Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2016, 8(4):202-206

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis of 1,3-disubstituted pyrazoles using ionic liquid

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ABSTRACT

Pyrazoles are well known five-membered nitrogen containing heterocyclic compounds possessing diverse bioactivities and are used extensively in pharmaceutical industry. Here we have used ionic liquid as a solvent which is highly efficient and environmentally friendly. We were interested in synthesizing 1,3-disubstituted pyrazoles using cinnamaldehyde as it gives complete regioselective product with only single isomers are obtained and the method gave us a excellent yields.

Key words: Ionic liquid, Pyrazole, N-Tosylhydrazine.

INTRODUCTION

Pyrazoles are one of the most prevalent heterocyclic compounds with a wide range of biological activities, such as antihyperglycemic, [**1**] anti-inflammatory,**[2]** antiobesity,**[3]** antitumor**[4]** antimycobacterial**,[5]** molluscicidal activity,**[6]** and cardiac hypertrophy suppression.**[7]**

Owing to the important features of pyrazoles, various synthetic methods are reported for the pyrazoles.Condensation of hydrazonyl halides with b-dicarbonyl compounds and 1,3-dipolar cycloaddition of diazo compounds with alkynes **[8–10]** are found to yield pyrazoles. 1,3,5-Trisubstituted pyrazolines have been synthesized by condensing chalcones with hydrazines. The pyrazolines on aromatization using various oxidants, PhI(OAc)2 **[11]**, MnO2 **[12]** and PBr3 **[13]** are found to give pyrazoles. The most widely used synthetic protocol for obtaining polysubstituted pyrazoles is by condensing 1,3-dicarbonyl compounds with hydrazines using acid catalysts like sulphuric acid **[14]**, polystyrensulphonic acid **[15]** and hydrochloric acid **[16].** To provide an efficient multicomponent one-pot synthesis for polysubstituted pyrazoles L.Shen et al. have recently reported the cyclocondensation of aldehydes, 1,3-dicarbonyl compounds and phenyl hydrazines using ytterbium perfluorooctanoate as rare earth condensing catalyst and IBX as an oxidant for obtaining good to moderate yields of polysubstituted pyrazoles **[17,18]**. This is a unique report however it has certain limitations as it needs non readily available and costly rare earth catalyst, ytterbium perfluorobutanoate. It has been revealed that silica chloride is gaining importance as catalyst in accelerating various organic transformations **[19–23]** and cyclocondensations leading of bioactive heterocycles **[19–23,27]**. Multicomponent reactions are convenient and are found in use in various organic transformations because of their several advantages **[24–26]**.

EXPERIMENTAL SECTION

General Considerations

All reagents and catalyst purchased from commercial sources were used as received. The solvent ionic liquid was prepared by reported procedure and used .^{1}H and ^{13}C spectra were taken on bruker AVANCE 400 MHz spectrometer with TMS as internal standard $CDCl_3$ as solvent.

Procedure for the synthesis 1,3-disubstituted pyrazoles

Preparation of 1-ethyl-3-phenyl-1H-pyrazole (4a) (72%).

A mixture of 1a (132 mg, 1.0 mmol) and $TsNHNH_2$ (205 mg,1.1 mmol) in ($C_3[min]_2 2[Br]^-$) (5 mL) were stirred at room temperature for 3h and then ($C_3[min]_2 2[Br]^-$) (5 mL), NaOH (44 mg, 1.1 mmol) were added and the mixture was heated at reflux for 15 h, then NaOH (104 mg, 2.5 mmol) and iodoethane (234 mg, 1.5 mmol) as a colourless oil were subsequently added and the mixture was stirred at room temperature for 1 h. The product was extracted with Et_2O and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel afforded the desired product 4a as a white crystalline solid . $^{\delta}$H (400 MHz, $CDCl_3$) 1.48 (3H, t, J 7.6 Hz), 4.17 (2H, q, J 7.6 Hz), 6.51 (1H, d, J 2.0 Hz), 7.26 (1H, t, J 7.2 Hz),7.36-7.39 (3H, m), 7.80 (2H, d, J 7.2 Hz); $^{\delta}$C (100 MHz, $CDCl_3$) 15.6,47.0, 102.5, 125.5, 127.3, 128.5, 129.4, 133.7, 151.1; HRMS (ESI): MH^+,found: 173.1070. $C_{11}H_{13}N_2$ requires 173.1073; nmax (liquid film)3063, 3035, 2982, 2939, 1605, 1500, 1457, 1352, 1225 cm^{-1}

Preparation of 1-allyl-3-phenyl-1H-pyrazole (4b).

Compound 4b (55%) was prepared following the procedure described for 4a by using 1a (132 mg,1.0 mmol), $TsNHNH_2$ (205 mg,1.1 mmol),NaOH (104 mg, 2.6 mmol), and allyl bromide (180 mg, 1.5 mmol) as colorless oil. $^{\delta}$H (400MHz, $CDCl_3$) 4.75 (2H, dt, J 5.6,1.2 Hz), 5.17-5.26 (2H, m), 5.99-6.08 (1H, m), 6.55 (1H, d, J 2.4 Hz), 7.25-7.29 (1H, m), 7.35-7.39 (3H, m), 7.79-7.81(2H,m); $^{\delta}$C(100MHz,$CDCl_3$) 54.7,102.9,118.4,125.5,127.4, 128.5,130.1,132.9,133.5,151.4; HRMS (ESI): MH^+, found: 185.1070. $C_{12}H_{13}N_2$ requires 185.1073; nmax (liquid film) 3066, 3035, 2985, 2925, 1500, 1458, 1355, 1327, 1226, 1074 cm^{-1}.

Preparation of 1-benzyl-3-phenyl-1H-pyrazole (4c).

Compound 4c (50%) was prepared following the procedure described for 4a A mixture of 1a (132 mg, 1.0 mmol) and $TsNHNH_2$ (205 mg,1.1 mmol) NaOH (44 mg, 1.1 mmol) ,NaOH (60 mg,1.5 mmol) and benzyl bromide (255 mg, 1.5 mmol) . $^{\delta}$H (400 MHz, $CDCl_3$) 5.32 (2H, s), 6.55 (1H, d, J 2.4 Hz), 7.20-7.23 (2H, m), 7.25-7.33 (5H, m), 7.35-7.39 (2H, m),7.81-7.82 (2H, m); $^{\delta}$C (100 MHz, $CDCl_3$) 56.0, 103.2, 125.6, 127.5,127.6, 127.9, 128.5, 128.7, 130.5, 133.5, 136.6, 151.5; HRMS (ESI):MH^+, found 235.1232. $C_{16}H_{15}N_2$ requires 235.1230, nmax (liquid film) 3126, 3107, 3062, 3033, 2936, 1498, 1455, 1078 $cm^{-1.}$

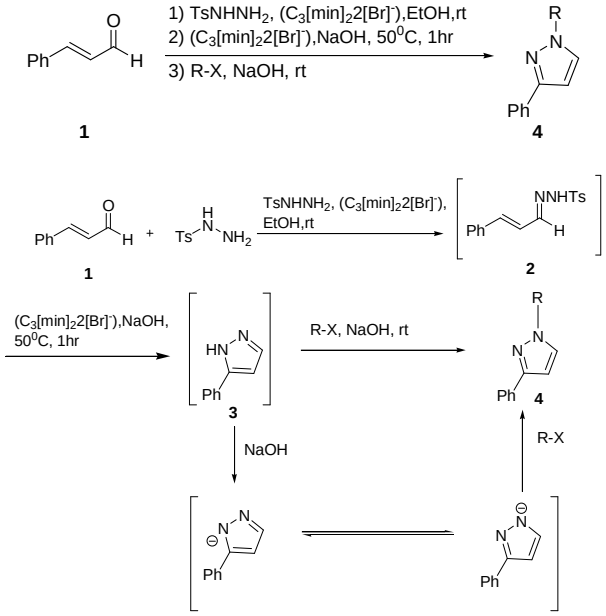
Preparation of 3-phenyl-1-(prop-2-yn-1-yl)-1H-pyrazole (4d).

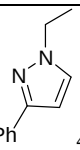
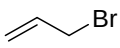
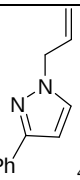
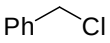
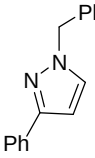
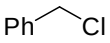
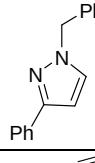
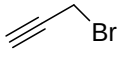
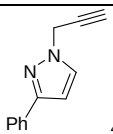
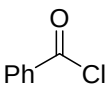
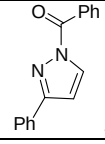
Compound 4d (65%) was prepared following the procedure described for 4a by using 1a (132 mg, 1.0 mmol), $TsNHNH_2$ (205 mg, 1.1 mmol), NaOH (104 mg, 2.6 mmol), and propargyl bromide (177 mg,1.5 mmol) as colorless oil. . $^{\delta}$H (400 MHz, $CDCl_3$) 2.49 (1H, t, J 2.8 Hz), 4.95 (2H, d, J 2.8 Hz), 6.57 (1H, d, J2.4 Hz), 7.26-7.30 (1H, m), 7.36-7.39 (2H, m), 7.60 (1H, d, J 2.4 Hz),7.78 (2H, dd, J 8.0,1.2 Hz); $^{\delta}$C (100 MHz, $CDCl_3$) 41.5, 74.7, 76.7, 103.3,125.6, 127.7, 128.5, 130.0, 133.2, 152.0; HRMS (ESI): MH^+, found:183.0919. $C_{12}H_{11}N_2$ requires 183.0917; nmax (liquid film) 3290, 3063,3037, 2925, 2127, 1500, 1459, 1337, 1227 cm^{-1}

Preparation of phenyl(3-phenyl-1H-pyrazol-1-yl)methanone(4e).

Compound 4e (68%) was prepared following the procedure described for 4a by using 1a (132 mg, 1.0 mmol), $TsNHNH_2$ (205 mg, 1.1 mmol), NaOH (104 mg, 2.6 mmol), and benzoyl chloride (210 mg, 1.5 mmol) as colorless oil. $^{\delta}$H (400 MHz,$CDCl_3$) 6.84 (1H, d, J 2.8 Hz), 7.35-7.44 (3H, m), 7.49-7.53 (2H, m),7.59-7.63 (1H, m), 7.85-7.88 (2H, m), 8.24-8.27 (2H, m), 8.45 (1H,d, J 2.8 Hz); $^{\delta}$C (100 MHz, $CDCl_3$) 107.1, 126.4, 128.0, 128.7, 129.1,131.5, 131.7, 131.78, 131.84, 132.9, 155.9, 166.0; HRMS (ESI): MNa^+,found: 271.0838. $C_{16}H_{12}N_2ONa$ requires 271.0842; nmax (liquid film) 3150, 3125, 3062, 1697, 1541, 1451, 1403, 1351, 1275 cm^{-1}.

Table: Synthesis of 1,3-disubstituted pyrazoles



Entry	Solvent	R-X	Product	Yield (%)
1	$(C_3[min]_22[Br]^-)$		 4a	72
2	$(C_3[min]_22[Br]^-)$		 4b	55
3	EtOH		 4c	50
4	$(C_3[min]_22[Br]^-)$		 4c	90
5	$(C_3[min]_22[Br]^-)$		 4d	65
6	$(C_3[min]_22[Br]^-)$		 4e	68

RESULTS AND DISCUSSION

From readily available and simple starting materials, such as p-toluenesulfonyl hydrazide ($TsNHNH_2$) and halides (R-X). Our study was performed with cinnamaldehyde (**1**) as a model substrate and NaOH as the base in EtOH (**Table)**. First, trapping of the intermediate 5-phenyl-1Hpyrazo (**3**) with benzyl bromide was attempted. The progress of pyrazole **3** formation was monitored by TLC, and when complete, NaOH and benzyl bromide were added. Under basic conditions, deprotonation of the NH moiety and rapid tautomerism . Then **4c** was obtained by a nucleophilic substitution reaction of with benzyl bromide. The structure of **4c** was unambiguously established by NMR analysis. However, the reaction of pyrazole **3** with benzyl bromide was quite slow, and the yield was only 50% after two days (**Table)**. Of the solvents screened, IL gave an excellent yield within 1 h (90%, entry **4**, **Table**). We then investigated the scope of **R-X**, and found benzoyl chloride, iodoethane, allyl bromide, and propargyl bromide all gave the corresponding pyrazole derivatives in good to high yields (**Table**). The reaction showed consistent, complete regioselectivity, with only single isomers obtained in all reactions. This regioselectivity could be a result of repulsion between the phenyl substituent and **R**.

CONCLUSION

Encouraged by this result, we have focused attention on the use of $C_3[min]_22[Br^-]$ (dicationic ionic liquid) as solvent as well as catalyst. It was found that the ionic liquid worked well and the conversion found to take place rapidly giving excellent yield. Synthesis of 1,3-disubstituted pyrazoles by using cinnamaldehyde gives complete regioselective product with only single isomers was obtained and the method gave us a excellent yields. Further studies on the biological activities of the products and application of this methodology to other interesting pyrazole derivatives are underway in our laboratory.

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