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N-Methyl pyridinium p-toluene sulfonate (NMPyTs) catalyzed synthesis of pyrano[2,3-c]pyrazoles

Vinod T. Kamble[a], Giribala M. Bondle,[b,*] Sandeep T. Atkore[c]

[a]*Organic Chemistry Research Laboratory, Department of Chemistry, Institute of Sciences, Nagpur-440001 Maharashtra, India*

[b]*Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad-431004 Maharashtra, India*

[c]*Organic Chemistry Research Laboratory, School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded-431606 Maharashtra, India*

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Abstract

A simple one pot synthesis of pyrano[2,3-c]pyrazoles was developed by a three component reaction of various benzaldehydes, malononitrile and 1-phenyl or hydro-3-methyl-1*H*-pyrazol-5(4*H*)-one in the presence of N-methyl pyridinium *p*-toluene sulfonate (NMPyTs) as catalyst. All of the synthesized compounds were identified by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. In the mentioned method, the use of thermal condition is avoided. The key advantages of this process are high yields, shorter reaction times, easy work-up, and purification of products by non-chromatographic method. The synthesis of pyrano[2,3-c] pyrazoles using NMPyTs as an efficient catalyst is the novel methodology work.

Keywords: 1-Phenyl-3-methyl-1H-pyrazol-5(4H)-one; pyridine; p-toluene methyl sulfonate; malononitrile.

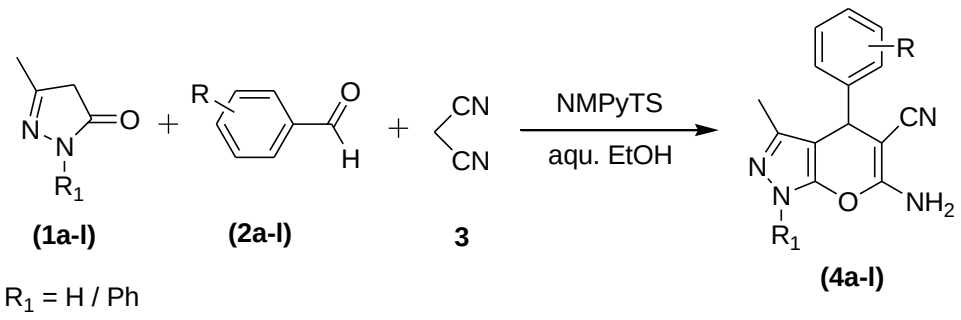
Introduction

Design and synthesis of pharmacologically active molecules are one of the principal challenges in medicinal chemistry. Pyrano pyrazoles possess various potential medicinal and biological activities so play an important role in the field of pharmacological chemistry. Many of these compounds posses anti-tumor [1], anti-cancer [1], anti-bacterial [2] and vasodilatory activity [3], analgesic [4], anti-inflammatory properties [5], and also serve as potential inhibitors of human Chk1 kinase [6]. Therefore, considerable attention has been focused on the synthesis and the development of new methodologies of pyrano pyrazoles. Pyrano pyrazoles were first obtained in 1973 by reaction between 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene [7]. The 2-amino-4-substituted pyrano [2,3-c] pyrazole-3-carbonitriles were obtained in 1974 by addition of malononitrile to 4-arylidene-3-methyl-2-pyrazolin-5-one [8]. Afterwards, several other synthetic approaches to the synthesis of these compounds were reported. These approaches include one-pot three-

*Corresponding author: Giribala M. Bondle
Tel: +91 (9890766118), Fax: +91 (9890766118)
E-mail: gmbondle@gmail.com

component condensation of pyrazolone derivatives, malononitrile and aromatic aldehydes or pyrazole-aldehydes [9], three-component cyclocondensation of substituted piperidin-4-ones, pyrazol-5-ones and malononitrile [10] four-component reaction of aldehydes, ethyl acetoacetate, malononitrile with hydrazine hydrate [11-13,15-28], two component reaction of 3-methyl-2-pyrazolin-5-one with benzylidene malononitriles [14], and four-component reaction involving aromatic aldehydes, Meldrum's acid, hydrazine hydrate, and ethyl acetoacetate. Various catalysts and conditions have been used to synthesis pyrano pyrazoles, *via* reactions mentioned above. Some of those catalyst are triethylamine in ethanol or water [9a] *p*-dodecylbenzene sulfonic acid (DBSA) in water at 60 °C [9c], hexadecyltrimethylammonium bromide (HTMAB) at 60-80 °C [9d], ammonium acetate in ethanol [9g], triethyl benzyl ammonium chloride (TEBACl) at 90 °C in water solution [9i], piperidine in ethanol or water [9h], cinchona alkaloid organocatalysts in dichloromethane [14], per-6-amino-β-cyclodextrin (per-6-ABCD) [15], Brønsted-acidic ionic liquid under solvent-free conditions [16], [Bmim]OH [17], L-proline and γ-alumina [18], silicotungstic acid ($H_4[SiW_{12}O_{40}]$) [19], glycine [20], NaOH in EtOH under microwave irradiation [21], dodecyl trimethylammonium bromide [22], iodine in water [23], L-proline at 50 °C in [Bmim]BF_4 [24], silica in water [25], nanostructured MgO [26], $Ba(OH)_2$ in water at reflux [27], and cetyltrimethylammonium chloride (CTACl) [28]. Other non-catalytic methods were applied to the synthesis of these compounds. For example, there was a synthesis in aqueous ethanol at 100 °C for 2.5 h [29], four component reactions in boiling water for 2-6 h [30], ultrasound activated reaction [9j], synthesis under microwave irradiation [31], and reaction in solvent-free conditions [32]. All listed above methods suffer from one or many drawbacks such as the use of organic solvents, long reaction time, strong acid or base catalysts, required special apparatus (e.g. microwave and ultrasound irradiation) and harsh reaction conditions.

Thus, the development of new environmental friendly, more effective procedure for the synthesis of pyrano pyrazoles is of significant interest. In the presented work, we have introduced the new catalyst N-methyl pyridinium-*p*-toluene sulfonate which catalyzes this reaction very smoothly at room temperature (Scheme 1).



Scheme 1.

Experimental section

Melting points were determined and are uncorrected in open glass capillary tubes. Completion of the reaction was checked by TLC on silica gel-G plates of 0.5 mm thickness and with iodine, as

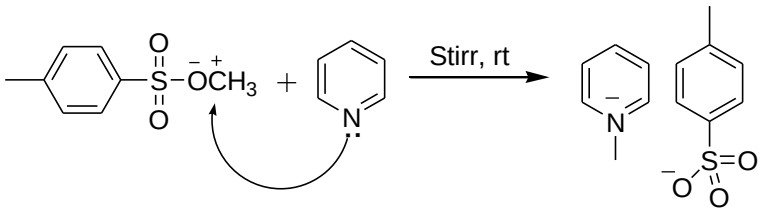
detecting agent. IR spectra were recorded using KBr pellet method on Shimadzu FT-IR-8400 instrument. Mass spectra were recorded on Shimadzu LC-MS-QP-2010 model using Direct Injection Probe technique. ^{1}H NMR and ^{13}CNMR spectra were determined in DMSO-*d*6 solvent on a Bruker Ac 400 MHz spectrometer. Analytical, physical and spectral data of the synthesized compounds are given in supplementary material to this paper.

General procedure for the synthesis of Pyranopyrazoles (4a-l)

In a 25 mL round bottom flask, 1-phenyl-3-methyl-1*H*-pyrazol-5(4*H*)-one (1mmol), aldehyde (1mmol), malononitrile (1mmol) and 3mol% of N-methyl pyridinium-*p*-toluene sulfonate (NMPyTs) were taken and the reaction mixture was stirred at room temperature in 2 mL equimolar mixture of EtOH:H_2O (1:1) for appropriate time. The progress of the reaction was monitored by TLC. The crude product (**4a-l**) was separated by filtration, washed with water to remove the catalyst and air-dried. The pure product was obtained by recrystallization in ethanol.

Procedure for the synthesis of N-methyl pyridinium p-toluene sulfonate (NMPyTs)

Methyl-*P*-toluene sulfonate (5.70 g, 30 mmol) was added to pyridine (6 mL, 60 mmol) with constant stirring at room temperature. After stirring 20 minutes, the excess pyridine was removed with a rotary evaporator on a water bath at 60 ^{o}C to afford a quantitative yield of NMPyPTS as slightly hygroscopic colorless crystals. Recrystallization from acetone gave pure salt (4g, 90 %) yield.



Scheme 2. Synthesis of N-methyl pyridinium-p-toluene sulfonate (NMPyTs)

Spectral data of synthesized compounds

*6-Amino-5-cyano-3-methyl-4-phenyl-1,4-dihyropyrano [2,3-c] pyrazole (**4a**)*

White crystals, M. p.: 242 ^{o}C. IR (KBr, cm^{-1}): 3450, 3370, 3116, 2195, 1645, 1610, 1605, 1483, 1390, 1240, 1022, 860; ^{1}H-NMR (400MHz, $CDCl_3$, δ/ppm): 1.80 (s, 3H, CH_3), 4.62 (s, 1H, CH), 6.95 (s, 2H, NH_2), 7.16-7.45 (m, 5H, Ar-H), 12.16 (br s, 1H, NH). ^{13}C-NMR (100MHz, $CDCl_3$, δ/ppm): 11.4, 24.8, 70.4, 112.2, 126.3, 127.2, 129.3, 130.9, 140.2, 143.9, 152.3, 160.0. HRMS (ESI) = *m/z* calculated for $C_{14}H_{12}N_4O$ $[M+H]^+$ 253.1089, found 253.1091(Rel. Int. 100%).

6-Amino-5-cyano-4(4-nitrophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole (4b)

Brown solid, M. p.: 250 ^{o}C. IR (KBr, cm^{-1}): 3385, 3278, 2189, 1622, 1456. ^{1}H-NMR (400MHz, $CDCl_3$, δ/ppm): 1.76 (s, 3H,CH_3), 4.45 (s,1H, CH), 7.65 (s, 2H, NH_2), 7.78-7.94(m, 4H, ArH), 12.04 (s, 1H, NH); ^{13}C-NMR (100MHz, $CDCl_3$, δ/ppm): 11.4, 23.3, 70.7, 112.8, 127.9,126.0, 130.0, 135.5, 141.9, 150.4, 154.2, 160.4. HRMS (ESI) = *m/z* calculated for

$C_{14}H_{11}N_5O_3$ $[M+H]^+$ 298.0940, found 298.0989 (Rel. Int. 100%).

6-Amino-5-cyano-4(3-nitrophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole (4c)

Brown solid M. p.: 235 °C. IR (KBr, cm^{-1}): 3385, 3278, 2189, 1622, 1456. ^{1}H-NMR (400MHz, $CDCl_3$, δ/ppm): 1.83 (s, 3H, CH_3), 4.98 (s, 1H, CH), 7.12 (s, 2H, NH_2), 7.89 (s, 1H), 8.12-8.05 (m, 3H, ArH), 12.16 (s, 1H). ^{13}C-NMR (100MHz, $CDCl_3$, δ/ppm): 11.4, 23.3, 70.7, 112.8, 127.9, 126.0, 130.0, 135.5, 141.9, 150.4, 154.2, 160.4. HRMS (ESI) = *m/z* calculated for $C_{14}H_{11}N_5O_3$ $[M+H]^+$ 298.0940, found 298.0989 (Rel. Int. 100%).

6-Amino-5-cyano-4(4-methylphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole(4d)

White crystals. M. p. 197 °C. IR (KBr, cm^{-1}): 3492, 3250, 3150, 2930, 2200, 1620, 1595, 1508, 1410, 1260, 1180, 1050, 835. ^{1}H-NMR (400MHz, $CDCl_3$, δ/ppm) 1.76 (s, 3H, CH_3), 2.28 (s, 3H CH_3), 4.50 (s, 1H, CH), 6.49 (s, 2H, NH_2), 6.61-6.99 (m, 4H, Ar-H), 12.09 (br s, 1H, NH). ^{13}C-NMR (100MHz, $CDCl_3$, δ/ppm): 11.8, 22.1, 25.3, 71.4, 112.1, 116.2, 128.0, 129.3, 135.6, 141.8, 142.1, 153.4, 159.2. HRMS (ESI) = *m/z* calculated for $C_{15}H_{14}N_4O$ $[M+H]^+$ 267.1245; found, 267.1252 (Rel. Int. 100%).

6-Amino-5-cyano-4(4-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole (4e)

White crystals, M. p. 211 °C. IR (KBr, cm^{-1}): 3481, 3253, 2925, 2191, 1642, 1600, 1492, 1392, 1258, 1172, 1031, 870, 804, 565. ^{1}H-NMR (400MHz, $CDCl_3$, δ/ppm) 1.75 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 4.50 (s, 1H, CH), 6.45 (s, 2H, NH_2), 6.8-7.2 (m, 4H, Ar-H), 12.05 (brs, 1H, NH). ^{13}C-NMR (100MHz, $CDCl_3$, δ/ppm): 11.5, 24.5, 55.4, 70.4, 114.7, 115.2, 127.8, 129.2, 140.5, 143.8, 153.3, 159.9, 160.0. HRMS (ESI) = *m/z* calculated for $C_{15}H_{14}N_4O_2$ $[M+H]^+$ 283.1195, found 283.1198 (Rel. Int. 100%).

6-Amino-5-cyano-4(4-hydroxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole (4f)

White crystals, M.p. 225°C. ^{1}H-NMR (400MHz, $CDCl_3$, δ/ppm) 1.76 (s, 3H, CH_3), 4.46 (s, 1H); 5.49(s, 1H); 6.68-6.92 (m,4H, ArH), 6.49 (s, 2H, NH_2), 12.04(s, 1H). ^{13}C-NMR (100MHz, $CDCl_3$, δ/ppm): 12.0, 25.0, 71.0, 113.6, 119.5, 127.0, 130.2, 141.5, 143.8, 153.4, 154.5, 159.1. HRMS (ESI) = *m/z* calculated for $C_{14}H_{12}N_4O_2$ $[M+H]^+$ 269.1038; Found, 269.1052 (Rel. Int.100%)

6-Amino-5-cyano-4(4-N,N-dimethylaminophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole (4g)

Yellow crystals, M.p. 217 °C. IR (KBr, cm^{-1}): 1053, 2189, 3172, 3305 ،3385. ^{1}H-NMR (400MHz, $CDCl_3$, δ/ppm):1.78 (s, 3H, CH_3), 3.34 (s, 6H, 2x CH_3), 4.44 (s, 1H), 6.64 (s, 2H, NH_2), 6.66-6.96 (m, 4H, ArH), 12.02 (s, 1H). ^{13}C-NMR (100MHz, $CDCl_3$, δ/ppm): 11.5, 25.6, 40.83, 71.6, 111.1, 114.8, 126.9, 130.0, 137.5, 141.0, 153.0, 157.1, 159.4. HRMS (ESI) = *m/z* calculated for $C_{16}H_{17}N_5O$ $[M+H]^+$ 296.1511, found 296.1525 (Rel. Int. 100%).

6-Amino-5-cyano-4(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole (4h)

White crystals. M.p.: 232 °C. IR (KBr, cm^{-1}): 3490, 3253, 2930, 2260, 1650, 1610, 1508, 1399, 1270, 1200, 1050, 750. ^{1}H-NMR (400MHz, $CDCl_3$, δ/ppm): 1.78 (s, 3H, CH_3), 4.54 (s, 1H, CH), 6.92 (s, 2H, NH_2), 7.16-7.37 (m, 4H, Ar-H), 12.1 (br s, 1H, NH). ^{13}C-NMR (100MHz, $CDCl_3$, δ/ppm): 11.7, 24.4, 70.4, 112.1, 126.7, 127.6, 130.1, 134.2, 141.4, 142.1, 153.6, 159.3. HRMS (ESI) = *m/z* calculated

for $C_{14}H_{11}Cl\ N_4O$ $[M+H]^+$ 287.0699; found, 287.0699 and 289.0699 (Rel. Int. 100%).

6-Amino-5-cyano-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-c]pyrazole (4i)

White crystals. M. p. 169 ^oC. IR (KBr, cm^{-1}): 3472, 3320, 2195, 1660, 1590, 1264, 1125, 1027, 753. ^{1}H-NMR (400MHz, $CDCl_3$, δ/ppm): 1.72 (s, 3H, CH_3), 4.60(s, 2H, NH_2), 4.68 (s, 1H, CH), 6.93-7.47 (m, 10H, Ar-H). ^{13}C-NMR (100MHz, $CDCl_3$, δ/ppm): 12.9, 29.4, 71.5, 112.3, 126.1, 127.2, 130.3, 141.0, 155.1, 177.1. HRMS (ESI) = *m/z* calculated for $C_{20}H_{16}N_4O$ $[M+H]^+$ 329.1333; found, 329.1340 (Rel. Int. 100%).

6-Amino-5-cyano--3-methyl-4(4-methoxyphenyl)-l-phenyl-1,4-dihydropyrano[2,3c]pyrazole(4j)

White crystals. M. p. 174 ^oC. IR (KBr, cm^{-1}): 3395, 3322, 2192, 1660, 1595, 1394, 1250, 1128, 813. ^{1}H-NMR (400MHz, $CDCl_3$, δ/ppm): 2.06 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 4.60 (s, 1H, CH), 7.11(s, 2H, NH_2), 7.24-7.96 (m, 9H, Ar-H). ^{13}C-NMR (100MHz, $CDCl_3$, δ/ppm): 11.5, 24.5, 55.3, 70.5, 114.0, 115.7, 120.0, 127.0, 129.9, 140.5, 141.0, 153.9, 159.9, 160.0. HRMS (ESI) = *m/z* calculated for $C_{21}H_{18}\ N_4O_2$ $[M+H]^+$ 359.1456; found, 359.1458 (Rel. Int. 100%).

6-Amino-5-cyano-4(4-hydroxyphenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (4k)

White crystals, M. p.: 212 ^oC. IR (KBr, cm^{-1}): 3414, 3314, 2178, 1658, 1594, 1398, 1258, 1128, 1026, 754. ^{1}H-NMR (400MHz, $CDCl_3$, δ/ppm): 1.99 (s, 3H, CH_3), 4.45 (s, 1H, CH), 5.00 (s,1H,OH), 6.44 (s, 2H, NH_2), 6.55-6.58 (m, 4H, ArH), 7.01-7.02(m, 5H, ArH). ^{13}C-NMR (100MHz, $CDCl_3$, δ/ppm): 11.9, 24.7, 71.0, 77.4, 115.0, 119.4, 127.0, 130.1, 141.6, 143.2, 153.4, 154.5, 159.1. HRMS (ESI) = *m/z* calculated for $C_{20}H_{16}N_4O_2$ $[M+H]^+$ 345.1336; found, 345.1342(Rel. Int.100%).

6-Amino-4(4-chlorophenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (4l)

White crystals, M. p. 173 ^oC. IR (KBr, cm^{-1}): 3468, 3325, 2200, 1662, 1596, 1390, 1262, 1122, 1016, 752. ^{1}H-NMR (400MHz, $CDCl_3$, δ/ppm): 1.82 (s, 3H, CH_3), 4.58 (s, 1H, CH), 6.68 (s, 2H, NH_2), 6.81-7.09 (m, 5H, Ar-H), 7.16-7.23(d, 4H, ArH). ^{13}C-NMR (100MHz, $CDCl_3$, δ/ppm): 11.7, 24.4, 70.4, 112.1, 126.7, 127.6, 130.1, 134.2, 141.4, 142.1, 153.6, 159.3. HRMS (ESI) = *m/z* calculated for $C_{20}H_{15}ClN_4O$ $[M+H]^+$ 363.0928; found, 363.0935 and 365.0935(Rel. Int. 100%).

Results and discussion

An initial study was performed by treating a mixture of 1-phenyl-3-methyl-1*H*-pyrazol-5(4*H*)-one (1mmol), 4-methoxy benzaldehyde (1mmol) and malononitrile (1mmol) in water (1 mL) without any catalyst and it was found that, the reaction was not possible in water at room temperature (Table 1, Entry 1). As the reaction requires a catalyst, we performed the reaction using 0.5 mol% NMPyTs and the result revealed that the reaction was possible at room temperature with moderate yield (Table 1, Entry 2). To improve the yield of product, we continued our efforts by changing the mol% of catalyst from 0.5 to 5 and a good result (Table 1, Entry 6) was given by model reaction within 25 minute when 3 mol% NMPyTs catalyst was employed.

Table 1. Optimization of the catalytic amount of NMPyTs for model reaction at room temperature

Entry	Catalyst load (mol%)	Time (min)	Yield (%)
1	---	340	00
2	0.5	50	40
3	1.0	45	67
4	1.5	40	78
5	2.0	30	80
6	**3.0**	**25**	**85**
7	3.5	35	80
8	4.0	40	80
9	5.0	40	80

Table 2. Optimization of the reaction condition using various solvents[a]

Entry	Solvent	Time (min)	Yield (%)
1	Neat	25	85
2	H_2O	50	83
3	EtOH	40	82
4	CH_3CN	55	71
5	THF	60	70
6	CH_2Cl_2	60	43
7	$CHCl_3$	120	55
8	**EtOH:H_2O (1:1)**	**15**	**91**
9	CH_3CN:H_2O (1:1)	40	76
10	THF:H_2O (1:1)	35	75
11	CH_2Cl_2:H_2O (1:1)	120	62
12	$CHCl_3$:H_2O (1:1)	120	66

[a]Using 3 mol%of NMPyTs at room various solvents

We also studied the effect or various solvents on the same reaction in presence of NMPyTs catalyst at room temperature. The results reported in (Table 2) indicate that solvents affect the efficiency of the reaction. Initially, the model reaction was carried out under the solvent free condition, the product was observed on TLC plate. Interestingly, the use of aprotic organic and polar protic solvents such as acetonitrile, ethanol and tetrahydrofuran (Table 2, Entries 3-5) afforded good results for pyrano pyrazole derivatives within 40-60 minutes. After this, the model reaction was performed using an equal volume of organic solvents and water (Table 2, Entries 8–12). We were pleased to see that, the reaction proceeds smoothly at room temperature in an equimolar volume of EtOH:H_2O (1:1) (Table 2, Entry 8) with 91% yield of product in 15 minutes. On the basis of these observations, 2 mL equimolar mixture of EtOH:H_2O (1:1) optimized the solvent system for the reported method. With the optimized reaction conditions in hand, we next examined the feasibility of the catalyst for synthesis of pyrano pyrazole derivatives by condensing variously substituted aromatic aldehydes, 1-phenyl / 1-hydro-3-methyl-1*H*-pyrazol-5(4*H*)-one and malononitrile (Scheme 1) with 3mol% NMPyTs in aqu. EtOH at room temperature and the results were recorded in Table 3. The reactions proceeded efficiently to furnish the corresponding pyrano pyrazoles 4a-l in good to excellent yields. All the products were confirmed by their melting point and spectral characterization.

Table 3. Synthesis of 6-amino-4-aryl-3-1,4-dihydropyrano [2,3-c] pyrazole-5-carbonitrile derivatives (**4a-l**)

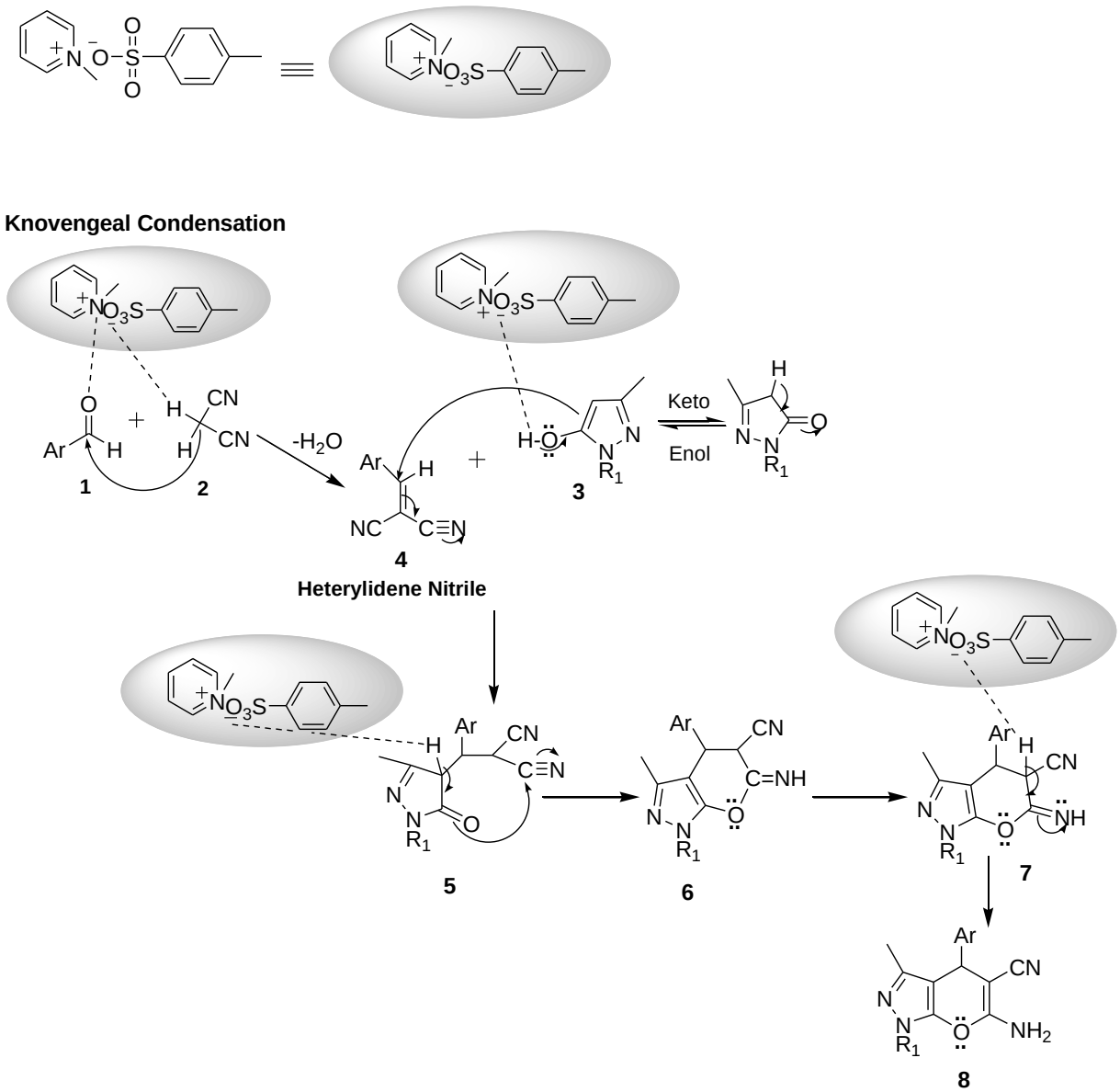
Product	Aldehyde	R_1	Time (min)	Yield (%)	MP(°C) Found / lit[ref]
4a	PhCHO	H	45	85	242/ 245-246[33]
4b	4-NO_2-C_6H_4CHO	H	35	87	250/ 251-252[33]
4c	3-NO_2-C_6H_4CHO	H	35	85	235/ 232-233[33]
4d	4-CH_3-C_6H_4CHO	H	20	90	197/ 197-198[33]
4e	4-OCH_3-C_6H_4CHO	H	20	91	211/ 212-213[33]
4f	4-OH-C_6H_4CHO	H	20	90	225/ 223-224[33]
4g	4-N(Me)$_2$-C_6H_4CHO	H	30	94	217/ 219-220[33]
4h	4-Cl-C_6H_4CHO	H	45	92	232/ 234-235[33]
4i	PhCHO	Ph	45	82	169/ 168-170[34]
4j	4-OCH_3-C_6H_4CHO	Ph	30	86	174/ 170-172[34]
4k	4-OH-C_6H_4CHO	Ph	30	85	212/ 211-212[34]
4l	4-Cl-C_6H_4CHO	Ph	60	79	173/ 174-175[34]

Reagents and condition: aryl aldehyde (1mmol), 1-phenyl or 3-methyl-1H-pyrazol-5(4H)-one (1 mmol), malononitrile (1mmol), NMPyTs (3 mol%), 2mL equimolar mixture of EtOH:H_2O (1:1) at room temperature.

The possible mechanism for the formation of pyrano pyrazole compound in presence of N-methyl pyridinium-*p*-toluene sulfonate is proposed as below where the main role of N-methyl-pyridinium cation is to increase the electrophilicity of the carbonyl carbon by bonding with oxygen and increase the nucleophilicity of the active methylene group by coordinating the negative ion with hydrogen of malononitrile (Scheme 3). First, knovengeal product **4** is formed by reactsing aryl aldehyde and malononitrile. Methine carbon of **4** is activated by NMPyTs and it reacts with C-H activated compound **3** in Michael fashion, giving intermediate **5**. Intermediate **5** undergoes intramolecular cyclization followed by tautomerization leading to pyran derivatives **8**.

Conclusion

All these facts have strengthened ourselves to find a newer eco-friendly method and prompted us to employ N-methyl pyridinium- *p*-toluene sulfonate (NMPyTs) as a catalyst for efficient and high-yielding synthesis of pyrano pyrazole derivatives at room temperature (Scheme 1). The reported method is rapid and facile, also devoid of unnecessary derivatization and generation of a hazardous substance.



Scheme 3. Possible mechanism for the formation of pyrano pyrazole **4**

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