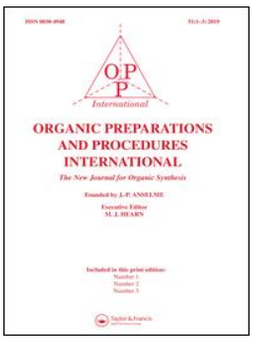

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OPPI BRIEF

Catalytic Application of 1,4-Piperazinediethanesulfonic Acid (PIPES) for the One-pot Multicomponent Synthesis of Pyrano[4,3-b]pyrans

Nader Ghaffari Khaligh[a], Taraneh Mihankhah[b], and Mohd Rafie Johan[a]

[a]Nanotechnology and Catalysis Research Center, Institute of Postgraduate Studies, University of Malaya, Kuala Lumpur, Malaysia; [b]Environmental Research Laboratory, Department of Water and Environmental Engineering, School of Civil Engineering, Iran University of Science and Technology, Tehran, Iran

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Pyrans have been extensively explored in both academic organizations and pharmaceutical industries owing to their biological characteristics, including anticancer activity.[1,2] Among the pyrans, pyrano[4,3-*b*]pyran derivatives have shown such pharmacological properties as antiviral,[3] antimicrobial,[4] antifungal,[5,6] and antioxidant[7] activities. Due to their wide range of applications, several methods have been developed for the synthesis of pyrano[4,3-*b*]pyrans as valuable lead compounds; and all of these methods have their merits and limitations.[3,8–16] Some of the drawbacks include: the use of catalysts containing metals, which are not desirable because of their toxicity or waste generation; high costs and time-consuming procedures for the preparation of catalysts; long reaction times; high temperatures or low yields.

Good and coworkers had earlier suggested 1,4-piperazinediethanesulfonic acid (PIPES) as a buffer for biological applications.[17] PIPES is not prone to complex formation with metal ions and has a pK_a near to physiological pH, so PIPES has been used as a buffering agent in biological, biochemical and environmental studies.[18] PIPES is a substance which is commercially available, non-toxic, thermally stable, inexpensive, easy to handle and easy to store. In past efforts, we have used the planetary ball mill for the synthesis of pyrano[4,3-*b*]pyrans,[15–16] Schiff bases,[19,20] and arylidene analogues of Meldrum's acid.[21] We would now like to report on the catalytic efficiency of PIPES for the synthesis of pyrano[4,3-*b*]pyrans under mild conditions. To the best of our knowledge, PIPES has not been exploited previously in organic synthesis as an organocatalyst. This is part of a wider exploration by our laboratory to develop more reactions using PIPES as a desirable organocatalyst in organic transformations.

In order to establish the optimum conditions, 4-chlorobenzaldehyde (**1a**), malononitrile, and 4-hydroxy-6-methyl-2-pyrone were chosen as the model reactants. The model reactants were ground through the ball milling process at room temperature under catalyst-free and solvent-free conditions. With no catalyst, even after 4 hours, TLC analysis showed that the aldehyde remained, and there was no new spot for the putative product 2-amino-4-(4-chlorophenyl)-7-methyl-5-oxo-4*H*,5*H*-pyrano[4,3-*b*]pyran-3-carbonitrile

CONTACT Nader Ghaffari Khaligh, ngkhaligh@gmail.com Nanotechnology and Catalysis Research Center, 3rd Floor, Block A, Institute of Postgraduate Studies, University of Malaya, 50603 Kuala Lumpur, Malaysia

Table 1. Optimization of the synthesis of pyrano[4,3-*b*]pyrans.[a]

Entry	Loading **TMDPS** (mol%)	Number of milling ball	Speed (rpm)	Milling ball diameter (mm)	Milling time (min)	Yield (%)[b]
1	0	5	300	7	240	-[c]
2	10	5	300	7	240	78
3	10	5	300	7	60	77
4	10	5	300	7	30	73
5	5	5	300	7	30	61
6	10	5	400	7	30	77
7	10	5	500	7	30	88
8	**10**	**5**	**600**	**7**	**30**	**94**
9	10	5	600	5	30	42
10	10	2	600	10	30	81

[a]Reaction conditions: 4-chlorobenzaldehyde (**1a**) (5.0 mmol), 4-hydroxy-6-methyl-2-pyrone (5.0 mmol), malononitrile (5.0 mmol), room temperature.
[b]Isolated yield.
[c]Monitored by TLC, see Experimental section.

(**2a**) (Table 1, Entry 1). By manipulating the parameters shown in Table 1, we deduced that Entry 8 represented the optimized reaction conditions.

Then we studied the scope and generality of the present protocol for the synthesis of pyrano[4,3-*b*]pyran derivatives through our ball milling process under optimized reaction conditions (Scheme 1).

Substituted pyrano[4,3-*b*]pyrans (**2a-o**) were obtained in good to excellent yields (Table 2). The electron-withdrawing substituents on the benzaldehyde ring afforded higher yields than electron-donating substituents at the same positions, probably due to the enhanced electrophilicity of the aldehyde (Table 2, Entries 1,4,9,13 *versus* 5,7,10,12). Even the benzaldehydes bearing acid-sensitive methoxy substituents gave the respective products in good yield without decomposition (Table 2, Entries 5,7,12).

A comparison of the current method with a few previously reported methods is shown in Table 3.

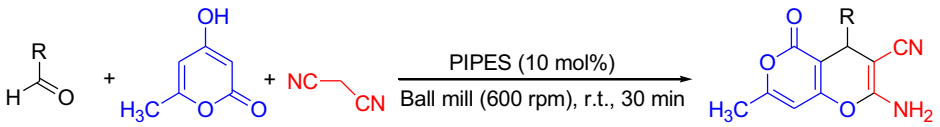
A scale up experiment was carried out through the condensation reaction of 4-chlorobenzaldehyde (50.0 mmol), malononitrile (50.0 mmol), and 4-hydroxy-6-methyl-2-pyrone (50.0 mmol) under optimized reaction conditions. This afforded **2a** in 83% yield within 30 min.

We found that the recovered PIPES (see Experimental section) could be dried and re-used in subsequent runs. During three subsequent runs, representative products **2a, 2b**, and **2c** were obtained in the presence of recycled PIPES in a range of yields of 94-90%, 85-83%, and 86-82%, respectively.

In conclusion, the catalytic efficiency of PIPES was demonstrated for the synthesis of pyrano[4,3-*b*]pyrans using the ball milling process for the first time. The current protocol has such advantages as simplicity, solvent-free conditions at room temperature, high yields, short reaction times, and recyclability. We hope that these promising results will foster further research for the catalytic applications of PIPES in organic synthesis.

Experimental section

All chemicals were analytical grade and purchased from Sigma Aldrich, Merck, and Fluka Chemical Companies and used without further purification. All the products are known compounds and were characterized by their melting points. The purity



1(a-o) **2(a-o)**

Scheme 1. Over-all reaction.

Table 2. The catalytic application of PIPES in the synthesis of pyrano[4,3-*b*]pyran derivatives.[a]

Entry	Aldehydes **1(a-o)**	Pyrano[4,3-b]pyran **2(a-o)**	Yield (%)[b]	Melting point (°C) Found	Melting point (°C) Reported[ref.]
1	4-Cl-C_6H_4-	**2a**	94	221-223	228-230[22]
2	C_6H_5-	**2b**	85	247-248	236[22]
3	4-CH_3-C_6H_4-	**2c**	86	225-226	218-220[22]
4	4-NO_2-C_6H_4-	**2d**	94	218-220	220-222[22]
5	4-(CH_3O)-C_6H_4-	**2e**	86	205-207	210-212[12]
6	2-Cl-C_6H_4-	**2f**	84	260-261	258-260[14]
7	3,4,5-(CH_3O)$_3$-C_6H_2-	**2g**	82	228-230	227-229[14]
8	4-Br-C_6H_4-	**2h**	88	219-221	217-219[12]
9	4-F-C_6H_4-	**2i**	92	220-222	223-225[3]
10	4-(CH_3)$_2$CH-C_6H_4-	**2j**	84	222-223	220-222[14]
11	3,5-Cl_2-C_6H_4-	**2k**	87	212-214	212-214[14]
12	2-(CH_3O)-C_6H_4-	**2l**	80	238-239	242-244[14]
13	4-CF_3-C_6H_4-	**2m**	92	215-216	217-219[14]
14	3,5-F_2-C_6H_3-	**2n**	89	241-243	240-241[14]
15	3,5-(CF_3)$_2$-C_6H_4-	**2o**	90	243-244	245-247[14]

[a]Reaction conditions: aldehyde **1(a-o)** (5.0 mmol), malononitrile (5.0 mmol), 4-hydroxy-6-methyl-2-pyrone (5.0 mmol), PIPES (0.5 mmol), revolution rate (600 rpm), five milling balls with diameter 7 mm, milling time (30 min), room temperature.
[b]Isolated yield.

Table 3. Comparison of the present protocol with other reported strategies for the synthesis of 2-amino-4-phenyl-7-methyl-5-oxo-4H,5H-pyrano[4,3-*b*]pyran-3-carbonitriles.

Entry	Catalyst	Catalyst loading (mol%)	Conditions	Time (min)	Yield (%)	Ref.
1	[BMIM][BF_4]	664	80 °C	180	85	3
2	[NH_4][OAc]	10	Solvent-free, grinding, r.t.	10	94	7
3	4-(Succinimido)-1-butane sulfonic acid	4.2	Neat, 60 °C	60	88	10
4	[BBMIm][HSO_4]	120.5	Solvent-free, 60 °C	35	94	12
5	TMDPS	5	Milling, r.t.	30	84	14
6	BBSI-HSO4	5	Milling, r.r.	30	89	15
7	TMDP	20	Milling, r.t.	90	85	16
8	Succinimide-*N*-sulfonic acid	10	Solvent-free, 60 °C (Solar energy)	35	94	22
9	KF-Al_2O_3	50 mg per mmol	EtOH, reflux	480[a]	76[a]	24
10	Piperidine	1-2 drops per mmol	MeOH, reflux	60	79	25
11	Thiourea dioxide	10	H_2O, 80 °C	40	92	26
12	Urea	10	EtOH:H_2O (1:1 v/v), r.t.	420	81	27
13	TMGT	1.0	Solvent-free, 100 °C	60	77	28
14	Porcine pancreas lipase	120 U	*i*-Propanol, 60 °C	600	89	29
15	–	–	H_2O, 80 °C	630	65	30
16	PIPES	10	Milling, r.t.	30	85	This work

[a]2-Amino-4-(4-chlorophenyl)-7-methyl-5-oxo-4*H*,5*H*-pyrano[4,3-*b*]pyran-3-carbonitrile.

determination of the substrates and reaction monitoring were accomplished by TLC using silica gel SIL G/UV 254 plates and eluent (ethyl acetate:*n*-hexane 2:8). Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes and are uncorrected. In all the cases the ^{1}H NMR spectra were recorded with Bruker 400 MHz instruments. All chemical shifts are quoted in parts per million (ppm) relative to TMS using deuterated solvent. Ball-milling was performed in a Retsch PM100 planetary ball mill using the stainless steel chamber and two or five stainless steel balls (diameter: 5, 7 or 10 mm) with 300-600 rpm.

Typical catalytic application of PIPES for the synthesis of pyrano[4,3-b]pyran derivatives

The aldehyde (5.0 mmol), malononitrile (5.0 mmol), 4-hydroxy-6-methyl-2-pyrone (5.0 mmol) and PIPES (10 mol%) were milled vigorously using the planetary ball mill at room temperature for 30 min. The reaction mixture was washed with dilute hydrochloric acid (5%) and the product was separated by simple filtration. The dry solid crude product was purified by recrystallization from ethanol and did not require further purification. All the compounds had melting points and ^{1}H NMR spectra identical to the literature values.[3,12,14,22] The PIPES could be regenerated from the aqueous acid wash through neutralizing by $NaHCO_3$ and washing with methanol and evaporating of solvent. The regenerated PIPES was applied for another run. Listed below are representative ^{1}H NMR spectra of less common products.

2-Amino-4-(4-fluorophenyl)-7-methyl-5-oxo-4H,5H-pyrano[4,3-b]pyran-3-carbonitrile (2i)

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.25-7.12 (m, 6H), 6.28 (s, 1H), 4.31 (s, 1H), 2.22 (s, 3H) ppm.

2-Amino-4-(4-isopropylphenyl)-7-methyl-5-oxo-4H,5H-pyrano[4,3-b]pyran-3-carbonitrile (2j)

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.20-7.18 (m, 3H), 7.10 (d, 2H, J = 8.8 Hz), 6.28 (s, 1H), 4.25 (s, 1H), 2.85 (s, 1H), 2.21 (s, 3H), 1.20 (s, 3H), 1.18 (s, 3H) ppm.

2-Amino-4-(3,5-dichlorophenyl)-7-methyl-5-oxo-4H,5H-pyrano[4,3-b]pyran-3-carbonitrile (2k)

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.46 (t, J = 1.8 Hz, 1H), 7.20-7.18 (m, 2H), 6.98 (s, 2H), 6.30 (s, 1H), 4.46 (s, 1H), 2.28 (s, 3H) ppm.

2-Amino-4-(2-methoxyphenyl)-7-methyl-5-oxo-4H,5H-pyrano[4,3-b]pyran-3-carbonitrile (2l)

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.20-7.18 (m, 1H), 7.05-6.98 (m, 2H), 6.92-6.87 (m, 3H), 4.70 (s, 1H), 3.68 (s, 3H), 2.30 (s, 3H) ppm.

2-Amino-4-(4-trifluoromethyl-phenyl)-7-methyl-5-oxo-4H,5H-pyrano[4,3-b]pyran-3-carbonitrile (2m)

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.70 (d, J = 8.4 Hz, 2H), 7.51 (s, 2H), 7.46 (d, J = 8.4 Hz, 2H), 4.58 (s, 1H), 2.91 (s, 3H) ppm.

2-Amino-4-(3,5-difluorophenyl)-7-methyl-5-oxo-4H,5H-pyrano[4,3-b]pyran-3-carbonitrile (2n)

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.33 (s, 2H), 7.16-7.08 (m, 1H), 7.01-6.94 (m, 2H), 6.30 (s, 1H), 4.43 (s, 1H), 2.25 (s, 3H) ppm.

2-Amino-4-(3,5-bis(trifluoromethyl)phenyl)-7-methyl-5-oxo-4H,5H-pyrano[4,3-b]pyran-3-carbonitrile (2o)

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.02 (s, 1H), 7.96 (s, 2H), 7.41 (s, 2H), 6.32 (s, 1H), 4.72 (s, 1H), 2.25 (s, 3H) ppm.

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ORCID

Nader Ghaffari Khaligh http://orcid.org/0000-0001-9585-9253
Taraneh Mihankhah http://orcid.org/0000-0003-3104-5220
Mohd Rafie Johan http://orcid.org/0000-0003-1133-9977

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