these compounds was established based on their melting points and spectral analysis (IR, ^{1}H NMR and LC-MS).

Stepwise synthesis: A mixture of appropriate 1,3-diphenylpyrazolin-5-(4*H*)-4-carbaldehyde **4**(**a-h**) (5 mmol), pyrazolones **9**(**a, b**) (5 mmol) and sulfamic acid (20 mol%) was thoroughly grind with pestle in an open mortar at room temperature. Reaction progress

was monitored by TLC. Upon completion of the reaction, isolation and purification of the crude products **6**(**a-n**) was carried out by using above methodology. All the synthesized products are stable, coloured solids and authenticity of these compounds was established based on their melting points and spectral analysis (IR, ^{1}H NMR and LC-MS).

Spectral data for compound **6**(**a-n**):

(*Z*)-3-Methyl-1-phenyl-4-(1-phenyl-3-*p*-tolyl-1*H*-pyrazol-4-yl)methylene)-1*H*-pyrazol-5(4*H*)-one (**6a**): IR (KBr, cm^{-1}): 3125.7, 2982, 1675; ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 2.42 (s, 3H, -CH_3), 7.38-7.99 (m, 15H, aromatic protons and 1H olefinic proton), 10.88 (s, 1H pyrazole ring proton); LC-MS: *m/z* 405 (Q+1).

(*Z*)-3-Methyl-4-((3-(3-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**6b**): IR (KBr, cm^{-1}): 3539, 312, 3152, 1625, 1590, 778; ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 2.30 (s, 3H, -CH_3), 7.18-7.96 (m, 14H, aromatic protons and 1H olefinic proton), 10.60 (s, 1H, pyrazole ring proton); LC-MS: *m/z* 450 (Q+1).

(*Z*)-4-((3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**6c**): IR (KBr, cm^{-1}): 3108, 3072, 2902, 1624, 1573,743; ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 2.39 (s, 3H, CH_3), 7.20-8.48 (m, 14H, aromatic protons and 1H olefinic proton), 10.66 (s, 1H, pyrazole ring proton); LC-MS: *m/z* 439 (Q+1).

(*Z*)-3-Methyl-1-phenyl-4-((1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)methylene)-1*H*-pyrazol-5(4*H*)-one (**6d**): IR (KBr cm^{-1}): 3128.7, 2985, 1670; ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 2.30 (s, 3H, -CH_3), 3.41(s, 3H, -CH_3), 7.26-7.71 (m, 15H, aromatic protons and 1H olefinic proton), 9.22 (s, 1H, pyrazole ring proton); LC-MS: *m/z* 419 (Q+1).

(*Z*)-4-((3-(4-Bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**6e**): IR (KBr cm^{-1}): 3125.7, 2982, 1675; ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 2.34 (s, 3H, -CH_3), 7.18-7.14 (m, 14H, aromatic protons and 1H olefinic proton), 9.25 (s, 1H, pyrazole ring proton); LC-MS: *m/z* 494 (Q+1).

(*Z*)-4-((3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**6f**): IR (KBr, cm^{-1}): 3325, 3158, 1620, 1574, 1435; ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 2.33 (s, 3H, CH_3), 3.62 (s, 3H, OCH_3), 7.26-7.72 (m, 15H, aromatic protons and 1H olefinic proton), 9.63 (s,1H pyrazole ring proton); LC-MS: *m/z* 435 (Q+1).

(*Z*)-4-((3-(3-Nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (**6h**): IR (KBr, cm^{-1}): 1625, 1590, 778; ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 7.28-7.71 (m, 20H, aromatic protons and 1H olefinic proton), 9.44 (s, 1H, pyrazole ring proton); LC-MS: *m/z* 512 (Q+1).

(*Z*)-4-((3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-1,3-diphenyl-1*H*-pyrazol-5(4H)-one (**6i**): IR (KBr, cm^{-1}): 1625, 1590, 778; ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 7.25-7.91 (m, 20H, aromatic protons and 1H olefinic proton), 9.42 (s, 1H, pyrazole ring proton); LC-MS: *m/z* 499 (Q-1).

(*Z*)-1,3-diphenyl-4-((1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)methylene)-1*H*-pyrazol-5(4*H*)-one (**6j**): IR (KBr, cm^{-1}): 3325, 3158, 1620, 1574, 1435 ; ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 2.33 (s, 3H, -CH_3), 7.25-7.91 (m, 20H, aromatic protons and 1H olefinic proton), 7.27 (s, 1H, pyrazole ring proton); LC-MS: *m/z* 481 (Q+1).

(*Z*)-Ethyl-4-((3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4(5*H*)-ylidene)methyl)-1-phenyl-1*H*-pyrazole-3-carboxylate (**6m**): IR (KBr, cm^{-1}): 1720, 1625,1354, 792; ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 1.4 (s, 3H, -CH_3), 2.4 (s,3H, -CH_3), 4.4(s,2H, -CH_2), 7.2-7.2 (m, 10H, aromatic protons and 1H olefinic proton), 10.1 (s, 1H, pyrazole ring proton); LC-MS: *m/z* 399 (Q-1).

(*Z*)-4-((3-Methyl-5-oxo-1-phenyl-1*H*-pyrazol-4(5*H*)-ylidene)methyl)-1-phenyl-1*H*-pyrazole-3-carboxylic acid (**6n**): IR (KBr, cm-1): 3353,1756, 1625,1342, 778; ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 2.18(s, 3H, -CH_3), 7.23-7.84 (m, 11H, aromatic protons and 1H olefinic proton), 10.31 (s, 1H, pyrazole ring proton), 13.10 (s, br, 1H, -COOH D_2O exangeble); LC-MS: *m/z* 371 (Q-1).

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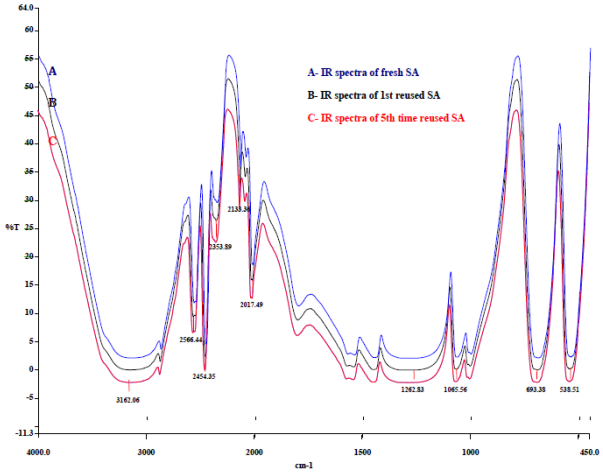
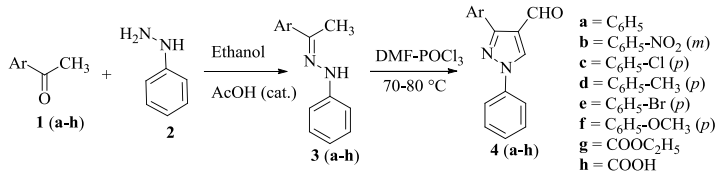
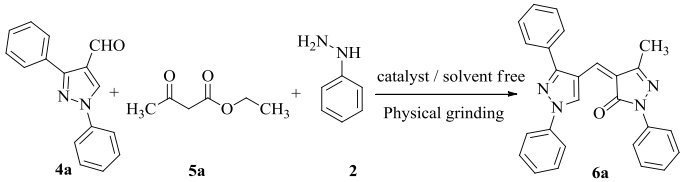


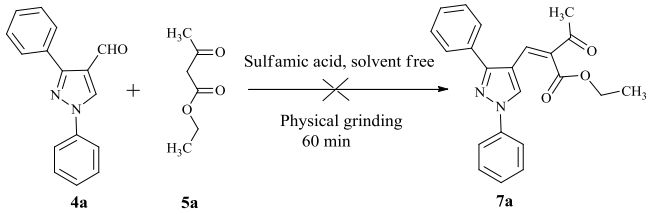
Fig. 1. IR spectra of sulfamic acid.



Scheme 1. Synthesis of 1, 3-diphenylpyrazolin-5-(4*H*)-4-carbaldehyde **4**(**a**-**h**).

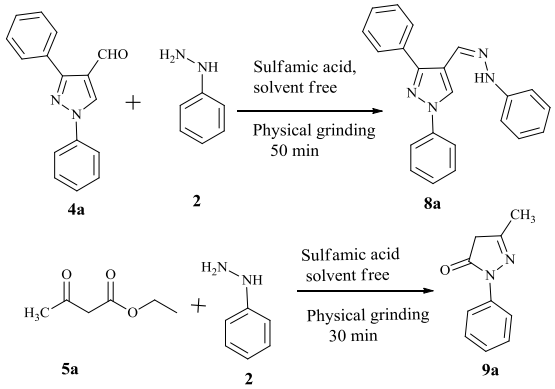


Scheme 2. One-pot synthesis of 4-((1,3-diphenyl-1*H*-pyrazol-4-yl) methylene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-ones **6a**.

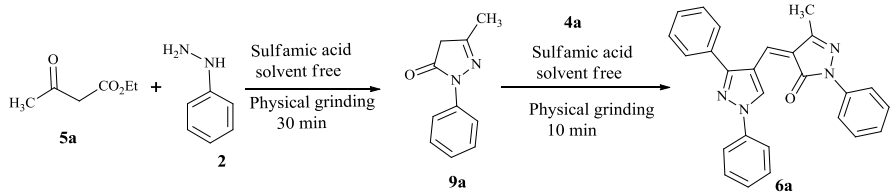


4a **5a** **7a**

Scheme 3. Condensation of **4a, 5a** in the presence of SA under solvent-free conditions.

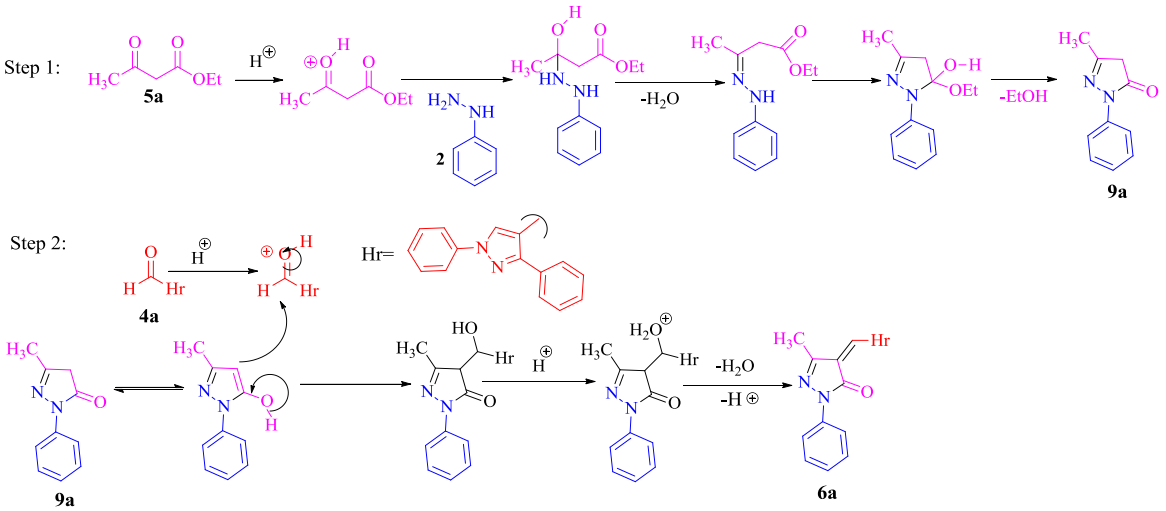


Scheme 4. Synthesis of hydrazone **8a** and pyrazolones **9a.**



5a **2** **9a** **6a**

Scheme 5. Stepwise synthesis of compound **6a**.



Scheme 6. Plausible mechanism for the synthesis of **6a**

Table 1
Optimisation of reaction conditions for the synthesis of **6a**.[a]

Entry	Catalyst	Time (min)	Yields (%)[c]
1	Catalyst-free/Solvent-free	100[b]	Nil
2	Proline/Solvent free	60[b]	62
3	$InCl_3$/Solvent free	40[b]	88
4	Montmorillonite K10/Solvent free	50[b]	68
5	Amberelyst-15/Solvent free	70[b]	80
6	Sulfamic acid (5 mol%) /Solvent free	40[b]	74
7	Sulfamic acid (10 mol%) /Solvent free	35[b]	78
8	Sulfamic acid (20 mol%) /Solvent free	35[b]	92
9	Sulfamic acid (30 mol%) /Solvent free	35[b]	92
10	Sulfamic acid (20 mol%)/Water	180	Nil
11	Sulfamic acid (20 mol%)/Ethanol	90	86
12	Sulfamic acid (20 mol%)/Methanol	90	80
13	Sulfamic acid (20 mol%)/DMF	180	Nil
14	Sulfamic acid (20 mol%)/Tetrahydrofuran	180	Nil
15	Sulfamic acid (20 mol%)/Chloroform	180	Nil

[a] Reaction conditions: One-pot reaction of **4a** (5 mmol, 1.24 g), **5a** (5 mmol, 0.6 mL) and **2** (5 mmol, 0.5 mL) were reacted in the presence of various catalysts under different conditions.
[b] Reaction carried out under solvent-free physical grinding conditions.
[c] isolated yields.

Table 2
Comparing the catalytic activity of sulfamic acid for the synthesis of **6a** with reported catalysts

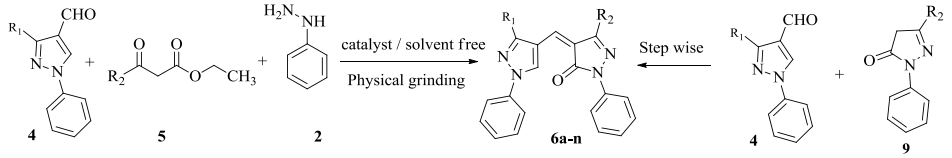
No.	Catalyst/ conditions	Time	Yields (%)	Ref.
1	Methanol/ Piperidine/Reflux	12h	74	17
2	Ionic liquid / RT	20 min	78	18
3	AcONa/PEG-400/60 °C	12 h	78	19
4	B_2O_3-ZrO_2/H_2O/reflux	25 min	70	20
5	Sulfamic acid / solvent free	35min	92[a]	Present work
6	Sulfamic acid / solvent free	10 min	96[b]	Present work

[a] One-pot synthesis of compound **6a**.

[b] Stepwise synthesis of compound **6a**.

Table 3

One-pot synthesis of 4-pyrazolylmethylene pyrazol-5(4*H*)-ones **6(a-n)**.[a]



Entry	R_1	R_2	Product	One-pot		Step wise		mp. (°C) (Lit.)
				Time (min)	Yield (%)[b]	Time (min)	Yield (%)[b]	
1	Ph-	CH_3	**6a**	35	92	10	96	212-214 (212) [18]
2	3-NO_2-Ph-	CH_3	**6b**	40	90	12	92	242-244 (242) [18]
3	4-Cl-Ph-	CH_3	**6c**	38	89	10	95	240-242 (238) [20]
4	4-CH_3-Ph-	CH_3	**6d**	36	90	10	95	232-234 (235) [20]
5	4-Br-Ph-	CH_3	**6e**	38	89	11	95	228-230 (228) [18]
6	4-OCH_3-Ph-	CH_3	**6f**	40	85	15	94	168-170 (167-169) [19]
7	Ph-	Ph	**6g**	36	89	11	95	186-188
8	3-NO_2-Ph-	Ph	**6h**	37	90	14	95	244-248
9	4-Cl-Ph-	Ph	**6i**	43	90	13	92	202-204
10	4-CH_3-Ph-	Ph	**6j**	40	89	10	94	208-210
11	4-Br-Ph-	Ph	**6k**	40	88	13	92	194-196
12	4-OCH_3-Ph-	Ph	**6l**	45	90	15	94	204
13	-$COOC_2H_5$	CH_3	**6m**	38	92	15	92	226-228
14	-COOH	CH_3	**6n**	38	92	15	92	>250

[a] Reaction conditions: One-pot reaction of **4a** (5 mmol, 1.24 g), **5a** (5 mmol, 0.6 mL) and **2** (5 mmol, 0.5 mL) were ground in the presence 20 mol% SA under solvent-free conditions.

[b] Refer to the yields of crude product.

Table 4
Recyclability of the catalyst[a]

No. of cycles	Fresh	Run 1	Run 2	Run 3	Run 4
Yield (%)[b]	92	92	90	88	85
Time (min)	35	35	37	40	42

[a] Reaction conditions: One-pot reaction of **4a** (5 mmol, 1.24g), **5a** (5 mmol, 0.6 mL) and **2** (5 mmol, 0.5 mL) were ground in the presence 20 mol% SA under solvent-free conditions.

[b] Refer to the yields of crude product.