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Microwave-assisted and Zn[L-proline]$_2$ catalyzed tandem cyclization under solvent free conditions: Rapid synthesis of chromeno[4,3-*c*]pyrazol-4-ones

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Abstract

Present study and investigations reveals that, the hydrazones of 3-acetyl-4-hydroxycoumarin undergo ring cyclization to give, 3-methyl-1-substituted phenyl-1*H*-chromeno[4,3-*c*]pyrazol-4-ones (2a–m) under the influence of microwave irradiation and by using Zn[L-proline]$_2$, a novel Lewis acid catalyst. The overall yields of the products were found to be 82–93%. Without use of the catalyst, no reaction progress was observed. No significant changes in the overall yields of the products were observed at high microwave power and at high temperatures. The reusability of the catalyst was also checked and found up to seven cycles.

Keywords: MWI; Zn[L-proline]<rk-sub>; Tandem cyclization; Chromeno-pyrazoles; Recyclability of the catalyst

1. Introduction

The development of benign synthetic methodology for fine and specialty chemicals comprises the replacement of volatile organic compounds (VOCs) by water, room temperature ionic liquids (RTILs), supercritical fluids, immobilized solvents, fluorous solvents, solventless conditions and poly(ethylene glycol) [1] because organic solvents are often harmful to the environment, which may lead frequently to government restrictions and high waste disposal costs [2].

Pyrazole derivatives have a long history of application in the pharmaceutical industry [3] as part of biologically active pharmaceuticals [4,5]. The activities exhibited by them include, selective COX-II inhibitor, as versatile pharmacophore of variety of biologically active heterocycles [6], potential antiviral [7], antimalarial [8], serum cholesterol lowering [9], in the treatment of esophageal and gastrointestinal mucosal injuries [10], brain injury [11], as immunostimulatory [12], antianginal [13] and antitumor agents [14], as non benzodiazepine anxiolytics [15,16], and HIV-reverse transcriptase inhibitors [17,18] and herbicides [19].

In view of the diverse pharmacological profile of condensed pyrazoles, we have synthesized a series of chromeno[4,3-*c*]pyrazoles, through the hydrazones 3-acetyl-4-hydroxycoumarin and their subsequent ring closure to afford the title compounds. All the title compounds have been synthesized by non-conventional heating technique, *i.e.*, microwave irradiation and by using novel Lewis acid catalyst, Zn[L-proline]$_2$ under solventfree conditions. The reusability of the catalyst was also checked and it was found to be up to seven cycles. The concentration of the catalyst was taken constant throughout the experiments. The substrates were found to be unreacted without use of the catalyst. In fact, current protocol is the benign protocol by blending of microwave assisted organic synthesis (MAOS) and avoiding the use of VOCs as a reaction media Scheme 1.

2. Experimental

All the chemicals and solvents were purchased from Spectrochem, Mumbai (India) and used without further purification. Melting points were measured in open capillary tubes with an Electrothermal-9200 melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on Bruker Avance II 300 MHz spectrometer in DMSO d_6. Chemical shifts (δ) are given in ppm relative to TMS, coupling constants *(J)* in Hz. Mass spectra were recorded on Shimadzu GCMS-QP2010 while, IR spectra were recorded on a Shimadzu FTIR-8400 using KBr optics. Microwave synthesizer, (Questron Technologies

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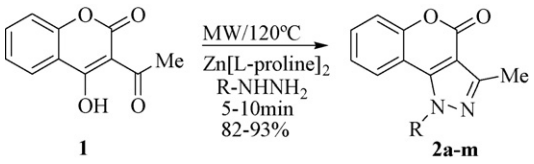


Scheme 1.

Corporation, Canada) QPro-M model monomode open-vessel was used for the synthesis.

2.1. Synthesis of 3-acetyl-4-hydroxychroman-2-one (1)

It was synthesized according to reported procedure [21].

2.2. General procedure for the synthesis of 3-methyl-1-substituted phenyl-1H-chromeno[4,3-c]pyrazol-4-ones (2a–m)

3-Acetyl-4-hydroxycoumarin (4 mmol) and phenyl hydrazine (5 mmol) were thoroughly mixed with 0.2 mmol of the catalyst and adsorbed on 5 g of neutral alumina. The alumina supported mixture was subjected to microwave irradiation (200 W) at 120 °C. The reaction was monitored at 2 min time interval. After the completion of reaction, as indicated by TLC (ethyl acetate:hexane 7:3), the reaction mixture was washed with ethyl acetate and brine, dried over anhydrous sodium sulphate. The solvent was removed *in vacuo* and the resulting crude products were directly charged on silica gel column and eluted with a mixture of ethyl acetate-*n*-hexane (7:3), to afford the pure title compounds. The above mentioned procedure was followed for all the experiments. The reaction time and yields are depicted in Table 1.

2.2.1. 3-Methyl-1-phenyl-1H-chromeno[4,3-c]pyrazol-4-one [2a]

White solid, m.p.: 188–190 °C, ^{1}H NMR(DMSO d_6): δ = 2.26(s, 3*H*, –CH_3), 7.5–7.9(m, 9*H*, Ar–H), IR(KBr): ν = 3039, 2951, 1735, 1632, 1591 cm^{-1}, mass (EI): *m/z* 276.

2.2.2. 3-Methyl-1-(4-chlorophenyl)-1H-chromeno[4,3-c]pyrazol-4-one [2b]

White solid, m.p.: 164–165 °C, ^{1}H NMR(DMSO d_6): δ = 2.27(s, 3*H*, –CH_3), 7.12(d, *J* = 8.5, 2*H*, Ar–H), 7.09(d, *J* = 8.2, 2*H*, Ar–H), 7.21–7.52(m, 4*H*, Ar–H); IR(KBr): ν = 3081, 2969, 1725, 1642, 1539, 1100 cm^{-1}, mass (EI): *m/z* 310, (M + 2)312.

2.2.3. 3-Methyl-1-(4-methylphenyl)-1H-chromeno[4,3-c]pyrazol-4-one [2c]

Pale yellow solid, m.p.: 199–200 °C, ^{1}H NMR (DMSO d_6): δ = 2.24(s, 3*H*, –CH_3), 1.9(s, 3*H*, –CH_3), 7.13(d, *J* = 8.7, 2*H*, Ar–H), 7.15(d, *J* = 8.7, 2*H*, Ar–H), 7.20–7.35(m, 4*H*, Ar–H); IR(KBr): ν = 3055, 2951, 1729, 1644, 1575 cm^{-1}, mass (EI): *m/z* 290.

2.2.4. 3-Methyl-1-(4-fluorophenyl)-1H-chromeno[4,3-c]pyrazol-4-one [2d]

White solid, m.p.: 194–196 °C, ^{1}H NMR (DMSO d_6): δ = 2.25(s, 3*H*, –CH_3), 7.99(d, *J* = 8.1), 2*H*, Ar–H), 7.75(d, *J* = 8.1, 2*H*, Ar–H), 7.37–7.60(m, 4*H*, Ar–H) IR(KBr): ν = 3037, 2963, 1729, 1631, 1565, 1243, 1089 cm^{-1}, Mass (EI): *m/z* 294.

2.2.5. 3-Methyl-1-(3-methylphenyl)-1H-chromeno[4,3-c]pyrazol-4-one [2e]

White solid, m.p.: 205–207 °C, ^{1}H NMR (DMSO d_6): δ = 2.25(s, 3*H*, –CH_3), 2.0(s, 3*H*, –CH_3), 7.21–7.68(m, 8*H*, Ar–H); IR (KBr): ν = 3049, 2947, 1723, 1641, 1521 cm^{-1}, Mass (EI): *m/z* 290.

2.2.6. 3-Methyl-1-(2-chlorophenyl)-1H-chromeno[4,3-c]pyrazol-4-one [2f]

Pale yellow solid, m.p.: 199–200 °C, ^{1}H NMR (DMSO d_6): δ = 2.21(s, 3*H*, –CH_3), 7.25–7.67(m, 8*H*, Ar–H); IR(KBr): ν = 3089, 2950, 1729, 1649, 1569, 1054 cm^{-1}, mass (EI): *m/z* 310, (M + 2) 312.

2.2.7. 3-Methyl-1-(3-chlorophenyl)-1H-chromeno[4,3-c]pyrazol-4-one [2g]

Pale yellow solid, m.p.: 178–180 °C, ^{1}H NMR (DMSO d_6): δ = 2.10(s, 3*H*, –CH_3), 7.23–7.68(m, 8*H*, Ar–H), IR(KBr): ν = 3050, 2957, 1729, 1642, 1590, 1075 cm^{-1}, mass (EI): *m/z* 310, (M + 2) 312.

2.2.8. 3-Methyl-1-(2-nitrophenyl)-1H-chromeno[4,3-c]pyrazol-4-one [2h]

White solid, m.p.: 200–202 °C, ^{1}H NMR (DMSO d_6): δ = 2.1(s, 3*H*, –CH_3), 8.21-7.69(m, 8*H*, Ar–H); IR(KBr): ν = 3029, 2969, 1725, 1651, 1594, 1515 cm^{-1}, mass (EI): *m/z* 321.

2.2.9. 3-Methyl-1-(3-nitrophenyl)-1H-chromeno[4,3-c]pyrazol-4-one [2i]

White solid, m.p.: 197–199 °C, ^{1}H NMR (DMSO d_6): δ = 1.9(s, 3*H*, –CH_3), 8.25–7.69(m, 8*H*, Ar–H); IR(KBr): ν = 3017, 2957, 1721, 1651, 1600, 1527 cm^{-1}, mass (EI): *m/z* 321.

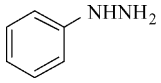
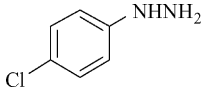
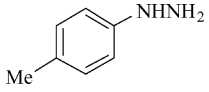
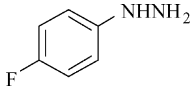
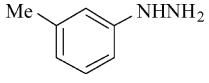
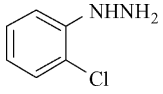
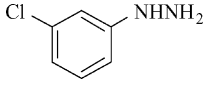
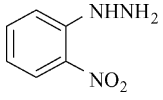
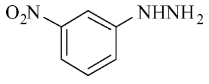
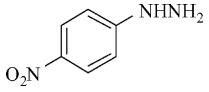
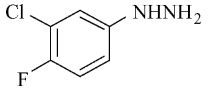
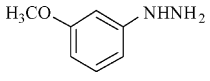
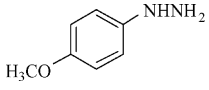
2.2.10. 3-Methyl-1-(4-nitrophenyl)-1H-chromeno[4,3-c]pyrazol-4-one [2j]

White solid, m.p.: 191–193 °C, ^{1}H NMR (DMSO d_6): δ = 2.23(s, 3*H*, –CH_3), 8.25(d, *J* = 7.9, 2*H*, Ar–H), 7.79(d, *J* = 8.2, 2*H*, Ar–H), 7.44–7.29(m, 4*H*, Ar–H); IR(KBr): ν = 3010, 2960, 1731, 1633, 1589, 1510 cm^{-1}, mass (EI): *m/z* 321.

2.2.11. 3-Methyl-1-(3-chloro-4-fluorophenyl)-1H-chromeno[4,3-c]pyrazol-4-one [2k]

White solid, m.p.: 185–187 °C, ^{1}H NMR (DMSO d_6): δ = 1.8(s, 3*H*, –CH_3), 7.99–7.41(m, 7*H*, Ar–H); IR(KBr):

Table 1
Synthesis of 3-methyl-1-substituted phenyl-1*H*-chromeno[4,3-*c*]pyrazol-4-one from corresponding phenylhydrazines under different microwave condition and temperature by using 0.2 mmol, Zn[L-proline]$_2$ as a catalyst

Entry	Phenylhydrazines (R)	Products	Microwave power (200W) at 120 °C		Microwave power (400W) at 120 °C		Microwave power (400W) at 160 °C	
			Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
1		2a	7	92	5	90	5	87
2		2b	5	90	5	89	5	86
3		2c	8	93	7	93	7	87
4		2d	5	89	5	89	5	85
5		2e	7	90	5	89	5	88
6		2f	9	89	7	88	7	86
7		2g	8	88	8	88	8	84
8		2h	10	91	8	86	8	87
9		2i	7	90	5	89	5	87
10		2j	10	92	10	90	8	88
11		2k	5	91	5	90	5	86
12		2l	10	91	10	91	8	87
13		2m	8	90	5	88	5	87

ν = 3045, 2959, 1739, 1641, 1231, 1089 cm^{-1}, mass (EI): *m/z* 328, (M + 2) 330.

2.2.12. 3-Methyl-1-(3-methoxyphenyl)-1H-chromeno[4,3-c]pyrazol-4-one [2l]

White solid, m.p.: 165–166 °C, ^{1}H NMR (DMSO d_6): δ = 2.4(s, 3*H*, −CH_3), 3.39(s, 3*H*, −OCH_3), 7.65–7.49(m, 8*H*, Ar–H); IR(KBr): ν = 3025, 2955, 1720, 1639, 1269 cm^{-1}, mass (EI) *m/z* 306.

2.2.13. 3-Methyl-1-(4-methoxyphenyl)-1H-chromeno[4,3-c]pyrazol-4-one [2m]

White solid, m.p.: 171–172 °C, ^{1}H NMR (DMSO d_6): δ = 2.21(s, 3*H*, −CH_3), 3.4(s, 3*H*, −OCH_3), 6.78(d, *J* = 10.4, 2*H*,

Ar–H), 6.81(d, $J = 10.4$, 2*H*, Ar–H), 7.75–7.43(m, 4*H*, Ar–H), IR(KBr): $\nu = 3021, 2955, 1721, 1645, 1251\ cm^{-1}$, mass (EI) *m/z* 306.

3. Results and discussion

Zn[L-proline]$_2$ complex was synthesized by stirring 10 mmol of L-proline and 5 mmol of zinc nitrate solution at room temperature according to reported by Sivamurugan et al. [20]. In the present study, our initial experiment was carried out with 3-acetyl-4-hydroxycoumarin and phenyl hydrazine (Entry 1, Table 1). Both the substrates were thoroughly mixed with catalyst and adsorbed on neutral alumina by stirring them in a suitable volatile solvent, *e.g.*, chloroform and removing the solvent thereafter under reduced pressure. The alumina supported mixture was subjected to microwave irradiation (200 W) at 120 °C. The reaction was monitored at 2 min time interval. To our surprise the reaction was found to finish within 7 min with 92% yields. In the second experiment, 4-chlorophenylhydrazine (Entry 2, Table 1) used as a substrate with 3-acetyl-4-hydroxycoumarin, the reaction was found to furnish with 90% yields within 5 min. In the third experiment, when phenylhydrazine possessing electron withdrawing substituent (*i.e.*, 3-nitrophenylhydrazine, Entry 9, Table 1) was used, the reaction was found to complete within 7 min (Yield 90%). Spurred by the findings as discussed above, more reactions were carried out with phenylhydrazines, comprising various electron releasing and electron withdrawing substituents in the aromatic nucleus (Table 1). In all the cases the yields were obtained in the range of 83–95%.

3.1. Effect of catalyst

The catalyst plays an important role in the formation of chromeno[4,3-*c*]pyrazoles *via* tandem cyclization. The concentration of the catalyst was taken constant in all the experiments. Devoid of the catalyst the substrates were found to remain unreacted even after prolong microwave irradiations at 200 W and 120 °C.

3.2. Effect of microwave power at high temperature

Effect of microwave power plays pivotal role in microwave assisted organic synthesis. Microwave effect caused by uniqueness of the microwave dielectric heating mechanism. This effect is termed as "Specific Microwave Effect" and such effect can not be achieved or duplicated by conventional heating. The efficiency of "Microwave flash heating" not only reduces chemical reaction times from hrs to min but it is also known to reduce side reactions, increase yields and improved reproducibility of temperature. In order to check the effect of microwave power, the same experiments of Table 1 were carried out at 400 W power and two different temperatures *i.e.*, 120 and 160 °C. The results are summarized, in Table 1. From the findings, we conclude that the partial yield loss was observed at high microwave power (400 W) and at high temperature (160 °C). This may be due to the decomposition of the substrates or products were observed at high temperature and at high microwave power.

Table 2
Recyclability study of Zn[L-proline]$_2$ catalyst with different substrates

Entry[a]	Number of run	Microwave power (200 W) at 120 °C	
		Time (min)	Yield (%)
1	2nd run	7	92
1	3rd run	7	89
1	4th run	7	87
1	5th run	7	86
1	6th run	7	84
1	7th run	7	80
11	2nd run	5	89
11	3rd run	5	87
11	4th run	5	85
11	5th run	5	83
11	6th run	5	81
11	7th run	5	78
13	2nd run	8	87
13	3rd run	8	85
13	4th run	8	84
13	5th run	8	82
13	6th run	8	80
13	7th run	8	79

[a] Entry refers according to reactions of Table 1.

3.3. Recyclability study

The reusability of the catalyst was checked at 200 W power and at 120 °C. After the completion of reaction for the first run, the reaction mixture was thoroughly washed with ethyl acetate and filtered. This process was repeated until complete removals of the products from the catalyst were observed. And hence alumina supported catalyst was also recovered. Further the catalyst was washed with methanol and dried in vacuum at 70 °C for 6 h. The dried catalyst was used for next successive runs and the same procedure was adopted for all the recyclability studies. The reaction time and yield for the different cycles are depicted in Table 2. From the findings, we conclude that the catalytic activity diminishes gradually for the next successive runs.

4. Conclusions

In conclusion, this paper describes a convenient and efficient process for the synthesis of chromeno-pyrazoles *via* tandem cyclization. The salient features of this protocol are simple experimental procedure, rapid synthesis due to microwave heating, mild reaction condition, greater selectivity, less cumbersome work-up, harmless to environment by avoiding the use of VOCs as a reaction media, reusability of Zn[L-proline]$_2$, simplicity in operation, improved yields and acceleration of the reaction rate, cleaner reaction profile, which make it a convenient, economic and user friendly process for the synthesis chromeno[4,3-*c*]pyrazoles.

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