Indian Journal of Chemistry
Vol. 48B, May 2009, pp. 718-724

Note

Synthesis and antimicrobial activity of 4-[5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl]-dihydropyridines and 4-[5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl]-3,4-dihydropyrimidin-2-ones

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Received 27 August 2008; accepted (revised) 28 November 2008

New derivatives of dihydropyridine and dihydropyrimidone are synthesized by Hantzsch cyclization and modified Bignelli's cyclization, respectively. The antimicrobial activity of these compounds is also described. The compounds **2a, 3d, 3e** and **3f** show good activity.

Keywords: Dihydropyridine, dihydropyrimidone, Hantzsch cyclization, β-ketoester or β-diketone

After the synthesis of dihydropyridine by Hantzsch[1], extensive research into the reaction mechanisms and utility of dihydropyridines was carried out. The research on 1,4-dihydropyridines is of current interest due to their valuable activity as calcium channel antagonists[2]. For example, 4-aryl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate derivatives such as nifedipine[3] are widely used for the treatment of cardiovascular diseases (hypertension and angina pectoris). In recent years interest has also focused on aza-analogs of dihydropyridines. For example, dihydropyrimidones show a very similar pharmacological profile to classical dihydropyridine calcium channel modulators[4].

Derivatives of dihydropyridines and dihydropyrimidones exhibit a wide range of other biological activities such as anti-inflammatory, antifungal[5] and antibacterial activities[6]. These compounds are potential new lead for the development of anticancer drugs [7].

The main aim is to synthesize derivatives of dihydropyridines and dihydropyrimidines having a heterocyclic ring at the 4 position and to screen these compounds for their antibacterial properties. It is well known that halogen derivatives of pyrazoles are used as drugs and agrochemicals[8]. Thus, the 1,4-dihydropyridine and dihydropyrimidone systems with the 5-chloropyrazole unit are combined.

Strategies for the synthesis of the dihydropyridines and dihydropyrimidinones have varied from one-pot[9] to multistep approaches[10]. Biginelli's initial one-pot reaction of β-keto ester, aryl aldehyde and urea under strongly acidic conditions in a protic solvent frequently afforded low (20-50%) yields[11] of dihydropyrimidinones. Subsequent multistep synthesis produced somewhat higher yields but lacked the simplicity of the one-pot synthesis[12]. More recently, new conditions for the synthesis of dihydropyrimidinones have been reported[13]. However, in spite of their advantage and potential utility, some of them suffer from drawbacks such as long reaction times, expensive catalysts or lower yields.

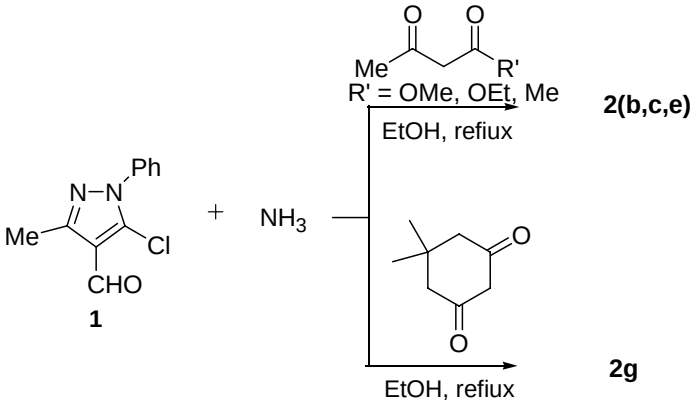
Results and Discussion

Herein one-pot synthesis of new dihydropyridines and dihydropyrimidin-2(1*H*)-ones having a 5-chloropyrazole unit at 4-position of dihydropyridine or dihydropyrimidone ring is reported.

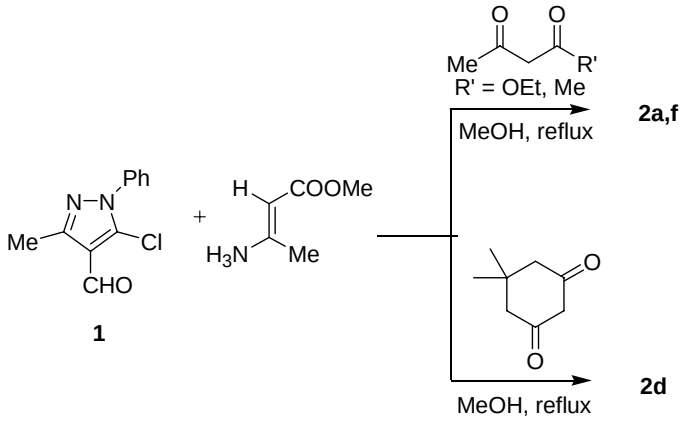
Aldehyde **1** (Ref. 14) was prepared by the Vilsmeier-Haack reaction of the corresponding pyrazolone[15] with phosphorus oxychloride in *N*,*N*-dimethylformamide (DMF). 1,4-Dihydropyridine derivatives **2a-g**, having a 5-chloropyrazole on position 4 of 1,4-dihydropyridine ring, were synthesized by employing the Hantzsch method (method A) and modified Hantzsch method (method B).

Method A: The mixture of aldehyde, **1** (1 mole), β-ketoester or β-diketone (2 mole) and ammonia (3.5 mole) was refluxed together in dry ethanol for about 18-48 hr **(Scheme I**). Then the reaction-mixture was cooled and compounds **2b,c,e,g** were extracted with DCM which later purified by column chromatography using ethyl acetate and hexane as solvent system.

Method B: The mixture of aldehyde **1** (1 mole), β-ketoester or β-diketone (1 mole) and 3-amino-but-2-enoic acid methyl ester (methyl 3-aminocrotonate, 1 mole) was refluxed together in dry methanol for about 12-40 hr as indicated by TLC **(Scheme II).** Then the



Scheme I



Scheme II

reaction-mixture was cooled and compounds **2a,d,f** were extracted in ethyl acetate which later purified by column chromatography using ethyl acetate and hexane as solvent system.

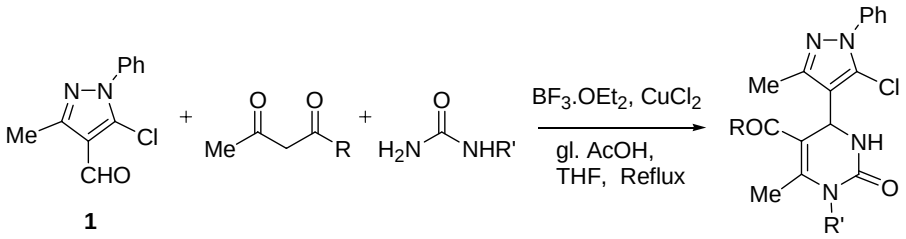
Reaction of aldehyde **1** with a β-ketoester or β-diketone and urea (or substituted urea) in the presence of $CuCl_2$/acetic acid/$BF_3.(OEt)_2$ in dry THF at reflux temperature afforded the corresponding dihydropyrimidin-2(1*H*)-one derivatives **3a-g** in moderate to good yields (50-70%, **Scheme III).**

We studied several conditions for the formation of dihydropyrimidin-2(1*H*)-ones, such as (i) I_2 in toluene, (ii) acetic acid/catalytic HCl, (iii) refluxing in ethanol containing catalytic HCl or H_2SO_4 and (iv) $BiNO_3$/acetonitrile. The reaction was rapid and produced good yields[16] when $BF_3.(OEt)_2$ was used in slight excess (1.3 equiv.) and $CuCl_2$ and acetic acid were used in catalytic amounts. Copper ion and $BF_3.(OEt)_2$ were chosen as additives for their known carbonyl-activating abilities.

Antimicrobial activity

The antibacterial properties of a compound (or suitable antibiotic) are noted by determining the sensitivity of the bacteria to a particular compound. First the lowest concentration of the compound that inhibits the growth of the bacteria is determined. MIC was done by Kirby-Bauer[17] disk assay disc diffusion method.

To perform the test, media-supplemented agar plates are inoculated with the bacteria of interest, and small antibiotic-impregnated disks are placed onto the agar surface. The plates are reincubated overnight (usually at 37°C) to expedite bacterial growth. The antibiotic diffuses out of the disk into the surrounding media. The concentration of antibiotic decreases as it



a) R = OEt, R' = H b) R = OMe, R' = H c) R = Me, R' = H
d) R = OEt, R' = Me e) R = OMe, R' = Me f) R = OEt, R' = Ph
g) R = OMe, R' = Ph

Scheme III

spreads out from the disc. After the incubation period, the plates are read by measuring the zone of inhibition (ZOI) of bacterial growth around each disk.

Experimental Section

All reagents used were of AR grade. THF was distilled from sodium/benzophenone prior to use. Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker 300 NMR spectrometer in DMSO-d_6 (with TMS for ^{1}H and chloroform-*d* for ^{13}C as internal references) unless otherwise stated. Mass spectra were recorded on Agluent 1100 ES-MS Karlsrhue Germany. Column chromatography was performed on silica gel (230-400 mesh). Micro-analyses were obtained with an Elemental Analysen-systeme GmbH VarioEL V3.00 element analyzer. The reactions were monitored by TLC using aluminium sheets with silica gel 60 F_{254} (Merck). All reactions were carried out under nitrogen atmosphere.

4-(5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diethyl dicarboxylate 2c. **Typical procedure**: A mixture of 0.5 g (0.227 mmole) of aldehyde **1**, 0.592 g (0.455 mmole) of ethyl acetoacetate and 0.193 g of ammonia was refluxed in ethanol for 5 hr. The product is extracted with ethyl acetate and solvent is removed at vacuum. After removal of solvent, the compound was then purified by column chromatography using ethyl acetate and hexane (1.5:8.5 v/v) to give pure **2c**. IR (KBr, cm^{-1}): 3391, 3281, 1701; ^{1}H NMR (300 MHz, DMSO-d_6) : δ 7.20-7.30 (m, 5H), 6.40 (s, 1H), 5.20 (s, 1H), 4.12 (q, 4H), 1.10-1.20 (t, 6H), 2.30 (s, 6H), 2.20 (s, 3H); ^{13}C NMR (300 MHz, DMSO-d_6): δ 166 (2), 151, 140.2, 139.7, 129.8(2), 128, 124, 115(2), 119, 100.6, 60.9 (2), 18.6 (2), 14.8(3), 9.3; MS (*m*/*z*): 442 (M^+); Anal. Calcd for $C_{24}H_{27}ClN_2O_4$: C, 65.08; H, 6.14; N, 6.32. Found: C, 64.90; H, 6.01; N, 6.38%.

In a similar manner, compounds **2b**, **2e** and **2g** were also synthesized.

4-(5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3-ethyl-5-methyl dicarboxylate 2a. **Typical procedure**: A mixture of 0.565 g (0.26 mmole) aldehyde **1**, 0.334 g (0.26 mmole) of ethyl acetoacetate and 0.296 g (0.26 mmole) of 3-amino-but-2-enoic acid methyl ester was refluxed together in dry methanol for about 2 hr as indicated by TLC. Then the reaction-mixture was cooled and compound **2a** was extracted in ethyl acetate which was later on purified by column chromatography using ethyl acetate and hexane as solvent system IR (KBr, cm^{-1}): 3384, 3289, 1695; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.27 (m, 5H), 6.14 (s, 1H), 5.0 (s, 1H), 4.20 (s, 3H), 3.60 (s, 2H), 2.20-2.30 (s, 9H), 1.26-1.30 (t, 3H); ^{13}C NMR (300 MHz, DMSO-d_6): δ 165 (2), 151, 142.7, 141.2, 138.7, 130(2), 128.8, 126, 118.8 (2), 104.7, 123.3(2), 59.9, 50.8, 18.6(2), 13.7 (2), 8.2; MS: (*m*/*z*) 442 (M^+); Anal. Calcd for $C_{23}H_{25}ClN_2O_4$: C, 64.41; H, 5.88; N, 6.53. Found: C, 64.90; H, 5.71; N, 6.60%.

In a similar manner, compounds **2d** and **2f** were also synthesized.

The physical and spectroscopic data of all synthesized compounds **2a-g** are given in **Table I** and **Table II** respectively.

5-Ethoxycarbonyl-6-methyl-4-[5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl]-3,4-dihydropyrimidin-2(1*H*)-one 3a. **Typical procedure**: A mixture of 0.85 g (0.386 mmole) of aldehyde, **1**, 0.542 g (0.386 mmole) of ethyl acetoacetate and 0.348 g (0.579 mmole) of urea was refluxed in dry THF (20 mL) in the presence of 0.56 g (0.502 mmole) of $BF_3.OEt_2$,

Table I — Analytical data of compounds **2a-g** and **3a-g**

Compd	Yield (%)	m.p. (°C)	Time (hr)	Found % (Calcd) C	H	N
2a	51	256-58	24	61.50	5.80	9.89
				(61.46	5.63	9.77)
2b	55	280-82	36	60.40	5.72	10.50
				(60.65	5.33	10.11)
2c	52	350-52	30	62.50	5.94	9.94
				(62.23	5.90	9.47)
2d	50	188-90	40	68.76	6.41	9.43
				(68.00	6.18	9.91)
2e	49	290-92	48	65.92	5.08	10.97
				(65.41	5.78)	10.95)
2f	58	320-21	12	63.94	5.24	10.38
				(63.08	5.55	10.51)
2g	56	290-91	18	70.09	6.24	10.00
				(69.89	6.52	9.06)
3a	71	234-36	12	57.75	5.08	14.97
				(57.45	5.12	14.81)
3b	60	245-46	10	56.67	4.72	15.56
				(56.84	4.84	15.26)
3c	55	237-39	10	59.30	4.94	10.17
				(59.45	4.80	10.01)
3d	59	184-86	10	58.76	5.41	14.43
				(58.56	5.50	14.25)
3e	54	180-82	11	57.75	5.08	14.97
				(57.50	4.81	14.71)
3f	50	Oily	12	63.94	5.14	12.38
				(63.78	5.28	12.15)
3g	55	Oily	11	62.99	5.24	12.78
				(63.09	5.01	13.01)

0.040 g (0.0386 mmole of gl. acetic acid and 0.0514 g (0.0386 mmole of $CuCl_2$ for 18-24 hr. The resulting mixture was then neutralized with aq. 10% Na_2CO_3 solution and the product was extracted with ethyl acetate (3 × 50 mL). After removal of solvent, the compound was then purified by column chromatography using ethyl acetate and hexane (3:7 v/v) to give pure of **3a**. IR (KBr, cm^{-1}): 3398, 3281, 1703; ^1H NMR (300 MHz, DMSO-d_6): δ 9.29 (s, 1H), 7.40-7.56 (m, 6H), 5.31 (s, 1H), 3.98 (q, 2H), 2.35 (s, 3H), 2.19 (s, 3H), 1.07 (t, 3H); ^{13}C NMR (300 MHz , DMSO-d_6): δ 165.1, 151.163, 148.3, 147.0, 137.7, 129.2, 128.16, 124.7, 120.8, 95.3, 67.9, 59.0, 45.95, 17.64, 14.15, 12.39; MS: (*m*/*z*) 374 (M^+); Anal. Calcd for $C_{18}H_{19}N_4O_3$: C, 57.75; H, 5.08; N, 14.97. Found: C, 57.45; H, 5.12; N, 14.81%.

In a similar manner compounds **3b-g** were synthesized. The data of all the compounds **3a-g** are given in **Tables I** and **III**.

Antibacterial activity

All the compounds **2a-g** and **3a-g** were evaluated for their antibacterial activity using conventional Kirby-Bauer method **Table IV**. Compounds **2a-g** and **3a-g** and reference drug (gentamycin) were dissolved in DMSO and solution was further diluted with DMSO to obtain different concentrations. To ensure that solvent had no effect on bacterial growth, a control test with DMSO was performed at same concentration used in experiment and found that DMSO has no effect on the bacterial growth.

Table II - Spectroscopic data of compounds **2a-g**

Compd	IR (cm^{-1})	^{1}HNMR (δ)	^{13}CNMR (δ)
2a	3390, 3301, 1705	7.27 (m, 5H), 6.14 (s,1H), 5.0 (s,1H), 4.20 (s, 3H), 3.60 (s, 2H), 2.3-2.2 (s, 9H), 1.26-1.30 (t, 3H)	165(2), 151, 142.7, 141.2, 138.7, 130(2), 128.8, 126, 118.8(2), 104.7, 123.3(2), 59.9, 50.8, 18.6(2), 13.7(2), 8.2
2b	3402, 3245, 1710, 1632	7.20-7.50 (m, 5H), 5.90 (s, 1H), 5.0 (s, 1H), 3.65 (s,6H), 2.29 (s, 6H), 2.20 (s, 3H)	166.6(2), 152, 141.2(2), 140(2), 129.1(2), 128, 126, 118(2), 104.7, 102(2), 55.8(2), 18.6(2), 13.3, 8.2
2c	3393, 3219, 1708	7.20-7.30 (m, 5H), 6.40 (s, 1H), 5.20 (s, 1H) 4.12 (q, 4H), 1.10-1.20 (t, 6H), 2.30 (s, 6H), 2.20 (s, 3H)	166(2), 151, 140.2(2), 139.7, 129.8(2), 128, 124, 115(2), 119, 100.6, 60.9(2), 18.6(2), 14.8(3), 9.3
2d	3401, 3319, 1713	8.90 (s, 1H), 7.10-7.60 (m, 5H), 4.90 (s, 1H), 4.22 (s, 3H), 1.15 (s, 3H), 1.10 (s, 3H), 2.20 (s, 6H), 2.10 (s, 2H), 2.0 (s, 2H)	193, 165, 151, 150.3, 139.1, 129.1(2), 128, 125, 119(2), 112.3, 58.2, 54, 50.8, 47.4, 44.4, 22.4(2), 21.2, 18.5, 10.2, 8.4
2e	3410, 3210 1695	7.20-7.50 (m, 5H), 6.40 (s, 1H), 5.21 (s, 1H), 3.78 (s, 6H), 2.25 (s, 3H), 2.10-2.20 (s, 9H)	196.5(2), 154, 138.2(2), 139.7, 125.1(2), 123, 122.3, 118(2), 119, 108.4(2), 22.5(2), 19(2), 9.15, 7.89
2f	3350, 1705, 1655	7.10-7.30 (m, 5H), 6.70 (s, 1H), 5.10 (s, 1H), 3.78 (s, 3H), 2.25 (s, 3H), 1.92 (s, 6H), 2.25 (s, 3H)	192, 160.15, 149, 141.2, 140.2, 139.1, 130(2), 128, 124, 117.8(2), 104.7, 109.6, 102.4, 49.8, 27, 17.7, 17.6, 13, 9.05
2g	3401, 1610, 1670	7.30-7.50 (m, 5H), 5.80 (s,1H), 2.50 (s, 4H), 2.20 (s, 3H), 1.50 (s, 4H), 1.34 (s, 12H), 4.9 (s, 1H)	196(2), 151, 145.48(2), 137, 128.1(2), 127, 124.3, 117(2), 111, 108.2(2), 53.5(2), 49(2), 29.8(4), 17(2), 11.3, 9.6

Table III - Spectroscopic data of compounds **3a-g**

Compd	IR (cm^{-1})	^{1}H NMR (δ)	^{13}C NMR (δ)
3a	3398, 3281, 1703	9.29 (s, 1H), 7.40-7.50 (m, 6H), 5.31 (s, 1H), 3.98 (q, 2H), 2.35 (s, 3H), 2.19 (s, 3H), 1.07 (t, 3H)	165.1, 151.163, 148.3, 147.0, 137.7, 129.2, 128.16, 124.7, 120.8, 95.3, 67.9, 59.0, 45.95, 17.64, 14.15, 12.39
3b	3319, 3243, 1703, 1644	9.30 (s, 1H), 7.40-7.50 (m, 6H), 5.31 (s, 1H), 3.51 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H)	166, 151, 148.69, 148.3, 138.04, 129.8, 128.8, 125.2, 121.1, 96.07, 70.2, 51.42, 46.3, 18.01, 12.717

—Contd

Table III - Spectroscopic data of compounds **3a-g**

Compd	IR (cm^{-1})	^1H NMR (δ)	^{13}C NMR (δ)
3c	3319, 3243, 1703, 1644	9.27 (s, 1H), 7.64 (s, 1H), 7.40-7.50 (m, 5H), 5.38 (s, 1H), 2.25 (s, 3H), 2.22 (s, 3H), 2.13 (s, 3H)	196, 153, 151, 148, 138, 130, 129, 125, 120, 107.3 , 70.52, 46.67, 31.016, 19.44, 12.9
3d	3219.74, 1702.8, 1684.59	7.80 (s, 1H), 7.43-7.56 (m, 5H), 5.29 (s, 1H), 3.90-4.0 (q, 2H), 3.18 (s, 3H), 2.49 (s, 3H), 2.17 (s, 3H), 1.07-1.20 (t, 3H)	165, 152, 150, 147.6, 137, 129, 128, 124, 120.25, 98.56, 59.45, 44.75, 29.415, 16.011, 14.08, 12.46
3e	3335.09, 1706.20, 1688.83, 1628.27	7.78 (s, 1H), 7.47-7.53 (m, 5H), 5.30 (s, 1H), 3.59 (s, 3H), 3.18 (s, 3H), 2.49 (s, 3H), 2.17 (s, 3H)	166, 153.2, 151.4, 148.5, 138.05, 129.99, 129.148, 125.5, 120.8, 99.31, 70.38, 51.89, 45.23, 30.23, 16.68, 12.86
3f	3401.7, 2961.7, 2918.3, 2849.7, 1692.5, 1635	7.98 (s, 1H), 7.43-7.52 (m, 10H), 5.47 (s, 1H), 3.60 (t, 2 H), 2.30 (s, 3H), 2.0 (s, 3H), 1.07-1.09 (q, 3H)	166, 152.3, 151, 147.7, 140.1, 138.4, 129.2, 128.7, 127.1, 124.2, 119, 118.1, 60.2, 33.2, 14.71, 13.7
3g	3245.8, 2924.1, 2852.3, 1695.6, 1594.6	7.99 (s, 1H), 7.46-7.54 (m, 10H), 5.47 (s, 1H), 3.64 (s, 3H), 2.34 (s, 3H), 2.02 (s, 3H)	165.4, 152.4, 151, 147.8, 139.9, 137.2, 129.5, 128.2, 126.3, 124.1, 128.5, 120, 119.0, 104.4, 58.8, 34.2, 15.2, 8.1

Table IV - Zone of inhibition of compounds **2a-g** and **3a-g**

Compd	Conc.(mg/ml)*	Zone of inhibition (mm) of various bacteria		
		Proteaus valgaris	*P. aeurginosa*	*E.coli*
2a	25	12	8	9
2b	12.5	0	9	0
2c	50	0	-	-
2d	100	8	8	0
2e	100	1.1	8	0
2f	6.25	-	8	0
2g	12.5	0	1.2	0
3a	10	0	0	9
3b	5	11	0	7
3c	2.5	0	0	7
3d	10	7	7	13
3e	10	11	7	7
3f	2.5	9	8	9
3g	6.25	0	8	7
4**	12.5	12	9	13

* DMSO is used as a solvent.
**Gentamycin.
Compound **2a** shows good zone of inhibition, whereas, compounds **3d**, **3e**, **3f** have moderate antibacterial activity against different type of bacteria as compared to gentamycin as standard drug.

Acknowledgement

We thank DST for financial support. One of the authors (SM) thanks DST for providing JRF.

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