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Author: Chen-Feng Zhou Jian-Jun Li Wei-Ke Su

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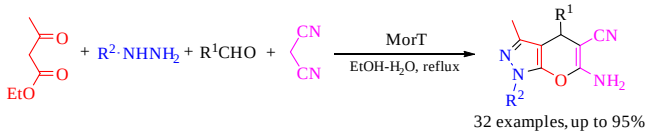
Graphical Abstract

Morpholine triflate promoted one-pot, four-component synthesis of dihydropyrano[2,3-*c*]pyrazoles

Chen-Feng Zhou[a,b], Jian-Jun Li[a,b,*], Wei-Ke Su[a,*]

[a] *National Engineering Research Center for Process Development of Active Pharmaceutical Ingredients, Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, Hangzhou 310014, China*
[b] *Key Laboratory for Green Pharmaceutical Technologies and Related Equipment of Ministry of Education, College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, China*



32 examples, up to 95%

A one-pot, four-component reaction of ethyl acetoacetate, hydrazine hydrate, aldehydes, and malononitrile was discussed using Lewis acid catalyst morpholine triflate (MorT) to afford a series of dihydropyrano[2,3-*c*]pyrazoles, which were generally catalyzed by organic alkalis. Moderate to excellent yields, no chromatographic purification, and evasion of environmentally hazardous solvents in the reaction process make this protocol very useful for academia and industry.

Original article

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[a] *National Engineering Research Center for Process Development of Active Pharmaceutical Ingredients, Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, Hangzhou 310014, China*
[b] *Key Laboratory for Green Pharmaceutical Technologies and Related Equipment of Ministry of Education, College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, China*

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ABSTRACT

A one-pot, four-component reaction of ethyl acetoacetate, hydrazine hydrate, aldehydes, and malononitrile was discussed using Lewis acid catalyst morpholine triflate (MorT) to afford a series of dihydropyrano[2,3-*c*]pyrazoles, which were generally catalysed by organic alkalis. Moderate to excellent yields, no chromatographic purification, and evasion of environmentally hazardous solvents in the reaction process make this protocol very useful for academia and industry.

1. Introduction

Over the past decades, green chemistry has evoked increasing interest in new, environmentally benign procedures such as multicomponent reactions, solvent-free syntheses, and reusable catalysts to save resources and energy [1]. Among these, multicomponent reactions (MCRs) are a very useful tool in synthetic organic chemistry as well as in drug discovery programs. With the developing awareness of environmentally benign chemical syntheses among the scientific community, designing chemical reactions without hazardous chemical ingredients to reduce or eliminate toxic waste and byproducts is the utmost priority for synthetic chemists. As organic solvents (THF, DMSO, DMF, $CHCl_3$, CCl_4, *etc.*) are considered to be the highest contributors to environmental pollution, synthetic utility is further made more attractive when environmentally-friendly solvents such as ethanol or water are used. The discovery of novel synthetic methodologies to prepare compound libraries using MCRs without the use of hazardous solvents is a significant and pivotal focal point in industry and academia [2].

The dihydropyrano[2,3-*c*]pyrazoles play an essential role as versatile synthetic building blocks and pharmacophores. Many of those compounds show different pharmacological effects such as antimicrobial [3], insecticidal [4], anti-inflammatory [5] and molluscicidal [6] activities. Furthermore, dihydropyrano[2,3-*c*]pyrazoles are reported as pharmaceutical ingredients, Chk1 inhibitors [7], and biodegradable agrochemicals [8].

In general, pyrano[2,3-*c*]pyrazoles have been synthesized *via* two-component reaction [9] involving pyran derivatives and hydrazine hydrate; three-component condensation [10] between *N*-methylpiperidone, pyrazolin-5-one and malononitrile in absolute ethanol; and more importantly four-component reactions of aldehyde, ethyl acetoacetate, hydrazine and malononitrile [11]. However, most of the protocols used nitrogenous based unrecoverable homogeneous catalysts like triethylamine [11a], piperidine [11b], L-proline [11c,d], per-6-amino-*β*-cyclodextrin [11e], hexadecyl dimethyl benzyl ammonium chloride [11f], basic ionic liquids [11g,h], disulfonic acid imidazolium chloroaluminate [11i], and meglumine [11j]. Several methods involving heterogeneous catalysts, such as amberlyst A21 [11k], γ-alumina [11l], and SnO_2 QDs [11m], have been reported. To the best of our knowledge, there are few methods available for the synthesis of highly functionalized dihydropyrano[2,3-*c*]pyrazoles frameworks in the presence of a Lewis acid. Thus, the development of a general MCR protocol using green Lewis acid catalyst leading to the pyrano[2,3-*c*]pyrazoles derivatives is highly desirable.

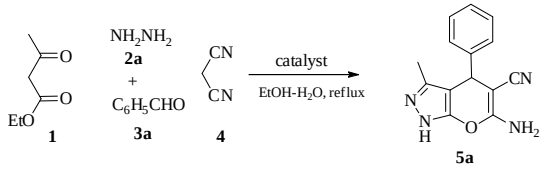
∗ Corresponding author.
E-mail address: lijianjun@zjut.edu.cn (Jian-Jun Li); pharmlab@zjut.edu.cn (Wei-Ke Su)

Organocatalysis is becoming an interesting area as it avoids the use of expensive and toxic metals. Ammonium triflate is a novel organocatalyst which has been applied in a variety of reactions and displayed great catalytic activity and efficiency [12]. Furthermore, ammonium triflate has many advantages, including easy separation, good reusability and environmental acceptability compared to traditional Lewis acid catalysts. In connection with our continuing studies on the development of one-pot multicomponent reactions catalyzed by ammonium triflates, we synthesized benzoxanthenes catalyzed by proline triflate (ProT) [12a] and 1,4-dihydropyridines catalyzed by diphenylammonium triflate (DPAT) [12b]. We also investigated some other reactions catalyzed by DPAT [12c] or ProT [12d]. Herein, we report an efficient and environmentally friendly method for the synthesis of dihydropyrano[2,3-*c*]pyrazoles catalyzed by MorT.

2. Experimental

Analytical grade solvents and commercially available reagents were used without further purification. Melting points were determined on a Büchi B-540 capillary melting point apparatus and uncorrected. All ^{1}H NMR and ^{13}C NMR spectra were recorded on a VARAIN-400 using DMSO-d_6 as the solvent with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ relative to TMS; the coupling constants J are given in Hz. Mass spectra were measured with a Thermo Finnigan LC Advantage (Agilent 1100). High resolution mass spectrometry (HRMS) was performed on an Agilent 6210 TOF LC/MS using ESI or EI (electrospray ionization) techniques.

General procedure for synthesis of dihydropyrano[2,3-*c*]pyrazoles (**5**) (Scheme 1): To a pre-stirred mixture of ethyl acetoacetate (**1**) (0.26 mL, 2.0 mmol), hydrazine hydrate (**2**) (0.13 mL, 2.5 mmol) in EtOH/H_2O (v/v = 9:1, 6 mL) was added aldehydes (**3**) (2.0 mmol) and malononitrile (**4**) (0.13 g, 2.0 mmol) followed by MorT (10 mol%). The resulting mixture was stirred under reflux. After completion of the reaction (monitored by TLC, *n*-hexane/ethyl acetate = 3:1), the precipitated product was filtered and washed with aqueous ethanol (10 mL). The crude residue was crystallized from ethanol/water (v/v = 9.5:0.5). ^{1}H NMR and ^{13}C NMR spectra for all compounds are available in Supporting information.



Scheme 1. General procedure for synthesis of dihydropyrano[2,3-*c*]pyrazoles.

Typical spectral data of some compounds are listed below, others are deposited in Supporting information.

6-Amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**5a**): Mp: 247-248 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.07 (s, 1H), 7.32-7.28 (m, 2H), 7.22-7.19 (m, 1H), 7.15 (d, 2H, *J* = 7.2 Hz), 6.86 (s, 2H), 4.58 (s, 1H), 1.77 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 160.5, 154.4, 144.1, 135.2, 128.1, 128.1, 127.2, 127.2, 126.4, 120.5, 97.4, 57.2, 36.2, 9.7; MS (ESI): *m/z* 251.3 [M-H]$^-$.

6-Amino-4-(4-fluorophenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**5b**): Mp: 223-224 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.09 (s, 1H), 7.21-7.17 (m, 2H), 7.12 (t, 2H, *J* = 8.8 Hz), 6.89 (s, 2H), 4.62 (s, 1H), 1.78 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.8, 160.5, 159.4, 154.4, 140.4, 135.3, 129.0, 120.4, 115.0, 114.8, 97.3, 57.1, 35.4, 9.7; MS (ESI): *m/z* 269.3 [M-H]$^-$.

6-Amino-3-methyl-4-(*p*-tolyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**5j**): Mp: 208-209 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.05 (s, 1H), 7.10 (d, 2H, *J* = 8.0 Hz), 7.03 (d, 2H, *J* = 8.0 Hz), 6.82 (s, 2H), 4.53 (s, 1H), 2.26 (s, 1H), 1.78 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 160.4, 154.5, 141.2, 135.4, 135.3, 128.7, 128.7, 127.1, 127.1, 120.6, 97.6, 57.4, 35.9, 20.7, 9.8; MS (ESI): *m/z* 265.3 [M-H]$^-$.

6-Amino-3-methyl-4-(4-nitrophenyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**5n**): Mp: 250-251 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.17 (s, 1H), 8.19 (d, 2H, *J* = 8.8 Hz), 7.45 (d, 2H, *J* = 8.8 Hz), 7.04 (s, 2H), 4.82 (s, 1H), 1.80 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 160.8, 154.4, 151.7, 146.1, 135.6, 128.6, 128.6, 123.6, 123.6, 120.2, 96.4, 55.9, 35.9, 9.8; MS (ESI): *m/z* 296.3 [M-H]$^-$.

6-Amino-4-(2,4-dichlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**5r**): Mp: 220-221 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.14 (s, 1H), 7.57 (d, 1H, *J* = 2.0 Hz), 7.39 (dd, 1H, *J* = 8.4 Hz), 7.20 (d, 1H, *J* = 8.0 Hz), 7.00 (s, 2H), 5.05 (s, 1H), 1.78 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.0, 154.6, 139.8, 135.2, 132.6, 131.9, 131.9, 128.6, 127.8, 120.0, 96.2, 55.3, 33.1, 9.4; MS (ESI): *m/z* 319.2 [M-H]$^-$.

6-Amino-4-(3,4-dimethylphenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**5s**): Mp: 201-202 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.02 (s, 1H), 7.04 (d, 1H, *J* = 7.6 Hz), 6.88-6.85 (m, 2H), 6.80 (s, 2H), 4.48 (s, 1H), 2.17 (s, 6H), 1.78 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 160.4, 154.4, 141.6, 135.8, 135.3, 134.2, 129.2, 128.2, 124.7, 120.6, 97.6, 57.5, 35.9, 19.5, 19.0, 9.8; MS (ESI): *m/z* 303.5 [M+Na]$^+$. HRMS (ESI$^+$, *m/z*): [M+H]$^+$, calcd. for $C_{16}H_{17}N_4O$: 281.1397, found: 281.1399.

6-Amino-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**5aa**): Mp: 168-169 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.78 (d, 2H, *J* = 7.6 Hz), 7.50-7.46 (m, 2H), 7.34-7.26 (m, 3H), 7.26-7.24 (m, 3H), 7.22 (s, 2H), 4.67 (s, 1H), 1.78 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 159.1, 144.9, 143.6, 143.3, 137.3, 129.0, 129.0, 128.2, 128.2, 127.5, 127.5, 126.7, 125.8, 119.7, 119.7,

119.7, 98.4, 58.2, 36.7, 12.6; MS (ESI): *m/z* 329.4 $[M+H]^+$. HRMS (ESI^+, *m/z*): $[M+H]^+$, calcd. for $C_{20}H_{17}N_4O$: 329.1397, found: 329.1406.

6-Amino-4-(4-isopropylphenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**5af**): Mp: 149-151 ^oC. ^1H NMR (DMSO-d_6, 400 MHz): δ 7.77 (d, 2H, J = 7.6 Hz), 7.49-7.45 (m, 2H), 7.32-7.28 (m, 1H), 7.21 (m, 2H), 7.19 (s, 2H), 7.15-7.13 (m, 2H), 4.63 (s, 1H), 2.90-2.83 (m, 1H), 1.79 (s, 3H), 1.19 (d, 6H, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 159.1, 146.6, 144.9, 143.5, 140.7, 137.3, 129.0, 129.0, 127.3, 127.3, 126.1, 126.1, 125.8, 119.8, 119.7, 119.7, 98.6, 58.2, 36.3, 33.0, 23.8, 23.8, 12.6; MS (ESI): *m/z* 371.5 $[M+H]^+$. HRMS (ESI^+ , *m/z*): $[M+H]^+$, calcd. for $C_{23}H_{23}N_4O$: 371.1866, found: 371.1866.

3. Results and discussion

We started our investigation by choosing different ammonium triflates (Fig. 1) for the optimization of reaction conditions catalyzing this four-component condensation using EtOH/H_2O as solvent (Table 1).

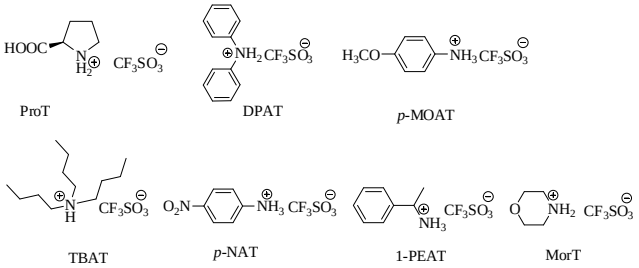
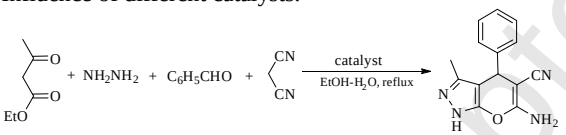


Fig. 1. Different kinds of ammonium triflates.

When the reaction was conducted without catalyst, only a low yield of product was obtained even after 12 h (Table 1, entry 1). This result suggested that catalyst played a critical role in this reaction. A number of ammonium triflate catalysts were examined to promote this reaction under reflux (Table 1, entries 2–8). MorT proved to be the most efficient one that gave the highest yield (92%) within 9 h (Table 1, entry 8). Morphine and HOTf were also examined to promote this transformation, as they can react with each other to afford MorT (Table 1, entries 9 and 10). It seemed that the catalytic activity of MorT was much better than HOTf but close to morphine. There are many papers related to the synthesis of dihydropyrano[2,3-*c*]pyrazoles catalysed by Lewis acid. Here, MorT was introduced as the Lewis acid catalyst leading to the pyrano[2,3-*c*]pyrazoles.

Table 1
Influence of different catalysts. [a]



1 **2a** **3a** **4** **5a**

Entry	Catalyst	Time (h)	Yield (%)[b]
1	/	12	33
2	ProT	12	36
3	DPAT	12	12
4	*p*-MOAT	12	18
5	TBAT	12	36
6	*p*-NAT	12	38
7	1-PEAT	12	20
8	MorT	9	92
9	HOTf	12	13
10	Morpholine	9	83

[a] Experimental conditions: benzaldehyde (2 mmol), hydrazine hydrate (2 mmol), malononitrile (2 mmol), ethyl acetoacetate (2 mmol), catalyst (10 mol %), reflux, EtOH-H_2O (9:1, 6 mL).
[b] Isolated yield based on **1**.

With regard to the choice of catalyst, we carried out the above reaction in various solvents. As shown in Table 2, when the reaction was performed under solvent-free conditions, low product yield was obtained (Table 2, entry 1). To find the best solvent for this transformation, the present four-component reaction was screened in H_2O, THF, DMSO, DMF, MeOH, EtOH, ^{i}PrOH and ethanol-water mixture. Among all these solvents, ethanol-water (9:1) was found to be the best one and afforded the highest yield (Table 2, entry 11). Therefore, ethanol-water was selected as the solvent system for the subsequent reaction.

Table 2
Optimization of reaction conditions. [a]

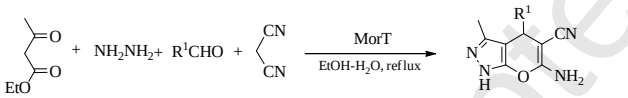
Entry	Solvent	Temp. (°C)	Time (h)	Yield of **5a** (%) [b]
1	/	85 [c]	12	33
2	H_2O	85 [c]	12	66
3	THF	reflux	12	31
4	DMSO	85 [c]	12	22
5	DMF	85 [c]	12	34
6	MeOH	reflux	12	79
7	^{i}PrOH	reflux	12	75
8	EtOH	reflux	12	70
9	EtOH/H_2O (1:1)	reflux	9	72
10	EtOH/H_2O (5:1)	reflux	9	85
11	EtOH/H_2O (9:1)	reflux	9	92

[a] Experimental conditions: benzaldehyde (2 mmol), hydrazine hydrate (2 mmol), malononitrile (2 mmol), ethyl acetoacetate (2 mmol), solvent (6 mL), MorT (10 mol %).
[b] Isolated yield based on **1**.
[c] Oil bath temperature.

Encouraged by the efficiency of the reaction protocol described above, the scope and specificity of this protocol were further investigated. A library of dihydropyrano[2,3-*c*]pyrazoles were constructed under the optimized reaction conditions (Table 3). A broad range of structurally diverse aldehydes were treated with hydrazine hydrate, malononitrile, and ethyl acetoacetate, and the results are depicted in Table 3. All reactions proceeded efficiently, and the desired products were obtained in moderate to excellent yields.

Irrespective of the presence of electron withdrawing or donating substituents in the *ortho*, *meta*, or *para* positions on the aromatic ring of aldehydes, the reactions proceeded smoothly to furnish the desired products in high yields (**5a-5z**). The reaction was relatively sensitive to the steric environment of the aromatic aldehydes, and longer reaction time was required for benzaldehyde containing substituents at 2-position (Table 3, entries 3, 5, 7, 17 and 18). A relatively low yield was observed when the aromatic aldehydes were occupied by two or more substituents (Table 3, entries 18-21). The reaction worked well for the aliphatic aldehydes under similar reaction conditions without the unwanted byproducts *via* side reactions such as aldo condensation and the Cannizzaro reaction (Table 3, entries 21-24). Heteroaromatic aldehydes, such as furan-2-carbaldehyde and pyridine-3-carboxaldehyde readily participated in this transformation, affording the pyranopyrazoles in high yields (Table 3, entries 25 and 26). In general, all the reactions listed in Table 3 were moderate to high-yielding (54%–95%) and in non-hazardous solvents (EtOH-H_2O) and the products could be recrystallized from ethanol to avoid column chromatography purification.

Table 3
Synthesis of dihydropyrano[2,3-*c*]pyrazole **5** from carbonyl compounds. [a]



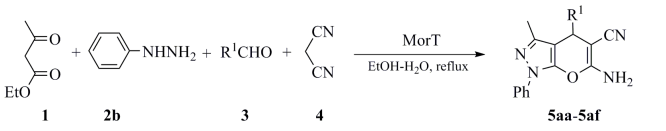
1 **2a** **3** **4** **5a-5z**

Entry	R^1	Time (h)	Product	Yield (%) [b]
1	C_6H_5-	9	**5a**	92
2	4-FC_6H_4-	8	**5b**	71
3	2-ClC_6H_4-	9	**5c**	94
4	4-ClC_6H_4-	7	**5d**	95
5	2-BrC_6H_4-	10	**5e**	82
6	4-BrC_6H_4-	7	**5f**	90
7	2-HOC_6H_4-	10	**5g**	92
8	3-HOC_6H_4-	8	**5h**	92
9	3-$CH_3C_6H_4$-	8	**5i**	87
10	4-$CH_3C_6H_4$-	9	**5j**	58
11	3-$CH_3OC_6H_4$-	7	**5k**	85
12	4-$CH_3OC_6H_4$-	8	**5l**	78
13	4-$CF_3C_6H_4$-	9	**5m**	63
14	4-$NO_2C_6H_4$-	6	**5n**	92
15	4-^{i}PrC_6H_4-	8	**5o**	65
16	4-$(CH_3)_2NC_6H_4$-	8	**5p**	62
17	2-F-6-Cl-C_6H_3-	12	**5q**	91
18	2,4-$Cl_2C_6H_3$-	10	**5r**	59
19	3,4-$(CH_3)_2C_6H_3$-	8	**5s**	74
20	2,4,5-$(CH_3O)_3C_6H_2$-	9	**5t**	75
21	3-C_6H_5O-4-F-C_6H_3-	8	**5u**	67
22	$CH_3CH_2CH_2$-	7	**5v**	54
23	$(CH_3)_2CH$-	7	**5w**	87
24	$(CH_3)_3C$-	9	**5x**	72
25	2-Furan-	7	**5y**	79
26	3-Pyridine-	8	**5z**	84

[a] Experimental conditions: aldehyde (2 mmol), hydrazine hydrate (2 mmol), malononitrile (2 mmol), ethyl acetoacetate (2 mmol), solvent (6 mL), MorT (10 mol %), reflux.
[b] Isolated yield based on **1**.

Additionally, the reaction went well when hydrazine hydrate was replaced with phenylhydrazine. We observed that it was a little sensitive to the steric environment of the hydrazine as a slightly longer reaction time was required for the reaction compared with Table 3 (Table 4, entries 1-6).

Table 4
Synthesis of dihydropyrano[2,3-*c*]pyrazole **5** from phenylhydrazine and carbonyl compounds. [a]

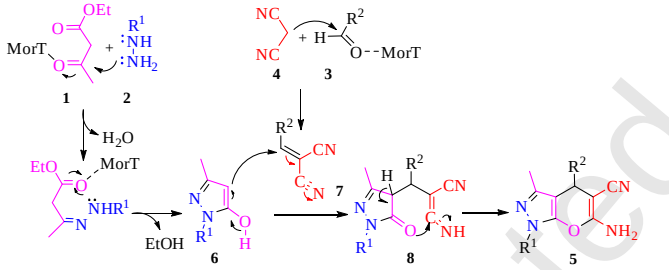


1 **2b** **3** **4** **5aa-5af**

Entry	R^1	Time (h)	Product	Yield (%) [b]
1	C_6H_5-	10	**5aa**	84
2	4-FC_6H_4-	12	**5ab**	57
3	4-ClC_6H_4-	12	**5ac**	70
4	4-$NO_2C_6H_4$-	12	**5ad**	87
5	4-$CH_3C_6H_4$-	10	**5ae**	82
6	4-^{i}PrC_6H_4-	12	**5af**	89

[a] Experimental conditions are same as that in Table 3.
[b] Isolated yield based on **1**.

The formation of product **5** is proposed to involve the following tandem reactions (Scheme 2): Firstly, pyrazolone **6** was formed by the reaction between **1** and **2**. The Knoevenagal condensation between **3** and **4** was carried out in the presence of MorT. Then, after Michael addition of **6** and **7**, followed by cyclization and tautomerization, the title product **5** was formed.



Scheme 2. Proposed mechanism for the formation of pyrano[2,3-*c*]pyrazoles.

4. Conclusion

In summary, we have developed an efficient method for the synthesis of a diverse range of dihydropyrano[2,3-*c*]pyrazoles using Lewis acid MorT as an eco-friendly catalyst. No chromatography, no hazardous organic solvents, and moderate to excellent yield of the products are the major achievements of this reaction protocol, which has potential to be extremely useful for synthetic applications. This method using Lewis acid is a useful supplement to the reported methods.

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