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RESEARCH ARTICLE

Synthesis and Characterization of Some New 4,5-Dihydropyrazolyl Thiazoles

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Abstract: The prepared starting material 2,4-bis (4-chlorobenzyloxy)acetophenone (**1**) has been reacted with different substituted benzaldehydes to give a series of new chalcones (**2a-j**). The prepared new chalcones were subjected to react with thiosemicarbazide according to the Michael addition reaction to afford new thiocarbamoylpyrazoline derivatives (**3a-j**). A thiocarbamoyl group in compounds (**3a-j**) was cyclized with *p*-bromophenacyl bromide to give a series of new 4,5-dihydropyrazolyl thiazoles (**4a-j**). The structures of the synthesized compounds were characterized by spectral methods: FT-IR, ^{1}H-NMR, ^{13}C-NMR and DEPT-135 spectra.

Keywords: Chalcones, Benzylation, Pyrazoline, Thiazole, Thiosemicarbazide

Introduction

Thiosemicarbazide is one of the most important precursor for the formation of different acyclic[1] and cyclic organic compounds, especially heterocyclic compounds containing nitrogen and sulfur heteroatoms[2]. Chalcones also can be used as a very useful precursor besides thiosemicarbazide and other reagents for the formation of different important heterocyclic compounds such as pyrazolines[3], thiadiazoles[4] and thiazepines[5]. Chalcones constitute a class of naturally occurring and synthetic compounds belonging to the flavonoid family[6]. It has been reported that chalcones, pyrazoline and thiazoles possess a wide spectrum of biological activity which include anti-malarial[7], anti-inflammatory[8], analgesic[9], antioxidant[10] and other antimicrobial activities[11]. The present investigation describes the synthesis and spectroscopic studies of some new compounds containing two different kinds of heterocyclic moieties, pyrazoline and thiazoles.

Experimental

Melting points were determined using a Gallen Kamp electrothermal melting point apparatus. IR spectra were recorded on FTIR-Thermo-Mattson-300 using KBr disc. ^{1}H NMR, DEPT-135 and ^{13}C NMR spectra were recorded on a Bruker(300MHz) with TMS as internal reference.

*Preparation of 2,4-bis (4-chlorobenzyloxy) acetophenone (**1**)*

The starting material (**1**) was prepared according to the procedure[12]. Washed several times with water and cold ethanol, dried and recrystallized from ethanol to obtain white crystals of 2,4-bis(4-chlorobenzyloxy)acetophenone (**1**): m.p. (106-107 ^{o}C), yield(6 g, 61%).

FT-IR (cm^{-1}):3093(C-H aromatic), 2933, 2880(C-H aliphatic), 1662(C=O), 1595, 1567(C=C), 1265(C-O). ^{1}H NMR(ppm): 2.45(s, 3H, CH_3), 5.19(s, 2H, CH_2-Bz`), 5.23(s, 2H, CH_2-Bz), 6.68(d, 1H, Ar-H_5),6.8(s, 1H, H_3); 7.46-7.54(m, 8H, 2Ar), 7.69(d, 1H, H_6).

^{13}C NMR(ppm): 32.23(CH_3), 69.21(Bz), 69.79(Bz`), 100.01($C_3$), 107.38($C_5$), 121.45($C_1$), 128.9($C_{2`}$), 130.15($C_{3`}$), 132.3($C_6$), 133.8($C_{4`}$), 135.88($C_{1`}$), 160.00($C_2$), 163.38($C_4$), 196.67(C=O).

Synthesis of 1-(2,4-bis(4-chlorobenzyloxy)phenyl)-3-(substitutedphenyl)prop-2-en-1-one(2a-j)[13]

The prepared 2,4-bis(4-chlorobenzyloxy)acetophenone (**1**) (0.02 mol) was dissolved in ethanol (5 mL) and added to the solution of (0.02 mol) of substituted benzaldehydes in ethanol (5 mL) and 2 mL of (4% ethanolic NaOH). The mixture was stirred at room temperature for (5-10 min). The mixture was solidified and the pale yellow chalcones were separated by suction filtration, washed with ethanol and water to neutralize, dried and purified by recrystallization from a suitable solvent (toluene or ethanol), the results are summarized in Table 1.

Table 1. Some physical properties of the synthesized chalcones (**2a-j**), pyrazolines (**3a-j**) and thiazoles (**4a-j**)

Products		Chalcones (**2a-j**)			Pyrazolines (**3a-j**)			Thiazoles (**4a-j**)		
		M.P	%	Time min.	M.P	%	Time h.	M.P	%	Time h.
a	3-Bz	128-130	95	5	168-170	76	5	184-186	80	2.5
b	4-CH_3	123-125	97	5	164-166	65	6	179-181	94	2
c	4-F	110-112	99	5	174-176	85	5	170-172	83	2
d	4-Bz	178-180	94	5	169-171	60	6	177-179	88	2.5
e	2-F	93-95	77	4	167-169	65	5	188-190	78	2
f	4-N(CH_3)$_2$	133-134	82	6	162-164	78	6	193-195	73	2
g	4-Br	160-162	97	1	155-157	96	6	158-160	50	2
h	4-OCH_3	112-114	80	10	172-174	83	6	202-204	87	1.45
i	2-Cl	130-132	99	1	207-209	70	6	241-243	79	2
j	H	107-110	95	5	245-247	89	6	199-201	74	2

2a: FT-IR(cm^{-1}): 1647(C=O), 1616,1602(C=C).^{1}H-NMR(ppm):5.1(s, 2H, CH_2-Bz), 5.06(s, 2H, CH_2-Bz`),4.9(s, 2H, $CH_2$-RBz),6.61-7.6(m, 21H, 5Ar-rings and α,β hydrogens).$^{13}$C-NMR(ppm): 69.2, 69.4, 69.5(3Bz), 100.61($C_3$), 106.6($C_5$), 114.53($C_{11}$), 114.58($C_1$), 116.4($C_{13}$), 121.11($C_{8,15}$), 127.8($C_{14}$), 128.81($C_{2`}$), 129.28 ($C_{3`}$),133.8($C_6$), 134.64($C_{4`}$), 135.26($C_{1`}$), 136.74($C_{10}$), 141.68($C_9$), 158.3($C_{12}$), 159.2($C_2$), 163.38($C_4$), 189.85(C=O).^{13}C-DEPT-135(ppm): -69.2, 69.4, 69.5(3Bz), 100.55(C_3), 106.6(C_5), 114.57(C_{11}), 116.4(C_{13}), 121.11($C_{8,15}$), 127.79(C_{14}), 128.82(C_2), 129.28(C_3), 133.8(C_6), 141.68(C_9).

2b: FT-IR(cm^{-1}): 1647(C=O), 1600,1583(C=C).^{1}H-NMR(ppm): 2.37(s, 3H, CH_3), 5.07(s, 2H, CH_2-Bz) 5.08(s, 2H, CH_2-Bz`), 6.61-7.85(m, 17H, 4Ar-rings and α,βhydrogens). ^{13}C-NMR(ppm): 21.5(CH_3), 69.5(2Bz), 100.55(C_3), 106.55(C_5), 122.72(C_1), 126.41 ($C_{11,15,8}$),

128.2($C_{12,14}$), 128.8($C_{2'}$), 129.11($C_{3'}$), 133.3(C_6), 134.11($C_{4'}$), 136.7 (C_{10}), 140.13(C_{13}), 140.4($C_{1'}$), 142.22(C_9), 159.35(C_2), 162.99(C_4), 189.85(C=O). ^{13}C-DEPT-135(ppm): 21.5(CH_3), -69.5(2Bz), 100.55(C_3), 106.55(C_5), 126.41 ($C_{11,15,8}$), 128.2($C_{12,14}$), 128.8($C_{2'}$), 129.11($C_{3'}$), 133.3(C_6), 142.22(C_9).

*Synthesis of 2- Pyrazolines3-(2,4-bis(4-chlorobenzyloxy)phenyl)-5-(substitutedphenyl) -4,5-dihydropyrazole-1-carbothioamide (**3a-j**)*[14]

Thiosemicarbazide (2.27 g, 0.025 mol) was added to methanolic suspension (20 mL) of the prepared chalcones (0.02 mol) and sodium hydroxide (0.8 g, 0.02 mol). The mixture was heated under reflux with stirring for an appropriate time to complete the reaction and the color was changed from yellow to white indicating the disappearance of the pale yellow chalcones. The pyrazolines (**3a-j**) were removed by suction filteration, washed with water to neutralize and then with ethanol. The products were dried and recrystallized from ethanol and the results are summarized in Table 1.

3a: FT-IR(cm^{-1}): 3495,3369(NH_2), 1598,1579(C=C,C=N), 1350(C=S).^{1}H-NMR(ppm): 3.75(dd, 1H, H_{8a}), 4.7(dd, 1H, H_{8b}), 5.1(s, 2H, CH_2-Bz), 5.06(s, 2H, CH_2-Bz`), 4.9(s, 2H, CH_2-RBz), 5.9(dd, 1H, H_9), 6.5-7.8(m, 21H, 5Ar-rings and NH_2).^{13}C-NMR(ppm): 44.5(C_8), 61.8(C_9), 69.2, 69.4, 69.5(3Bz), 99.56(C_3), 105.66(C_5), 110.93($C_{1,11}$), 112.3(C_{13}), 117.03(C_{15}), 127.5($C_{2'}$), 127.71($C_{3'}$), 128.74(C_{14}), 129.54(C_6), 133.42($C_{4'}$), 134.24($C_{1'}$), 154.4(C_{10}), 155.05(C_7), 157.5(C_{12}), 157.68(C_2), 160.68(C_4), 183.93(C=S). ^{13}C-DEPT-135(ppm): -44.5(C_8), 61.8(C_9), - 69.2, 69.4, 69.5(3Bz), 99.56(C_3), 105.66(C_5), 110.93($C_{1,11}$), 112.3(C_{13}), 117.03(C_{15}), 127.5($C_{2'}$), 127.71($C_{3'}$), 128.74(C_{14}), 129.54(C_6).

3b: FT-IR(cm^{-1}): 3491,3363(NH_2), 1602,1570(C=C,C=N), 1355(C=S).^{1}H-NMR(ppm): 2.3(s, 3H, CH_3), 3.3(dd, 1H, H_{8a}), 3.9(dd, 1H, H_{8b}), 5.12(s, 2H, CH_2-Bz,Bz`), 5.8(dd, 1H, H_9), 6.5-7.8(m, 17H, 4Ar-rings and NH_2).^{13}C NMR(ppm): 21.11(CH_3), 46.07(C_8), 62.95(C_9), 69.5(2Bz), 100.85(C_3), 106.90(C_5), 113.71(C_1), 125.39($C_{11,15}$), 128.74($C_{2'}$), 128.9($C_{12,14}$), 129.43($C_{3'}$),130.75(C_6), 134.55($C_{4'}$), 136.9(C_{13}), 137.10(C_{10}), 138.9($C_{1'}$), 155.6 (C_7), 158.78(C_2), 161.86(C_4), 173.15(C=S).^{13}C-DEPT-135(ppm): 21.11(CH_3), -46.07(C_8), 62.95(C_9), -69.5(2Bz), 100.85(C_3), 106.90(C_5), 125.39($C_{11,15}$), 128.74($C_{2'}$), 128.9($C_{12,14}$), 129.43($C_{3'}$), 130.75(C_6).

*Synthesis of 4,5-dihydropyrazolyl thiazoles: Synthesis of: 2-(3-(2,4-bis(4-chlorobenzyloxy)phenyl)-5-(Substitutedphenyl)-4,5-dihydropyrazol-1-yl)-4-(4-bromophenyl)thiazoles (**4a-j**)*[15]

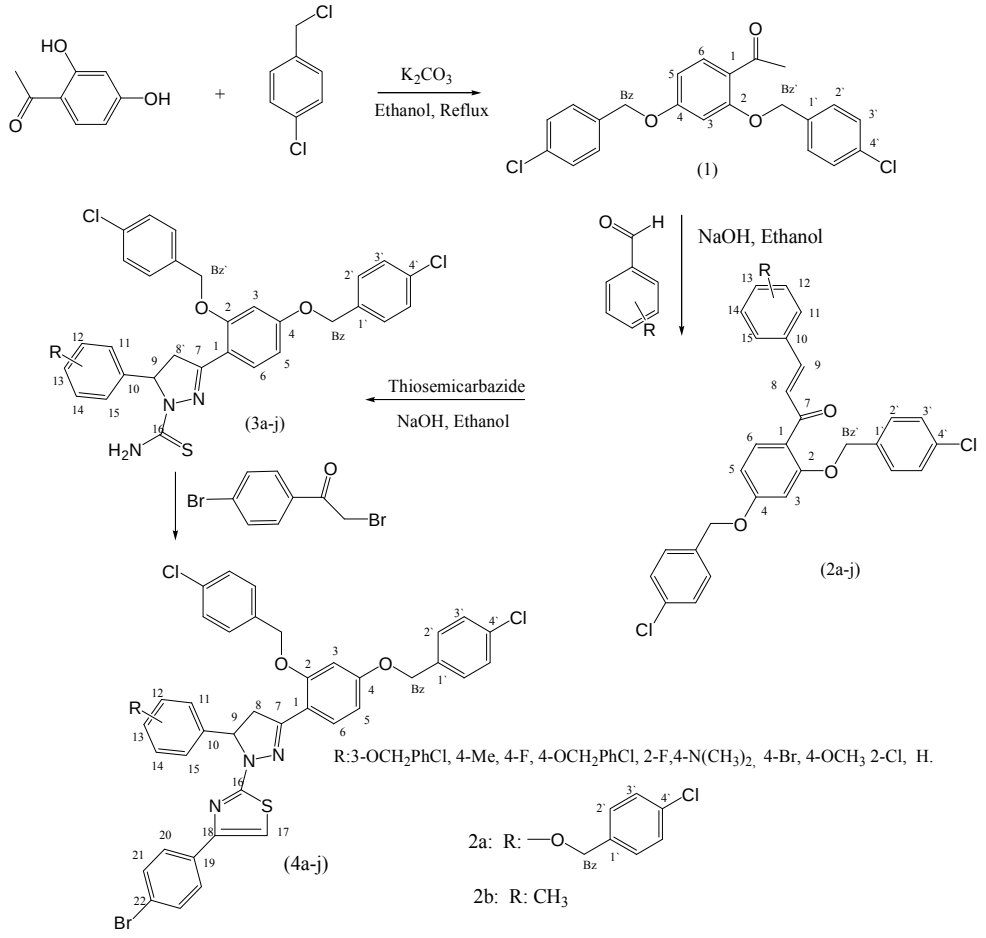
To a solution of the respective 2-pyrazoline-1-carbothioamides (**3a-j**) (0.002 mol) in absolute ethanol (6 mL), 4-bromophenacyl bromide (0.56 g, 0.002 mol) was added and the mixture was heated under reflux for an appropriate time to complete the reaction. On cooling, the separated solid was filtered, dried and crystallized from the toluene-ethanol, the results are summarized in Table 1.

4a: FT-IR(cm^{-1}): 1604,1585(C=C,C=N).^{1}H-NMR(ppm): 3.47(dd, 1H, H_{8a}), 3.88(dd, 1H, H_{8b}), 5.1(s, 2H, CH_2-Bz), 5.06(s, 2H, CH_2-Bz`), 4.9(s, 2H, CH_2-RBz), 5.52(dd, 1H, H_9), 6.5-7.8(m, 24H, 6Ar-rings).^{13}C-NMR(ppm):46.7(C_8), 64.15(C_9), 69.2, 69.4, 69.5(3Bz), 100.86(C_3), 103.47(C_{17}), 106.83(C_5), 113.11($C_{1,11}$), 113.88 (C_{13}), 119.42(C_{15}), 121.42(C_{22}), 127.5($C_{2'}$), 128.71($C_{3'}$), 128.4(C_{14}), 129.6(C_6), 130.6(C_{20}), 133.09(C_{21}), 134.5($C_{4'}$), 135.79(C_{19}),135.39($C_{1'}$), 150.37(C_{10}), 151.36(C_{18}), 152.9(C_7), 158.02(C_{12}), 158.75(C_2), 161.04(C_4), 164.02(C_{16}). ^{13}C-DEPT-135(ppm): -46.7(C_8), 64.15(C_9), -69.2, 69.4, 69.5(3Bz), 100.86(C_3), 103.47 (C_{17}), 106.83(C_5), 113.11(C_{11}), 113.88(C_{13}), 119.42(C_{15}), 121.42(C_{22}), 127.5($C_{2'}$), 128.71($C_{3'}$), 128.4(C_{14}), 129.6(C_6), 130.6(C_{20}), 133.09(C_{21}).

4b: FT-IR(cm^{-1}): 1601, 1580(C=C,C=N).^{1}H-NMR(ppm): 2.7(s, 3H, CH_3), 3.15(dd, 1H, H_{8a}), 3.87(dd, 1H, H_{8b}), 5.1(s, 2H, CH_2-Bz,Bz`); 5.4(dd, 1H, $H_9$), 6.7-7.8(m, 20H, 5Ar-rings).$^{13}$C-NMR(ppm): 19.5($CH_3$), 43.37($C_8$), 63.94($C_9$), 69.32(2Bz), 113.11($C_3$), 113.5($C_{17}$), 113.9($C_5$), 115.9($C_1$), 123.10($C_{22}$), 126.05($C_{11,15}$), 127.5($C_{2`}$), 128.31($C_{12,14}$), 128.81($C_{20}$), 128.95($C_{3`}$), 129.02($C_6$), 129.9($C_{21}$), 133.5($C_{4`}$), 135.2($C_{19}$),137.2($C_{1`}$), 140.02($C_{13}$), 142.5($C_{10}$), 143.22($C_{18}$), 152.5($C_7$), 160.2($C_2$), 161.2($C_4$), 163.25($C_{16}$).$^{13}$C-DEPT-135(ppm): 19.5($CH_3$), -43.37($C_8$), 63.94($C_9$), -69.32(2Bz), 113.11($C_3$), 113.5($C_{17}$), 113.9($C_5$), 126.05($C_{11,15}$), 127.5($C_{2`}$), 128.31($C_{12,14}$), 128.81($C_{20}$), 128.95($C_{3`}$), 129.02($C_6$), 129.9($C_{21}$).

Results and Discussion

The synthetic process of the newly target molecules 4, 5-dihydropyrazolyl thiazoles is outlined in Scheme 1. The formation of the synthesized chalcones (**2a-j**), pyrazolines (**3a-j**) and thiazoles (**4a-j**) were confirmed on the basis of their spectral methods. In the IR spectra of the synthesized chalcones the shifting of the absorption band of carbonyl group to lower wave numberaround 1647 cm^{-1} is a strong evidence for the formation of α,β-unsaturated carbonyl group.



Scheme 1

The ^{1}H NMR spectra of chalcones, showed the α- and β- protons in aromatic region δ 6.6-8.0 which hardly be distinguished from those of the aromatic ring protons. The distinct pick of ^{13}C NMR spectra of α,β-unsaturated carbonyl group (chalcone) is the β-carbon atom resonance around δ (140) downfield to the α-carbon atom around (120 ppm)[16]. Further support is come from the DEPT-135 spectra which was used to distinguish between non-protonated carbons, CH_3, CH and CH_2 protons, the DEPT-135 spectra showed a downward signal around δ -69 attributed to benzylic CH_2 carbon and the disappearance of non-protonated carbons.

The synthesized pyrazolines (**3a-j**) were confirmed according their spectral data's. In the IR spectra of pyrazolines, the appearance of a doublet signal at 3495, 3369 (cm^{-1}) attributed to NH_2 stretching vibration, and a strong band at 1350 for C=S and the disappearance of carbonyl group band at 1647 cm^{-1} for enone system is a good evidence for the formation of thiocarbamoyl group and the occurrence of cyclization reaction to give 2-pyrazolines. In the ^{1}H NMR spectra of the pyrazolines the protons attached to the C_8 and C_9 carbon atoms in the 2-pyrazoline ring gave an (ABX) spin system[17] which appeared three doublet to doublets(dd) signals around δ 3, 4, 5.5 ppm for two geminal and one vicinal protons unequivocally prove a 2-pyrazoline structure. Also the appearance of two signals around 40 and 60ppm in the ^{13}C NMR spectrum, and the appearance of two downward signals at -70 and -40 ppm attributed to CH_2 groups for benzyloxy group and pyrazoline ring respectively. In the DEPT-135 corroborate the 2-pyrazoline structure[18]. The structure of the target molecules 4, 5-dihydropyrazolyl thiazoles also confirmed. In the IR spectra the disappearance of NH_2 and C=S bands considered as a good evidence for the formation of thiazole rings. The ^{1}H NMR Figure 1 showed the (ABX) spin system same as compounds (**3a-j**). The ^{13}C NMR Figure 2 showed a signal at 103.47 for C_{17} and a distinct signal for each type of carbons in the molecule. The DEPT-135 Figure 3 perfectly coincided with expected structure.

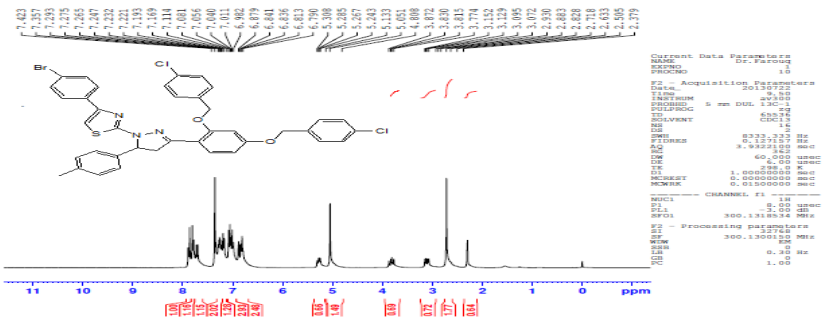


Figure 1. ^{1}H NMR spectrum of compound (**4b**)

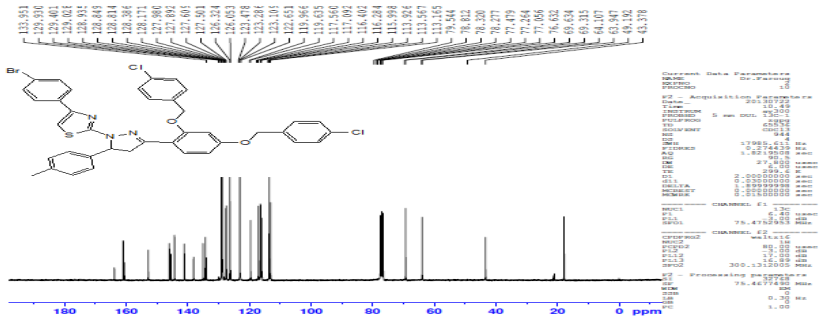


Figure 2. ^{13}C NMR spectrum of compound (**4b**)

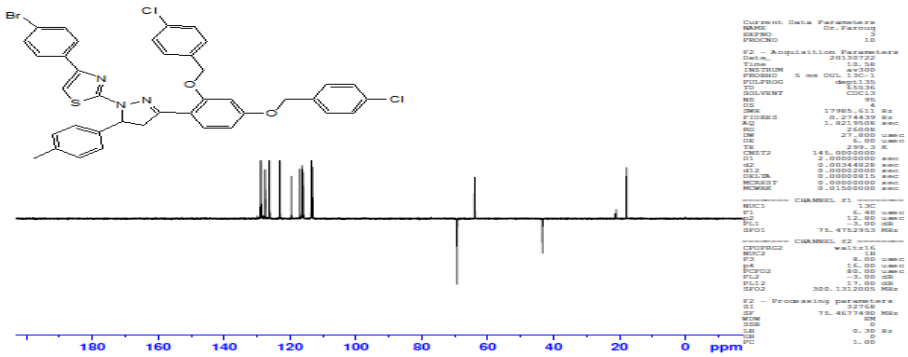


Figure 3. DEPT-135 NMR spectrum of compound (**4b**)

Conclusion

The preparation of thiocarbamoylpyrazoline derivatives from substituted chalcones and thiosemicarbazide were achieved in high yields on the basis of Michael addition reaction. A thiocarbamoyl moiety in the synthesized compounds can be used as a precursor group for further preparation such as cyclization with *p*-bromophenacyl bromide to give new 4, 5-dihydropyrazolyl thiazoles.

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