ACADEMIA ROMÂNĂ
Revue Roumaine de Chimie
http://web.icf.ro/rrch/

Rev. Roum. Chim.,
2015, *60*(11-12), 1025-1032

SILICA SULFURIC ACID AS A SOLID ACID CATALYZED SYNTHESIS OF 4,5,6,7-TETRAHYDRO-2*H*-PYRAZOLO[3,4-*b*]PYRIDINE-5-CARBONITRILES AND 1,4-DIARYL-4,5-DIHYDRO-3-METHYL-1*H*-PYRAZOLO [3,4-*b*]PYRIDINE-6(7*H*)-ONES

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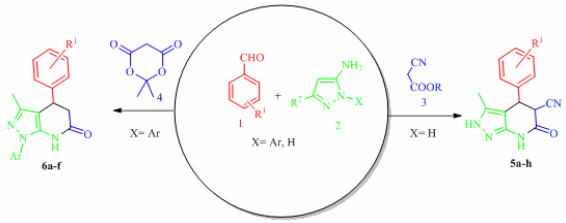
Received October 10, 2014

4-Aryl-3-methyl-6-oxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles in good to high yields at reflux conditions in presence and absence of silica sulfuric acid catalyst using an one-pot, three-component condensation reaction were synthesized. Then synthesis of 1,4-diaryl-4,5-dihydro-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-ones with silica sulfuric acid as a solid acid catalyst in acetonitrile has been described.



INTRODUCTION

One important aspect of clean technology is the use of environmentally friendly heterogeneous catalysts. Employing these catalysts reduces the pollution and waste material production. Besides, they have advantages over the conventional solution phase reactions because of the good dispersion of active reagent sites, associated selectivity and easier work-up.[1] Therefore, development of heterogeneous solid acid catalysts could have a major impact in industrial applications. Recently some of supported and/or immobilized heterogeneous catalysts have been reported.[2] One of these is silica sulfuric acid (SSA) that is solid acids which can be used for different organic functional group transformations either as reagent or as heterogeneous catalyst.[3]

Pyrazolo[3,4-*b*]pyridines and pyrazolo[1,5-*a*]pyrimidine, as condensed heterocycles, are attractive compounds for drug discovery since many of these scaffolds exhibit wide range of biological and pharmaceutical activities such as vasodilators to hypotensive, anti-inflammatory, analgesics and antipyretics,[4] inhibitors of xanthine oxidases,[5] inhibitors of B-Raf kinase,[6] inhibitors of cSRC kinase,[7] inhibitors of cyclin dependent kinase,[8] inhibitors of HIV reverse transcriptase,[9] anti-tumor and anti-proliferativeagents,[10] and anxiolytic[11] as well as treatment of Alzheimer's disease, gastrointestinal diseases, anorexia nervosa, drug and alcohol withdrawal symptoms, drug addiction and infertility.[12] The enlargement of simple synthetic methods for these derivatives is, therefore, important in organic synthesis.

A literature survey reveals that several methods have been reported for the synthesis of pyrazolopyridines,[13] so far, two report dealt with the synthesis of pyrazolo[3,4-*b*]pyridines (subclass of pyrazolopyridines). First report has been presented by Quiroga via two component reaction between aryliden Meldrum's acid derivatives and 1-aryl aminopyrazoles.[14] The other articles have

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been reported by Rahmati[15] and Zhang[16] via a three component reaction. However, these reactions require long reaction times, and use of toxic and homogeneous catalyst.

Because of the gifted biological potential of pyrazolo[3,4-*b*]pyridine and in continuation of our studies towards the heterocyclic synthesis,[17] herein we wish to report synthesis of 4-aryl-6-oxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile **5** and 1,4-diaryl-4,5-dihydro-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one **6** *via* two different one-pot three-component condensation reaction in the presence of SSA (Scheme 1). The principal advantages, scope and limitations of the method are also discussed.

EXPERIMENTAL

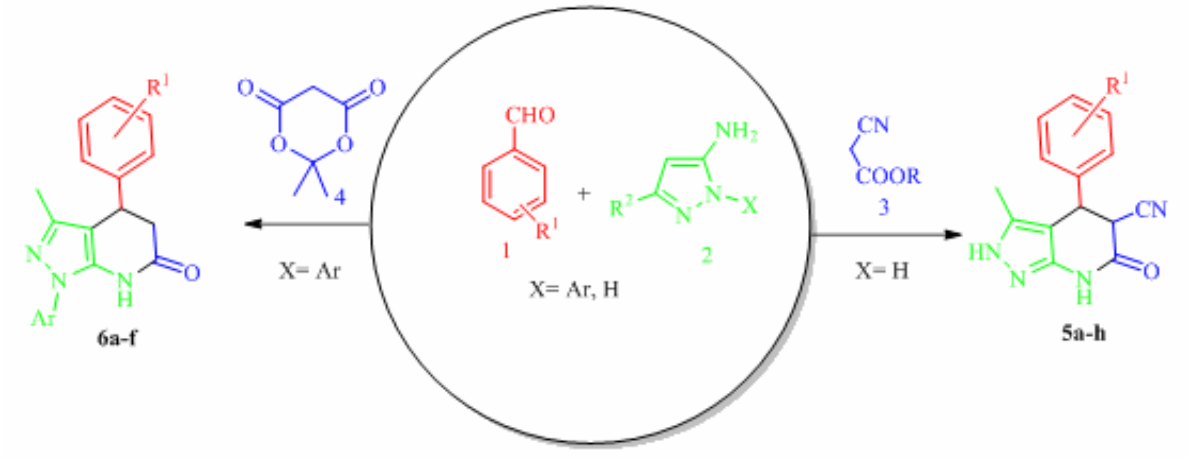
Method A: ***General procedure for the synthesis of 4-aryl-3-methyl-6-oxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridine-5-carbonitriles*** **(5a-h):** A solution of ethyl cyanoacetate (1mmol), aldehyde (1 mmol), 3-amin-5-methylpyrazole (1 mmol) was refluxed in ethanol (10 mL) for 24 h. After completion of the reactions, which has been followed by TLC (EtOAc*: n*-Hexene, 1: 2), the reaction mixture was left to be cooled. The residue was recrystallized gradually after one or two days.

Method B: ***General procedure for the synthesis of 4-aryl-3-methyl-6-oxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridine-5-carbonitriles*** **(5a-h):** A solution of ethyl cyanoacetate (1mmol), aldehyde (1 mmol), 3-amin-5-methylpyrazole (1 mmol) and SSA (0.1 g) was refluxed in ethanol (10 mL) for 12 h. After completion of the reactions, which has been followed by TLC (EtOAc:*n*-hexene, 1:2), the reaction mixture was filtered and left to be cooled. The residue was recrystallized gradually after one or two days.

General procedure for the synthesis of 1,4-diaryl-4,5-dihydro-3-methyl-1H-pyrazolo[3,4-b]pyridin-6(7H)-ones **(6a-f):** A solution of Meldrum's acid (1.1 mmol), aldehyde (1 mmol) and SSA (0.1 g) was refluxed in acetonitrile (10 ml) for 1 h. After 1-aryl-3-amino-5-methylpyrazole (1 mmol) was added to the mixture was refluxed in for 1 h. Then, it has been followed by TLC (EtOAc:*n*-hexene, 1:2). After completing, mixture was filtered and left to be cooled. Solvent removed by vacuum. The residue was recrystallized gradually from ethanol.

RESULTS AND DISCUSSION

Initial for optimization of experiment condition, in preparation of 4-aryl-3-methyl-6-oxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile, ethyl cyanoacetate, *p*-methoxybenzaldehyde and 3-amino-5-methylpyrazole have been selected as reactant in ethanol as solvent in the presence and absence of various heterogeneous catalysts. At first reaction was performed in the absence of catalysts at reflux condition (entry 1, Table 1). Then various heterogeneous catalysts have been used for this method (Table 1). The results show that among them silica sulphuric acid (SSA) is the best. In order to evaluate the efficiency of this methodology, selected reactants were further subjected to reaction using 0.30 mmol of H_2SO_4, $HClO_4$, acetic acid, sulfamidic acid and methanesulfonic acid (as homogeneous catalysts) under identical conditions. The results show that the efficiency of heterogeneous catalysts is better than homogeneous catalysts. In addition working with these acids is hard. These acids are corrosive to solid acids. Catalysts silica sulphuric acid,[18] MCM-SO_3H,[17,19] silica-bonded *S*-sulfonic acid (SBSSA)[20] and $HClO_4/SiO_2$[21] have been prepared by reported methods on literature.



Scheme 1 – Synthesis of 4-aryl-6-oxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles **5** and 1,4-diaryl-4,5-dihydro-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-ones **6**.

Table 1

Effects of various catalysts in synthesis of 4-aryl-3-methyl-6-oxo-4,5,6,7-^{tetrahydro}-2*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile[a]

Entry	Catalyst	Yield (%)[b]
1	-	74
2	Montmorillonite K-10	88
3	MCM-SO_3H	90
4	MCM-41	81
5	Silica-bonded *S*-sulfonic acid (SBSSA)	84
6	$HClO_4/SiO_2$	90
7	SSA	94
8	H_2SO_4	85
9	$HClO_4$	85
10	CH_3COOH	77
11	NH_2SO_3H	79
12	CH_3SO_3H	83

[a] *p*-methoxybenzaldehyde (1 mmol), 3-amino-5 methylpyrazole (1 mmol), ethyl cyanoacetate (1 mmol) in ethanol (5 mL), 24 h, 0.3 mmol or 0.3g (for solid acid) catalysts.
[b] Isolated yield.

Table 2

Effect of SSA amount, temperature and time on the yield of reaction[a]

Entry	SSA	Temperature (°C)	Time (h)	Yield (%)[b]
1	1.0 g	reflux	12	94
2	0.5 g	reflux	12	94
3	0.3 g	reflux	12	94
4	0.2 g	reflux	12	94
5	0.1 g	reflux	12	94
6	0.05 g	reflux	12	91
7	0.05 g	reflux	12	83
8	0.025 g	reflux	12	77
9	0.1 g	50	12	62
10	0.1 g	rt	12	35
11	0.1 g	reflux	8	89
12	0.1 g	reflux	16	94
13	0.1 g	reflux	24	94

[a] *p*-methoxybenzaldehyde (1 mmol), 3-amino-5-methylpyrazole (1 mmol), ethyl cyanoacetate (1 mmol) in ethanol (5 mL).
[b] Isolated yield.

The other advantage of this method is reusability of catalyst for five times without drop off efficiency (Table 3).

After choosing the best catalyst, the reaction was examined under different temperatures; the results showed that reflux condition is the best too and also the role of temperature in this reaction is important (Table 2). We also evaluated the amount of catalyst (Table 2). It was found that by increasing the amount of catalyst, the yields increased from 77-94% respectively. More amount of catalyst did not increase the yield. However, best amount of catalyst was 0.10 g.

Then, to explore the scope and limitations of this reaction, we have extended it to various substituted benzaldehydes with 3-amino-5-methylpyrazole in the presence of alkyl cyanoacetate and have prepared a library of 4-aryl-3-methyl-6-oxo-4,5,6,7-tetrahydro-2*H*-pyrazolo [3,4-*b*]pyridine-5-carbonitriles **5**. The results are shown in Table 4. As indicated in Table 4, the reaction proceeds efficiently with electron-withdrawing and electron-releasing substituted benzaldehydes.

Table 3

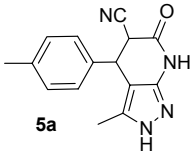
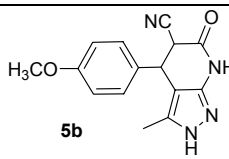
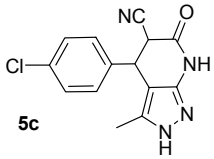
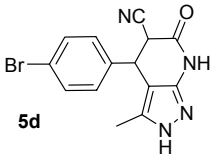
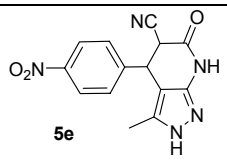
Recycle of SSA[a]

Cycle	SSA (g)	Yield(%)[b,c]
1	0.1	94
2	0.1	94
3	0.1	94
4	0.1	93
5	0.1	92

[a] Isolated yields of *p*-methoxybenzaldehyde (1 mmol), 3-amino-5-methylpyrazole (1 mmol), ethyl cyanoacetate (1 mmol) in ethanol (5 mL) at reflux conditions.

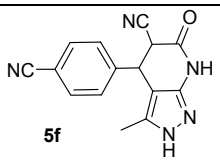
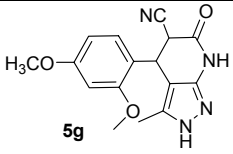
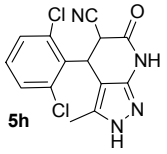
Table 4

Synthesis of 4-aryl-3-methyl-6-oxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles **5**

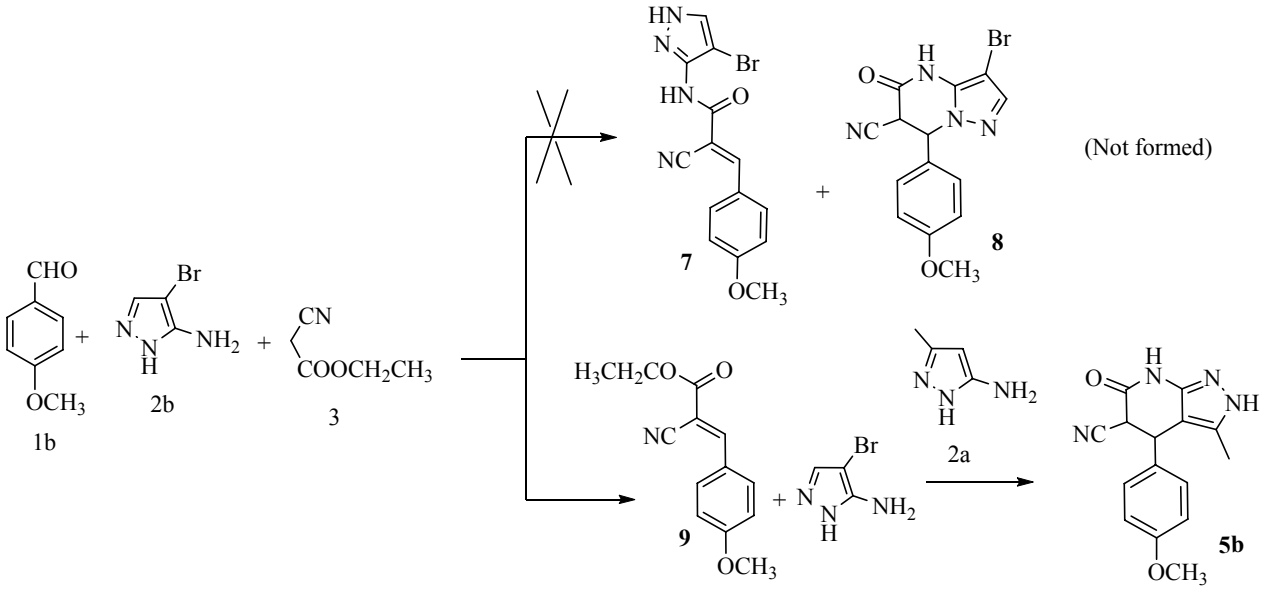
Entry	Ar in ArCHO	Product	Yield (%) (Trans:Cis ratio)[a]	Yield (%) (Trans:Cis ratio)[b]	Mp (°C)	
					Found	Reported [Lit.]
1	4Me-Ph-	 **5a**	70 (60/40)	90 (60/40)	316-317	315-318[15]
2	4-MeO-Ph-	 **5b**	74 (60/40)	94 (60/40)	323-324	323-325[15]
3	4Cl-Ph-	 **5c**	71 (57/43)	89 (57/43)	343-345	342-343[15]
4	4Br-Ph-	 **5d**	66 (58/42)	91 (58/42)	335-336	336-339[15]
5	4-NO_2-Ph-	 **5e**	61 (55/45)	87 (55/45)	327-328	327-328[15]

[c] Not formed

Table 4 (cotinued)

6	4CN-Ph-	 **5f**	63 (57/43)	83 (57/43)	335-337	344-345[15]
7	2,4-diMeO-Ph	 **5g**	76 (49/51)	95 (49/51)	336-337	335-336[15]
8	2,6-diCl-Ph	 **5h**	48 (68/32)	86 (68/32)	338-340	339-342[15]

[a] Isolated yield of method A: Aldehyde (1 mmol), 3-amino-5-methylpyrazole (1 m mol), ethyl cyanoacetate(1 m mol) in ethanol (5 ml) at reflux condition for 24 h.
[b] Isolated yield of method B: Aldehyde (1 mmol), 3-amino-5-methylpyrazole (1 m mol), ethyl cyanoacetate(1 m mol) in the presence of silica sulphuric acid (SSA) in ethanol (5 ml) at reflux condition for 12 h.
[c] *t*-Buthyl cyanoacetate (1 m mol) instead of ethyl cyanoacetate in ethanol (5 ml) at reflux condition.



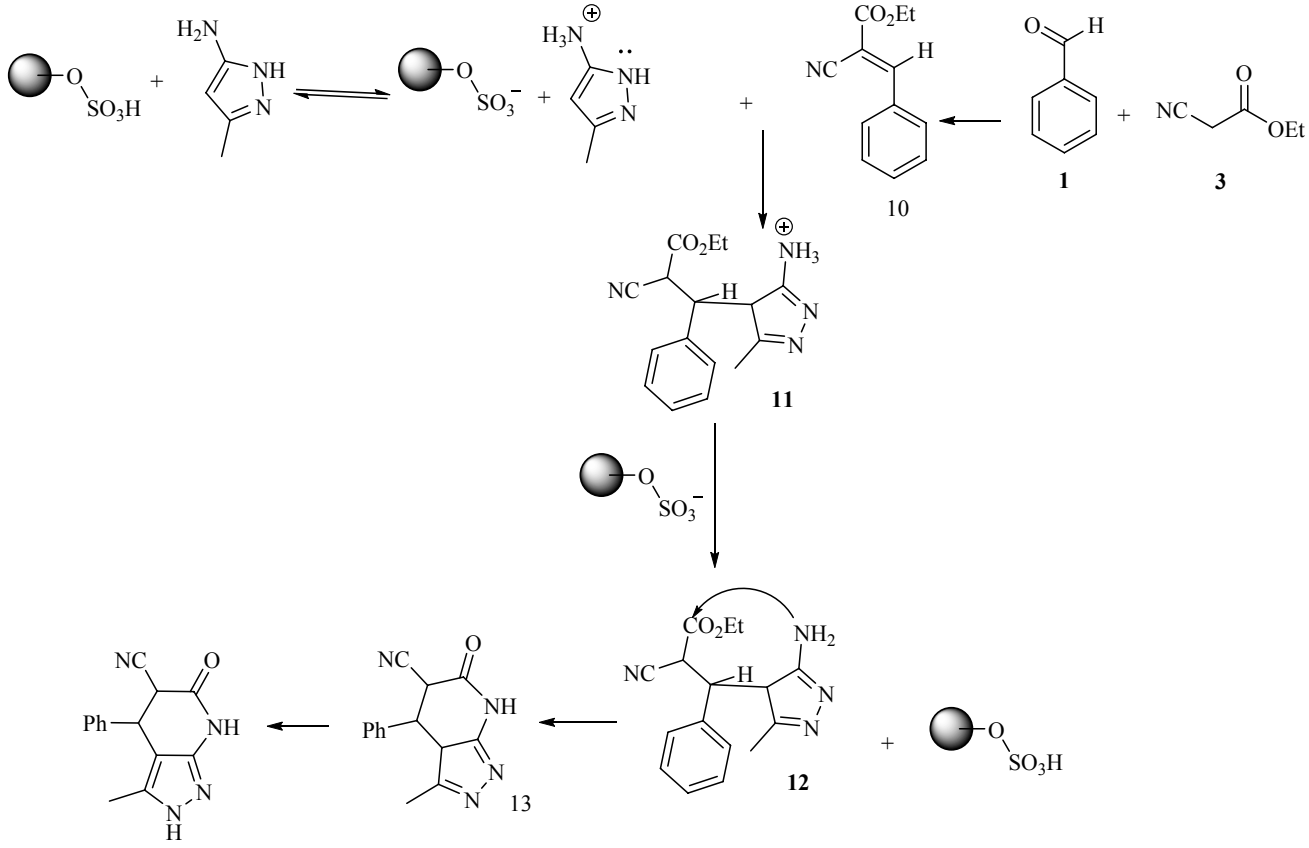
Scheme 2 – Comparative of two aminopyrazoles.

The structure of the products **5a–h** was deduced from their IR, ^{1}H NMR and ^{13}C NMR. The ^{1}H NMR spectroscopic data demonstrate during the reaction the yield of reaction by catalyst increased while *Cis* and *Trans* ratios don't change (Table 4).

It is important to note, when *t*-buthyl cyanoacetate was used instead of ethyl acetoacetate as reactant. It was found that *t*-buthyl cyanoacetate didn't participate in the reaction. (Table 4, Entry 2). The result has presented that steric hindrance effect in this reaction is important.

Under these conditions when other aminopyrazole such as 3-amino-4-bromo-pyrazole instead of 3-amino-5-methylpyrazole was used, no product was obtained. At this condition only intermediate was obtained. Then 3-amino-5-methylpyrazole was added to this mixture after 24 h and obtained product 5b. This point is important at mechanism of reaction (Scheme 2).

There has not been any established mechanism for the formation of 6-oxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*]pyridines, but reasonable possibilities are indicated in Scheme 4. The reaction presumably proceeds in several steps: at the first time, the acid and base reaction between SSA and 3-aminopyrazole produces 3-aminopyrazolium salt **10.** Then through a Michael addition, this compound is add to 3-benzylidene compounds **11,** which is produced by condensation of aldehydes **1** and ethyl cyanoacetate **3** through a Knoevenagel reaction, to give intermediates **12**, followed by its cyclization which results in ring systems **13**. Finally in the last step, compound **13** produces 6-oxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*]pyridines **4** by tautomerization (Scheme 3).



Scheme 3 – Probably mechanism for the synthesis of product **5**.

Table 5

Synthesis of 1,4-diaryl-4,5-dihydro-3-methyl-1H-pyrazolo[3,4-b]pyridin-6-one **6**[a]

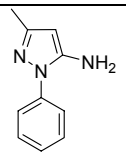
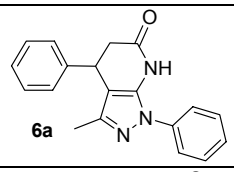
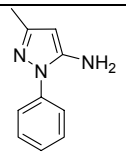
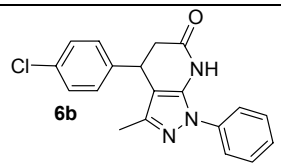
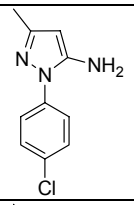
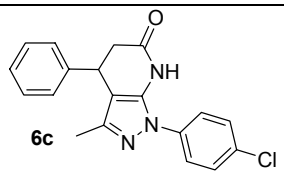
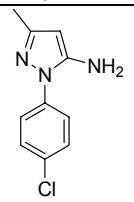
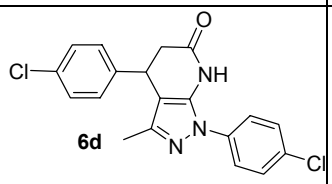
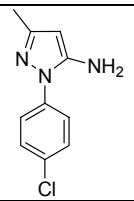
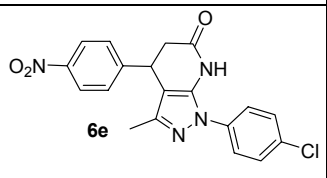
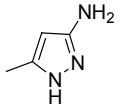
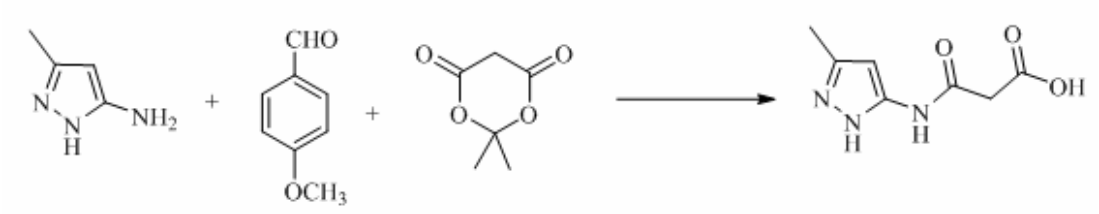
Entry	Ar- in ArCHO	Pyrazole	Product	Yield[b] (%)	Mp (°C)	
					Found	Reported [Lit.]
1	Ph-		 **6a**	82	154-155	156-157[16]
2	4Cl-Ph-		 **6b**	71	209-210	209-210[16]

Table 5 (continued)

3	Ph		 **6c**	64	196-197	194[14]
4	4Cl-Ph		 **6d**	62	156-157	154[14]
5	4NO_2-Ph-		 **6e**	79	197-199	198-199[14]
6	Ph-		-	-		-

[a] Isolated yield of method A: Aldehyde (1 mmol), 1-aryl-3-amino-5-methylpyrazole (1 m mol), Meldrum's acid (1 m mol), SSA (0.1 g) in acetonitrile (5 ml) at reflux condition for 12 h.
[b] Isolated yield.



Scheme 4 – Three component reaction 3-amino-5-methylpyrazole, Meldrum's acid and *p*-methoxybenzaldehyde.

Then, in continuation of enlargement of reaction, Meldrum's acid **4** has been utilized instead of ethyl cyanoacetate. 1,4-Diaryl-4,5-dihydro-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-ones **6** in good to high yield were obtained. First acetonitrile was used instead of methanol because Meldrum's acid slowly shattered at reflux condition in methanol. Then we found that reaction doesn't carry out with 3-amino pyrazoles that has hydrogen at nitrogen of ring. Yet, as indicated in Table 5, the reaction proceeds efficiently using different benzaldehydes with 1-aryl aminopyrazoles and Meldrum's acid.

The structure of the products **6a–e** was deduced from their melting point, IR and ^{1}H NMR.

We found that, when Meldrum's acid was treated with 3-amino-5-methylpyrazole in acetonitrile, the product **14** was obtained. This compound didn't participate in reaction with aldehyds as a three component reaction (Scheme 4), while 1-aryl-aminopyrazols did.

CONCLUSIONS

In conclusion, a novel and efficient three-component condensation reaction of an aldehyde, 3-amino-5-methylpyrazole and ethyl cyanoacetate was developed for the synthesis of 6-amino-4,7-dihydro-2*H*-pyrazolo[3,4-*b*]pyridines in the absence and presence of SSA catalyst. The simple one-pot nature of reaction, decreasing time of reaction, simple separation and reusing of catalyst, along with obviating the need for any modification of conditions of the educts makes it an interesting alternative to previous approaches. Also a safe catalyst was used in this reaction. In addition a new

three component method for the synthesis of 1,4-diaryl-4,5-dihydro-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-ones was presented. These methods are compatible in the field of combinatorial chemistry.

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