Novel synthesis of 1,3,5-trisubstituted 2-pyrazolines promoted by chlorotrimethylsilane

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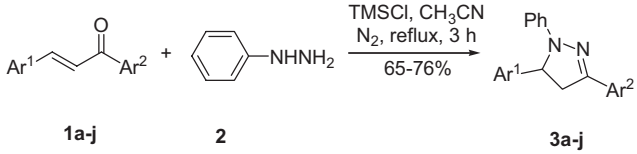
1,3,5-Trisubstituted-2-pyrazolines were effectively synthesised by utilising chlorotrimethylsilane as an efficient promoter in the cyclisation addition of phenylhydrazine to chalcones under nitrogen in acetonitrile. The clean, mild reaction conditions, high yields and a simple workup of target compounds were attractive features of the reaction which enables a facile preparative procedure for building the pyrazoline ring.

Keyword: 1,3,5-trisubstituted-2-pyrazoline, chlorotrimethylsilane, chalcone, cyclisation reaction, synthesis

The pyrazoline nucleus occurs in several natural compounds and pharmacologically active substances displaying a broad range of biological activity.[1-3] Often the type and degree of substitution about the pyrazoline ring can have a profound effect on the biological activity of a given substrate. The biological activity of substituted pyrazolines and their derivatives has been found to possess anti-WNV (West Nile Virus),[4] anti-inflammatory,[5-6] antimicrobial,[7] anti-arrhythmic, antipyretic, tranquilising, muscle relaxant, psycho analeptic agents,[8-10] and human leukocyte elastase inhibitors.[11] In addition to the synthetic applications, variously substituted pyrazolines and their derivatives have been employed in the study of heterocyclic chemistry. As important and valuable synthetic precursors[12-14] the pyrazolines may undergo double bond reduction to furnish the corresponding pyrazolidines. These heterocyclic adducts are not only versatile optically active building blocks for asymmetric synthesis[15-16] but also provide simple azaprolines as useful amino acid analogues.[17-21] Thus, it is necessary for significant effort to be made to develop novel preparations to the substituted pyrazolines. Although previous methods to substituted pyrazolines have been published,[7,22-29] we know that the more classical and convenient synthesis of the pyrazolines began with a Claisen–Schmidt condensation between a methyl aryl ketone and an aromatic aldehyde affording the stable chalcone intermediate. This reaction was conducted in the presence of a strong base, such as NaOH, in a minimal volume of methanol or ethanol. With little purification required, the chalcone was reacted with hydrazine or phenylhydrazine in ethanol in the presence of glacial acetic acid, which afforded the substituted pyrazoline. Otherwise the cyclisation reaction of the chalcone with phenylhydrazine is carried out by using microwave irradiation to afford the substituted pyrazolines under solvent-free and silica-supported conditions.[30] However, most of the methods have significant drawbacks such as low yields of the products, difficulties in workup and harsh reaction conditions. Since substituted pyrazolines and their derivatives are increasingly useful and important in pharmaceuticals and the synthetic applications, there remains a need for a more efficient and practical methods for the synthesis of substituted pyrazolines from commercially available chalcones precursor. Recently, chlorotrimethylsilane (TMSCl) was shown to be an effective promoter for the organic synthesis and organic reaction, including Michael addition reaction,[31] Knoevenagel condensation reaction,[32] and imino ene reaction.[33] It has also been reported as a mild useful and inexpensive Lewis acid catalyst for one-pot chemoselective multicomponent Biginelli reactions,[34] the biguanide formation with benzylamine and dicyandiamide,[35] and *direct* cross aldol additions and the related Claisen condensation using $TiCl_4/Bu_3N$.[36] Taking into account that the cyclisation reaction of the chalcone with phenylhydrazine is easily handled. Here we report a new method of preparation of 1,3,5-trisubstituted 2-pyrazolines by using TMSCl as a Lewis acid to promote the cyclisation reaction of the chalcone with phenylhydrazine. (Scheme 1)



1a-j **2** **3a-j**

Entry	Ar^1	Ar^2	Pyrazolines **3** yield (%)
a	Ph	4-MeOPh	74
b	4-^{i}PrPh	4-MeOPh	72
c	2,3-$(MeO)_2$Ph	4-MeOPh	70
d	2-MePh	2-Naphthyl	65
e	3-MePh	4-MeOPh	68
f	2-ClPh	4-MeOPh	70
g	4-MeOPh	Ph	74
h	Ph	Ph	73
i	4-BrPh	Ph	70
j	4-MeOPh	Ph	76

Scheme 1

Results and discussion

According to the literature,[37-39] we first prepared the intermediate chalcones (**1a–j**) from a Claisen–Schmidt condensation reactions between a methyl aryl ketone and an aromatic aldehyde in the presence of sodium hydroxide in ethanol. Subsequent cyclisation reaction with phenylhydrazine yielded the 1,3,5-trisubstituted pyrazoline. The formation of pyrazolines by the acid-catalysed cyclisation addition of phenylhydrazine to α,β-unsaturated ketone is well known. We thought that TMSCl should also promote the cyclisation reaction as an effective Lewis acid. To optimise the cyclisation reaction conditions, we carried out a model of the cyclisation reaction of 4-methoxychalcone (**1a**) and phenylhydrazine (**2**) in the presence of TMSCl. First we varied the solvent to determine which one would lead to a high yield of product (**3a**) (see Table 1).

The results (Table 1) showed that the cyclisation reaction of 4-methoxychalcone (**1a**) and phenylhydrazine (**2**) was promoted efficiently by TMSCl in most solvents, the best yield was recorded in acetonitrile (Table 1, entry 5). Next, we optimised the reaction temperature in acetonitrile under nitrogen (Table 2).

It was discovered that reflux temperature (90°C) was the optimum temperature for the cyclisation reaction using acetonitrile as reaction solvent. Then the effect of reaction time on the synthesis of pyrazoline **3a** was studied (Table 3).

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Table 1 Solvent influence on the preparation of pyrazoline (**3a**)[a]

Entry	Solvent	Yield (%)
1	DMSO	73
2	THF	62
3	DMF	70
4	Dioxane	60
5	CH_3CN	74
6	Toluene	55

[a]Conditions: 4-methoxychalcone (358 mg, 1.5 mmol), phenylhydrazine (216 mg, 2 mmol), TMSCl (325 mg, 3 mmol), solvent (25 ml), reaction temperature 90°C, nitrogen, 3 h.

Table 2 Effect of the reaction temperature on the preparation of pyrazoline (**3a**)[a]

Reaction temperature/°C	25	50	75	90(reflux)
Yield of pyrazoline (**3a**)/%	44	62	70	74

[a]Conditions: 4-methoxychalcone (358 mg, 1.5 mmol), phenylhydrazine (216 mg, 2 mmol), TMSCl (325 mg, 3 mmol), CH_3CN (25 ml), nitrogen, 3 h.

As shown in Table **3**, the reaction gave a satisfactory yield of **3a** for 3 h, and longer reaction time is not necessary. Thus, with these results in hand, we synthesised 1,3,5-trisubstituted-2-pyrazolines (**3a–j**) in yield varying from 65 to 76% by the cyclisation reaction of 1.5 mmol of appropriate 1,3-diphenyl-2-propen-1-one derivatives (**1a–j**) in 25 ml acetonitrile with 2.0 mmol phenylhydrazine in the presence of 3.0 mmol TMSCl at reflux for 3 h under nitrogen (Scheme 1).

Structure and chemical data for the synthesised compounds (**3a–j**) are given in experimental section. IR spectra of the products showed C=N stretching band at about 1595 cm^{-1}. ^1H NMR spectra, C_4-Ha, C_4-Hb and C_5-H protons of the pyrazoline ring were observed as doublet of at 3.06–3.26, 3.75–3.88, and 5.15–5.30 ppm (J = 12, 7 and J = 12 Hz). The protons belonging to the aromatic ring and substitutent groups were observed within the expected chemical shift values.

In summary, an efficient methodology for the synthesis of 1,3,5-trisubstituted-2- pyrazolines was developed which allows for the obtaining of target compounds in high yields (65–76%). Firstly chalcones (**1a–j**) were synthesised by condensing appropriate acetophenones with benzaldehyde derivatives in dilute ethanolic sodium hydroxide solution at room temperature according to Claisen–Schmidt condensation. Then 1,3,5-trisubstituted-2-pyrazolines were synthesised by the TMSCl-promoted cyclisation addition of phenylhydrazine to chalcones (**1a–j**) under nitrogen in acetonitrile. The optimised reaction conditions of the TMSCl-promoted cyclisation addition were studied and used for the preparation of all target compounds.

Experimental

Chalcones were prepared according to known literature procedure.[37-39] Elemental analytical data were obtained by using a model 240 elementary instrument, IR spectra were measured with a model 408 infrared spectrometer, ^1H NMR and ^{13}C NMR spectra were recorded on a JNM-90Q Spectrometer by using TMS as an internal standard ($CDCl_3$ as solvent).

General procedure for the preparation of 1,3,5-trisubstituted 2-pyrazolines (**3a–j**)

To a mixture of chalcone (1.5 mmol) and phenylhydrazine (216 mg, 2 mmol) in dry acetonitrile (25 ml) was added TMSCl (325 mg, 3 mmol) at room temperature under nitrogen. The resulting mixture was stirred under reflux for 3 h. After the mixture was cooled to room temperature, ice-water (10 ml) was added to the reaction mixture and the resultant mixture was extracted with CH_2Cl_2 (2 × 15 ml), the combined organic phase was washed with water and brine, dried over Na_2SO_4. Removal of solvent, the residues was purified by column chromatography (silica gel, EtOAc/CH_2Cl_2, 1/40) to give a product (**3a–j**).

Table 3 Effect of the reaction time on the preparation of pyrazoline (**3a**)[a]

Reaction time (h)	1.5	2.0	3.0	3.5
Yield of pyrazoline (**3a**)/%	38	62	74	74

[a]Conditions: 4-methoxychalcone (358 mg, 1.5 mmol), phenylhydrazine (216 mg, 2 mmol), TMSCl (325 mg, 3 mmol), CH_3CN (25 ml), nitrogen, reflux.

3-(4-methoxyphenyl)-1,5-diphenyl-4,5-dihydro-1H-pyrazole (**3a**)[30]: M.p. 135–136°C (hexanes/acetone); IR (KBr) υ 3023, 2839, 1598, 1494, 1378, 1115, 1025, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.65 (d, J = 8.4 Hz, 2H), 7.30–7.20 (m, 5H), 7.15 (t, J = 8.1 Hz, 2H), 7.04 (d, J = 7.5 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 6.75 (t, J = 7.2 Hz, 1H), 5.16 (dd, J = 6.9, 12.0 Hz, 1H), 3.79 (m, 4H), 3.06 (dd, J = 7.5, 17.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 160.0, 146.7, 145.1, 142.7, 129.0, 128.8, 127.4, 127.2, 125.8, 125.4, 118.7, 113.9, 113.2, 64.4, 55.3, 43.7; Anal. Calcd. for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53; Found: C, 80.33; H, 6.22; N, 8.40%.

5-(4-isopropylphenyl)-3-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (**3b**): M.p. 130–132°C (hexanes/acetone); IR (KBr) υ 3020, 2845, 1586, 1494, 1388, 1370, 1112, 1028, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.73 (d, J = 8.4 Hz, 2H), 7.32–7.20 (m, 8H), 6.96 (d, J = 8.7 Hz, 2H), 6.87 (t, J = 6.9 Hz, 1H), 5.18 (dd, J = 6.9, 12.0 Hz, 1H), 3.81 (m, 4H), 3.12 (dd, J = 7.5, 17.1 Hz, 1H), 2.96 (m, 1H), 1.32 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 160.1, 147.9, 146.8, 145.3, 140.2, 128.9, 127.2, 127.1, 125.8, 125.6, 118.7, 114.0, 113.3, 64.2, 55.2, 43.7, 33.7, 24.0; Anal. Calcd. for $C_{25}H_{26}N_2O$: C, 81.05; H, 7.07; N, 7.56; Found: C, 81.33; H, 6.98; N, 7.44%.

5-(2,3-dimethoxyphenyl)-3-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (**3c**)[40]: M.p. 120–122°C (hexanes/EtOAc); IR (KBr) υ 3445, 1597, 1516, 1498, 1479, 1252, 1065, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.65 (d, J = 8.4 Hz, 2H), 7.22–7.14 (m, 2H), 7.06–7.03 (m, 2H), 6.96–6.87 (m, 3H), 6.81–6.72 (m, 3H), 5.52 (dd, J = 7.2, 12.3 Hz, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 3.80 (m, 4H), 3.12 (dd, J = 7.5, 17.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 160.2, 152.9, 147.3, 146.0, 145.3, 136.3, 129.0, 127.3, 125.8, 124.7, 118.7, 114.1, 113.2, 111.6, 60.8, 59.1, 55.8, 55.4, 42.9; Anal. Calcd. for $C_{24}H_{24}N_2O_3$: C, 74.21; H, 6.23; N, 7.21; Found: C, 74.29; H, 6.38; N, 7.08%.

5-(2-methylphenyl)-3-(2-naphthyl)-1-phenyl-4,5-dihydro-1H-pyrazole (**3d**)[30]: M.p. 170–172°C (hexanes/acetone); IR (KBr) υ 3023, 2928, 2879, 1598, 1500, 1140, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, ppm): 8.02–6.65 (m, 16H), 5.26 (dd, J = 6.9, 12.0 Hz, 1H), 3.79 (dd, J = 6.9, 12.0 Hz, 1H), 3.06 (dd, J = 7.5, 17.1 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 146.7, 145.0, 140.1, 133.9, 133.3, 131.0, 129.1, 128.2, 127.3, 127.0, 126.4, 125.6, 125.0, 123.6, 119.2, 113.3, 61.2, 43.2, 20.1; Anal. Calcd. for $C_{26}H_{22}N_2$: C, 86.15; H, 6.12; N, 7.73; Found: C, 86.03; H, 6.00; N, 7.40%.

5-(3-methylphenyl)-3-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (**3e**)[30]: M.p. 114–115°C (hexanes/acetone); IR (KBr) υ 3404, 3022, 2939, 2839, 1598, 1495, 1378, 1115, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.55–6.67 (m, 13H), 5.06 (dd, J = 6.9, 12.0 Hz, 1H), 3.72 (m, 4H), 3.01 (dd, J = 7.5, 17.1 Hz, 1H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 160.0, 146.2, 145.1, 140.7, 137.1, 133.4, 130.1, 130.0, 128.9, 128.4, 127.2, 126.0, 125.5, 114.0, 113.4, 64.3, 55.3, 43.8, 21.1; Anal. Calcd. for $C_{23}H_{22}N_2O$: C, 80.67; H, 6.48; N, 8.18; Found: C, 80.39; H, 6.62; N, 8.30%.

5-(2-chlorophenyl)-3-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (**3f**)[30]: M.p. 150–151°C (hexanes/acetone); IR (KBr) υ 3404, 3020, 2936, 2835, 1598, 1495, 1378, 1115, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.70–6.88 (m, 13H), 5.62 (dd, J = 6.9, 12.0 Hz, 1H), 5.02 (dd, J = 6.9, 12.0 Hz, 1H), 3.88 (s, 3H), 3.11 (dd, J = 7.5, 17.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 160.0, 146.4, 145.1, 142.0, 140.8, 135.8, 130.5, 129.2, 127.2, 127.0, 125.5, 122.2, 120.3, 118.0, 113.8, 63.3, 55.0, 41.8; Anal. Calcd. for $C_{22}H_{19}ClN_2O$: C, 72.82; H, 5.28; N, 7.72; Found: C, 72.67; H, 5.22; N, 7.61%.

5-(4-Methoxyphenyl)-1,3-diphenyl-4,5-dihydro-1H-pyrazole (**3g**)[29]: As a yellow foam, IR (KBr) υ 3314, 3020, 2936, 2830, 1590, 1495, 1372, 1115, 746 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.64 (m, 2H), 7.33 (m, 2H), 7.1–7.2 (m, 4H), 7.06 (dd, J = 7.5, 7.1 Hz, 1H), 6.93 (m, 2H), 6.76 (m, 1H), 6.62 (m, 2H), 4.72 (dd, J = 12.3, 7.2 Hz, 1H), 3.17 (s, 3H), 3.05 (dd, J = 17.0, 12.3 Hz, 1H), 2.61 (dd, J = 16.8, 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 159.2, 146.9, 145.3, 135.0, 133.8, 129.4, 128.7, 127.2, 126.0 119.5, 114.6, 64.0, 54.5, 43.0; Anal. Calcd. for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53; Found: C, 80.38; H, 6.12; N, 8.39%.

1,3,5-triphenyl-4,5-dihydro-1H-pyrazole (**3h**)[30]: M.p. 110–112°C (hexanes/acetone); IR (KBr) υ 3384, 3018, 2936, 2835, 1598, 1500,

1372, 1115, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.72 (d, *J* = 8.4 Hz, 2H), 7.27–7.40 (m, 8H), 7.20 (t, *J* = 7.2 Hz, 2H), 7.10 (d, *J* = 9.0 Hz, 2H), 6.78 (t, *J* = 7.2 Hz, 1H), 5.30 (dd, *J* = 12.0 Hz, 7.2 Hz, 1H), 3.88 (dd, *J* = 12.0 Hz, 1H), 3.15 (dd, *J* = 17.4 Hz, 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 146.4, 144.6, 142.8, 132.7, 129.1, 128.5, 127.5, 125.7, 119.0, 114.4, 64.6, 43.2; Anal. Calcd. for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39; Found: C, 84.34; H, 6.10; N, 9.48%.

5-(4-Bromophenyl)-1,3-diphenyl-4,5-dihydro-1H-pyrazole (**3i**)[41]: M.p. 138–140°C (hexanes/acetone); IR (KBr) υ 3384, 3020, 2936, 2840, 1598, 1500, 1370, 1112, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.72(d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 9.0 Hz, 2H), 7.40–7.32 (m, 3H), 7.23–7.14 (m, 4H), 7.10 (d, *J* = 9.0 Hz, 2H), 6.78 (t, *J* = 7.2 Hz, 1H), 5.30 (dd, *J* = 12.0 Hz, 7.2 Hz, 1H), 3.82 (dd, *J* = 17.1 Hz, 12.0 Hz, 1H), 3.10 (dd, *J* = 17.1 Hz, 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 146.6, 144.2, 141.6, 132.3, 128.7, 127.6, 125.6, 121.3, 119.3, 113.3, 63.8, 43.3. Anal. Calcd. for $C_{21}H_{17}BrN_2$: C, 66.85; H, 4.54; N, 7.43; Found: C, 66.92; H, 4.50; N, 7.58%.

5-(4-Methoxyphenyl)-1,3-diphenyl-4,5-dihydro-1H-pyrazole (**3j**)[41]: M.p. 148–150°C (hexanes/acetone); IR (KBr) υ 3024, 2828, 1595, 1498, 1378, 1112, 1025, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.74 (d, *J* = 8.2 Hz, 2H), 7.38–7.18 (m, 7H), 7.10 (d, *J* = 8.2 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.77 (t, *J* = 7.0 Hz, 1H), 5.23 (dd, *J* = 12.0 Hz, 7.2 Hz, 1H), 3.80 (dd, *J* = 17.1 Hz, 12.0 Hz, 1H), 3.76 (s, 3H), 3.12 (dd, *J* = 17.1 Hz, 7.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 158.4, 146.6, 144.7, 134.6, 133.0, 128.6, 128.0, 127.2, 125.2, 119.2, 114.6, 113.5, 64.2, 55.4, 43.6; Anal. Calcd. for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53; Found: C, 80.30; H, 6.22; N, 8.37%.

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