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Synthesis of new heterocyclic compounds using 2-(4,7-dichloro-3,3-dimethyl-indolin-2-ylidene)malonaldehyde

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1-(2,5-Dichlorophenyl)hydrazine was converted via Fischer synthesis with isopropylmethylketone into 4,7-dichloro-2,3,3-trimethyl-3H-indole. Exposure of the indolenine to the vilsmeier reagent produced amino methylene malondialdehyde which reacted with hydrazine, arylhydrazine, urea, cyanoacetamide and thiourea to give pyrazols, pyrimidones and thiopyrimidone, respectively.

1. Introduction

The recognition of the power of the species produced by the combination of phosphoryl chloride with the amide of secondary amine (*N*-methylformanilide and dimethylformamide have been most often utilized) has its origin in paper in 1894[1]. Later work by Fischer, Muller and Vilsmeier[2] and then by Vilsmeier and Haack[3] and later by groups of Arnold[4-6], Meth-Cohn[7-9] and Perumal[10-13] clarified the process and made it into a widely used regimen of acylation, especially formylation of reactive aromatic and heteroaromatic compounds and indeed non-aromatic compounds. Baradarani and co-workers described the reaction of various 3*H*-indols with the Vilsmeier reagent formed from dimethyl formamide and phosphorus oxychloride to produce aminomethylene malondialdehyde[14-17]. The

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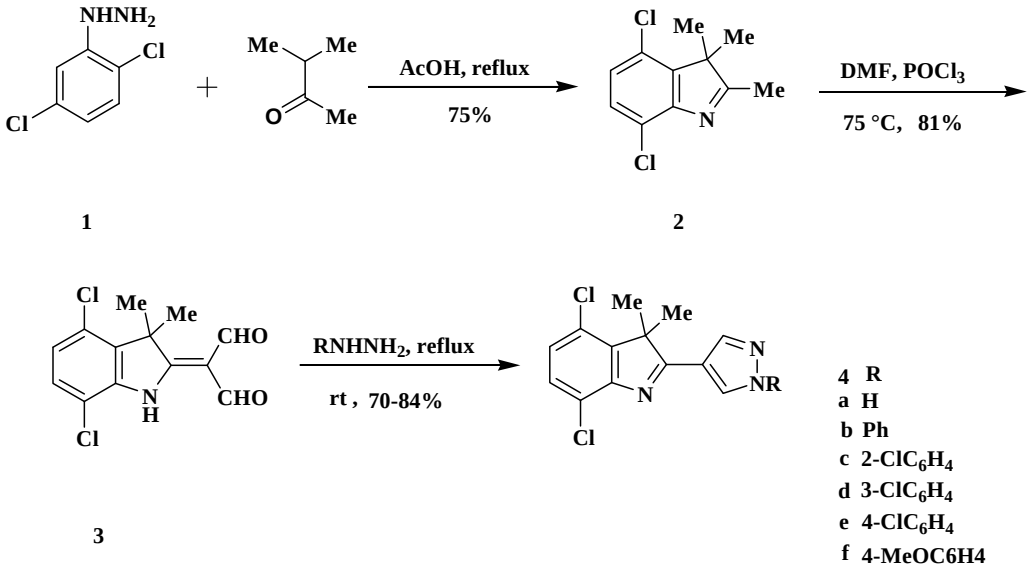
reaction of aminomethylene malondialdehyde with various aryl hydrazines led to form pyrazole ring on 3*H*-indole systems[14-17].

2. Results and Discussion

Diazotization of 2,5-dichloroanilin and subsequent reduction of diazonium salt with stannous chloride dihydrate produced the corresponding 1-(2,5-dichlorophenyl)hydrazine **1**. Reaction of compound **1** with isopropyl methyl ketone in a Fischer reaction and in hot acetic acid produced the indolenine **2** in acceptable yield. The structure of produced indolenine was evident from its molecular formula and spectral data, the six–hydrogen singlets for the geminal methyl groups, at δ 1.40 and singlet signal for imine–methyl groups, resonating at δ 2.28. Indolenine was then reacted with the Vilsmeier reagent to produce aminomethylene malondialdehyde **3**.

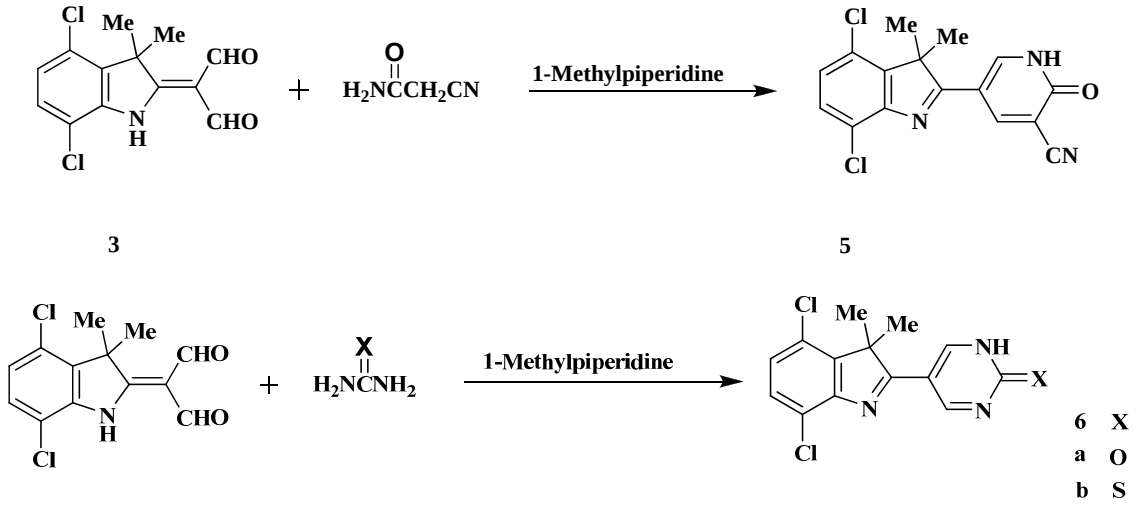
The structure of the aminomethylene malondialdehyde rests on the observation of two – hydrogen singlet at δ 9.85 for aldehyde protons. Absorption at 3432 cm^{-1} was evidence for the presence of N–H bond, further confirmed by ^{1}H-NMR one – hydrogen signal for the N–H, appearing at δ 13.63. The reaction of malondialdehyde with hydrazine, phenyl hydrazine, *para*–methoxy phenyl hydrazine, *ortho*, *meta* and *para*–chloro phenyl hydrazine produced pyrazoles, with migration of the double bond to reform the imine unite. Evidence for the ring closure came from a study of the ^{1}H-NMR spectra of the products, in particular of the signals from the newly formed pyrazole ring. The ^{1}H-NMR spectra of each of the pyrazoles carrying a substituent on a nitrogen **4a-f** had two one-hydrogen singlets, in the range of δ 8.29–8.42, for the pyrazole 5-hydrogen and *δ* 8.61–8.82 for the pyrazole 3-hydrogen.



Scheme 1

Condensation of malondialdehyde **3** and cyano acetamide, urea and thiourea has led to the formation of pyridone ring . The ^{1}H-NMR spectra of pyridine ring of **5** had two one – hydrogen singlet at δ 8.51 for the pyridine 6–hydrogen and δ 8.76, for the pyridine 4–hydrogen. The reaction of malondialdehyde **3** with urea and thiourea were produced the desired pyrimidine-2-(1*H*)-one and

pyrimidine-2-(1*H*)-thione in very good yields, respectively. Because of the insolubility of **6a** and **6b** they were identified by only their IR and high resolution mass spectra.



Scheme 2

3. Conclusions

Malondialdehyde **3** was synthesized in good yield by Vilsmeier-Haack formylation of 3*H*-indole **2**. Its condensation with hydrazine and various arylhydrazines afforded corresponding pyrazole derivatives. Also, reaction of **3** with urea and thiourea produced pyrimidone and thiopyrimidone derivatives respectively. On the other hand, condensation of **3** with cyanoacetamide afforded 2-oxo-2,5-dihydropyridine-3-carbonitrile derivatives **6a/6b**.

Experimental

Melting points were recorded on an electrothermal IA 9200 apparatus and are uncorrected. ^{1}HNMR and ^{13}CNMR spectra were recorded on Bruker Arance AQS 300 MHz spectrometers at 300 MHz and 75 MHz respectively. Chemical shifts are in parts per million (ppm) measured in $CDCl_3$ and DMSO as solvent and relative to TMS as the internal standard. Infrared spectra were recorded on a Thermonicolet Nexus 670 FTIR instrument and High resolution Mass spectra were recorded on a Agilent Technology HP), Ms model: 5973 network Mass, selective detector ion source: electron impact (EI) 70 eV, ion source temperature: 230 °C, analyzer: quadrupole, analyzer temperature: 150 °C, and relative abundances of fragments are quoted in parentheses after the *m/z* values.

General procedure for the synthesis of (2). A mixture of 1–(2,5–dichlorophenyl) hydrazine dihydrochloride (6 g , 26.25 mmol) and isopropyl methyl ketone (3.62 g , 42 mmol) was refluxed in acetic acid (20 mL) for 24 h and then cooled, diluted with water, and neutralized with 2M NaOH, then extracted with ethyl acetate (4×50 mL). Organic layer was dried over Na_2SO_4. The solvent was evaporated and the resulting viscous oil recrystallized from EtOH to give the indolenine identified as indolenines **2**.

4,7-Dichloro–2,3,3–trimethyl –3*H*– indole (2). 75% Yield; mp 96-98 °C; FT-IR (KBr) ν_{max}: 2971, 2930, 2870, 1709, 1580, 1451, 1396, 1092, 926, 792 cm^{-1}; ^{1}H-NMR (300MHz,$CDCl_3$), δ(ppm) : 1.40 (s, 6H, 2×CH_3), 2.28 (s, 3H,CH_3), 7.01 (d, *J* = 8.7 Hz,1H), 7.19 (d, *J* = 8.7 Hz,1H); ^{13}C-NMR (75

MHz, DMSO) δ (ppm): 15.44, 19.61, 57.23, 123.61, 126.91, 127.68, 129.22, 142.64, 151.68, 190.57; HRMS Found: *m/z* 227.0270 $[M]^+$.$C_{11}H_{11}Cl_2N$. Calculated: 227.0269 $[M]^+$.

General procedure for the synthesis of (3). To *N*,*N*-dimethyl formamide (19.14 mL) cooled in an ice bath was added dropwise phosphorus oxychloride (9.43 mL, 100 mmol) with stirring at below 10 °C . After this addition, a solution of indolenine **2** (5.34g, 23 mmol) in DMF (9.43 mL) was added dropwise. The cooling bath was removed and the reaction mixture was stirred at 75 °C for 4-6 h. The resulting solution was added to ice cooled water and made alkaline with NaOH (*aq*) solution. The resulting solution was extracted with ethyl acetate (4×50 mL). The organic layer was dried over Na_2SO_4. The solvent was evaporated and the resulting precipitate recrystallized from EtOH to give pure malondialdehyde **3**.

2-(4,7-Dichloro-3,3-dimethyl indoline-2-ylidene)malondialdehyde (3). 81% Yield; mp 167-169 °C; IRspectrum, ν, cm^{-1}: NH 3432, 1687, 1618, 1522, 1465, 1230, 1161, 934, 809, 765 cm^{-1}; ^{1}H-NMR (300MHz,$CDCl_3$), δ(ppm): δ 1.86 (s, 6H, 2×CH_3), 7.1 (d, *J* = 8.7 Hz, 1H), 7.25 (d, *J* = 9 Hz, 1H), 9.85 (s, 2H, 2×CHO), 13.67 (s, 1H, NH); ^{13}C-NMR (75 MHz, DMSO) δ (ppm): 19.72, 54.29, 109.40, 116.51, 127.49, 128.35, 129.49, 136.75, 139.02, 178.64, 187.44, 192.70;Mass spectrum (EI, 70 eV): *m/z:* 287(M^++4),285(M^++2), 283 (M^+), 254, 240 (100),212,177,140; HRMS Found: *m/z* 235.0163 $[M]^+$. $C_{13}H_{11}Cl_2NO_2$. Calculated: 283.0167 $[M]^+$.

General procedure for synthesis of (4a). A mixture of the malondialdehyde (5) (0.5 mmol) and hydrazine monohydrate (o.15 g, 3 mmol) in absolute ethanol (10 mL) was stirred at room temperature for 24h. After concentrating the solution, the resulting crystals were collected by filtration and recrystalized from EtOH to give the (**4a**).

4,7-Dichloro-3,3-dimethyl-2-(1*H*-pyrazole-4-yl)-3*H*-indole (4a). 70% Yield; mp 182-186 °C; FT-IR (KBr) ν_{max}: 3156, 1567, 1536, 1450, 1375, 1329, 1159, 956, 801 cm^{-1}; ^{1}H-NMR (300MHz,$CDCl_3$), δ(ppm): δ 1.68 (s, 1H, 2×CH_3), 3.76 (bs, 1H, NH), 7.08 (d, *J* = 8.4 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 1H), 8.36 (s, 2H, Pyrazole); ^{13}C-NMR (75 MHz, DMSO) δ (ppm): δ 20.89, 21.35, 53.42, 56.65, 123.59, 127.21, 127.46, 129.69, 135.49, 142.57, 150.90, 180.84; Mass spectrum (EI, 70 eV): *m/z:* 283(M^++4), 281(M^++2), 279 (M^+,100), 264, 237, 115; HRMS (EI) calcd. for $C_{13}H_{11}Cl_2N_3$ 279.0330, found 279.0320.

General procedure for the synthesis of (4b-4f). A mixture of the malondialdehyde (0.5 mmol) and arylhydrazine (0.55 mmol) in absolute ethanol (10 mL) was heated with stirring at reflux for 5-10 h. After cooling and concentrating the solution, the resulting crystals were collected by filtration and recrystallized from EtOH to give the corresponding pyrazoles.

4,7-Dichloro-3,3-dimethyl-2-(1-phenyl-1*H*-pyrazole-4-yl)-3*H*-indole (4b). 83% Yield; mp 182-186 °C; FT-IR (KBr) ν_{max}: 3110, 1871, 1555, 1503, 1451, 954, 754, 689cm^{-1}; ^{1}H-NMR (300MHz,$CDCl_3$), δ(ppm): δ 1.71 (s, 6H, 2×CH_3), 7.07 (d, *J* = 8.7 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 1H), 7.35 (m,1H, Ar), 7.49 (t, *J* = 7.8 Hz, 2H, Ar), 7.78 (d,*J* = 7.8 Hz, 2H, Ar), 8.33 (s, 1H,Pyrazole), 8.69 (s, 1H, Pyrazole); ^{13}C-NMR (75 MHz, DMSO) δ (ppm): 21.20, 56.74, 117.28, 119.53, 123.93, 126.93, 127.37, 127.52, 128.02, 129.55, 129.64, 139.34, 140.80, 142.10, 152.10, 180.21; Mass spectrum (EI, 70 eV): *m/z:* 359(M^++4), 357(M^++2), 355 (M^+), 256, 240(100),212, 177, 149, 115; HRMS (EI) calcd. for $C_{19}H_{15}Cl_2N_3$ 355.0643, found 355.0646.

4,7-Dichloro-2-(1-(3-chlorophenyl)-1*H*-pyrazole-4-yl)-3,3-dimethyl-3*H*-indole (4c). 84% yield; mp 110-112 °C; FT-IR (KBr) ν_{max}: 3143, 2979, 1555, 1517, 1448, 1255, 955, 826, 794 cm^{-1}; ^{1}H-NMR (300MHz,$CDCl_3$), δ(ppm): δ 1.74 (s, 6H, 2×CH_3), 7.12 (d, *J* = 8.7 Hz, 1H, Ar), 7.32 (d, *J*= 8.7 Hz, 1H, Ar), 7.53(d, *J*=8.7 Hz, 1H, Ar), 7.45 (t, *J*=7.8 Hz, 1H, Ar), 7.70 (d,1H, *J* = 7.8 Hz, Ar), 7.87 (s, 1H, Ar), 8.35 (s, 1H,Pyrazole), 8.82 (s, 1H,Pyrazole); ^{13}C-NMR (75 MHz, DMSO) δ (ppm): 21.21, 56.62, 117.31, 119.91, 127.24, 127.43, 127.58, 128.46, 129.70, 130.69, 135.25, 140.18, 141.25, 179.94; Mass spectrum (EI,70 eV):*m/z:* 395(M^++6), 393(M^++4), 391(M^++2), 389 (M^+), 374, 376, 149,111(100),75, 57; HRMS (EI) calcd. for $C_{19}H_{14}Cl_3N_3$ 389.0253, found 389.0253.

4,7-Dichloro-2-(1-(2-chlorophenyl)-1*H*-pyrazole-4-yl)-3,3-dimethyl-3*H*-indole (4d). 80% yield; mp 110-113 °C; FT-IR (KBr) ν_{max}: 3431, 2975, 2932, 1594, 1555, 1488, 1452, 956, 771 cm^{-1} ; ^{1}H-NMR (300MHz,$CDCl_3$), δ(ppm): δ 1.79 (s, 6H, 2×CH_3), 7.09 (d, *J* = 8.4 Hz, 1H, Ar), 7.29 (d, *J* = 8.4 Hz, 1H, Ar), 7.42-7.56(m,2H,Ar), 7.57(d, J=6.3 Hz, 1H,Ar), 7.64(d, J=6.3 Hz,1H, Ar), 8.42 (s, 1H, Pyrazole), 8.63 (s, 1H, Pyrazole); ^{13}C-NMR spectrum(75 MHz, $CDCl_3$), δ, ppm: δ 21.26, 56.74, 116.31, 116.41, 124,03, 127.oo, 127.36, 127.70, 127.88, 128.44, 129.60, 129.87, 130.82, 132.63, 137.40, 141.04, 142.95, 151.88, 180.09;395(M+6), Mass spectrum (EI, 70 eV): *m/z:* 393(M^++4), 391(M^++2), 389 (M^+),374, 376,149,111,75,57,43(100); HRMS (EI) calcd. for $C_{19}H_{14}Cl_3N_3$ 389.0253, found 389.0249.

4,7-Dichloro-2-(1-(4-chlorophenyl)-1*H*-pyrazole-4-yl)-3,3-dimethyl-3*H*-indole (4e). 81% Yield; mp 200-201°C; FT-IR (KBr) ν_{max}: 3110, 1554, 1498, 1449, 954, 828, 800 cm^{-1}; ^{1}H-NMR (300MHz,$CDCl_3$), δ(ppm): δ 1.71 (s, 6H, 2×CH_3), 7.08 (d, *J* = 8.4 Hz, 1H, Ar), 7.29 (d, *J* = 8.7 Hz, 1H, Ar), 7.47 (d, *J* = 8.4 Hz, 2H, Ar), 7.73 (d, *J* = 8.4 Hz, 2H, Ar), 8.32 (s, 1H, Pyrazole), 8.65 (s, 1H,Pyrazole); ^{13}C-NMR (75 MHz, DMSO) δ (ppm): 21.13, 56.74, 117.67, 120.66, 124.06, 127.03, 127.38, 127.88, 129.58, 129.74, 133.10, 137.90, 140.98, 143.01, 152.07, 179.95;Mass spectrum (EI, 70 eV): *m/z:* 395(M+6), 393(M+4), 391(M+2), 389 (M^+),374,376,149,111(100), 75, 57,43; HRMS (EI) calcd. for $C_{19}H_{14}Cl_3N_3$ 389.0253, found 389.0253.

4,7-Dichloro-2-(1-(4-metoxyphenyl)-1*H*-pyrazole-4-yl)-3,3-dimethyl-3*H*-indole (4f). 74% Yield; mp 171-176 °C; FT-IR (KBr) ν_{max}: 2977, 1563, 1556, 1488, 1452, 957, 771 cm^{-1}; ^{1}H-NMR (300MHz,$CDCl_3$), δ(ppm): δ 1,71 (s, 6H, 2×CH_3), 3.86 (s, 3H,CH_3), 7.00 (d, *J* = 8.7 Hz, 2H, Ar); 7.07 (d, *J* = 8.4, 1H, Ar), 7.27 (d, *J* = 8.4 Hz, 1H, Ar), 7.68 (d, *J* = 8.7 Hz, 2H, Ar), 8.29 (s,1H,Pyrazole), 8.61 (s, 1H,Pyrazole); ^{13}C-NMR (75 MHz, DMSO) δ (ppm): 21.26, 55.60, 56.71, 114.68, 116.90, 121.21, 123.87, 126.85, 127.36, 128.14, 129.54, 133.03, 140.48, 142.99, 158.10, 180.36;Mass spectrum (EI, 70 eV): *m/z:* 389(M^++4), 387(M^++2), 385 (M^+),149,115,69,57,55,43(100),41; HRMS (EI) calcd. for $C_{20}H_{17}Cl_2N_3O$ 385.0749, found 385.0754.

General procedure for synthesis of (5). To Solution of 2-cyano acetamide (0.105g, 1.25 mmol) in hot ethanol (95%, 10 mL), malondialdehyde (0.15 g, 0.5 mmol) and 1-methyl piperidine (0.014 mL) were added with shaking. The reaction mixture was refluxed for three days. After this time, the mixture was allowed to cool and filtered off. The crystals of the product were washed with 95% ethanol.

(*E*)-5-(4,7-Dichloro-3,3-dimethylindolin-2-ylidene)-2-oxo-2,5-dihydropyridine-3-carbonitrile (5).71% Yield; mp 320 °C; FT-IR (KBr) ν_{max}: 3435, 3092, 2928, 2889, 1663, 1518, 1453, 1235 cm^{-1}; ^{1}H-NMR (300MHz,$CDCl_3$), δ(ppm): 1.6 (s, 6H, 2×CH_3), 7.25 (d, *J* = 7.2 Hz, 1H, Ar), 7.43 (d, *J* = 7.2 Hz, 1H, Ar), 8.51 (s, 1H, Pyridine), 8.76 (s, 1H, Pyridine), 13.02 (s, 1H,NH); ^{13}C-NMR (75 MHz,

DMSO) δ (ppm): 20.36, 56.57, 104.88, 110.74, 115.10, 123.81, 126.98, 128.10, 130.21, 143.57, 144.02, 147.72, 150.90, 159.88, 180.67; HRMS (EI) calcd. for $C_{16}H_{11}Cl_2N_3O$ 331.0279, found 331.0276.

General procedure for the synthesis of (6a) and (6b)

Method A: To a solution of urea (23mg, 0.38 mmol) or thiourea (30 mg, 0.39 mmol) and malondialdehyde (100 mg, 0.35 mmol) in ethanol (10 mL), 1-methyl piperidine (0.014 mL) was added and reaction mixture refluxed. After completion of the reaction, the reaction mixture was cooled and the precipitate was filtered, washed with ethanol and dried in air.

Method B: A solution of malondialdehyde (100 mg, 0.35 mmol), urea (34 mg, 0.56 mmol) or thiourea (43 mg, 0.56 mmol) and HCl (37%, 0.035 mL) in ethanol (10 mL) was refluxed for overnight. To the cooled solution, ether was added dropwise until no more precipitate was formed. The resulted precipitate was filtered and dried in air.

5-(4,7-Dichloro-3,3-dimethyl-3*H*-indole-2-yl)pyrimidine-2-(1*H*)-one (6a).76% Yield; mp >300°C; FT-IR (KBr) ν_{max}:3429, 2980, 2929, 2866, 1728, 1624, 1497, 1446, 1390, 1261, 1240,1111, 994,790cm^{-1}; Mass spectrum (EI, 70 eV): *m/z:* 311(M^++4), 309(M^++2), 307(M^+,100), 265, 237, 212, 115; HRMS (EI) calcd. for $C_{14}H_{11}Cl_2N_3O$ 307.0279, found 307.0278.

5-(4,7-Dichloro-3,3-dimethyl-3*H*-indole-2-yl)pyrimidine-2-(1*H*)-thione (6b). 75% Yield; mp >300°C; FT-IR (KBr) ν_{max}: 3429, 3065, 2637, 2552, 1628, 1527, 1454, 1325, 1237, 1213, 985, 923,794cm^{-1}; HRMS (EI) calcd. for $C_{14}H_{11}Cl_2N_3S$ 323.0053, found 323.0053.

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