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Synthesis of 4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid derivatives and their antimicrobial activities

Abstract: The reaction of 1*H*-pyrazole-3-carboxylic acid chloride (**1**) with various hydrazine derivatives **2a–c** yielded the corresponding *N,N*-disubstituted 4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carbohydrazides **3a–c**. These products underwent Friedel-Crafts acylations with arenes to afford compounds **4a–c**. Treatment of **1** with aromatic diamines produced 1*H*-pyrazole-3-carboxamides **5a–c**, which were allowed to react with phenylhydrazine to give hydrazone derivatives **6a–c**. The structures of all new compounds were established by IR, ^{1}H and ^{13}C NMR data and elemental analyses. The new compounds were evaluated for antimicrobial activities against Gram (-), Gram (+) bacteria and two yeasts using the disc diffusion method. *N,N*-Dimethylhydrazide derivative **3a** is the most active compound of the series.

Keywords: Friedel-Crafts reaction; *N,N*-dialkylhydrazine; pyrazole-3-carboxylic acid.

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Introduction

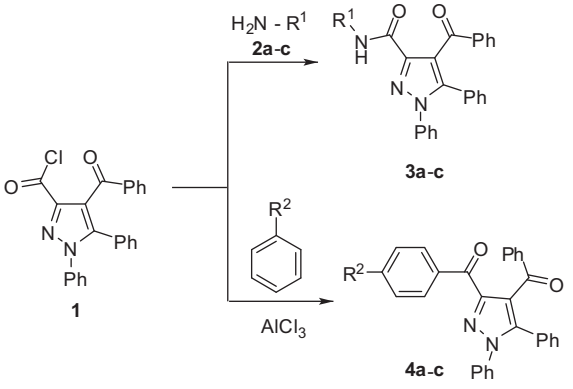
Pyrazole derivatives are an important class of heterocyclic compounds [1–8] that have considerable pharmacological activities including antibacterial, antifungal and hypoglycemic activities [9–14]. A number of hydrazide/hydrazone derivatives have also been claimed to possess interesting bioactivity, such as anticonvulsant, anti-inflammatory, antimalarial, analgesic, antiplatelets, antituberculosis and anticancer properties. Aroylhydrazide/hydrazones that are derivatives of heterocyclic compounds such as pyridine have attracted particular attention [15–19] in drug development [20]. Functionalization of 1*H*-pyrazole-3-carboxylic acid chloride (**1**) by the reaction with various diamines has been reported by Yıldırım and co-workers [3–5], but no reaction of 1*H*-pyrazole-3-carboxamides with nucleophiles has been described. Herein, we report the synthesis and characterization of pyrazole derivatives **3a–c**, **4a–c** and **6a–c**.

Results and discussion

Chemistry

The 1*H*-pyrazole-3-carboxylic acid chloride **1** was prepared using the literature procedure [1, 2]. The reaction of compound **1** with substituted hydrazines **2a–c** led to the formation of the corresponding products **3a–c** in good yields (63–87%) (Scheme 1). The progress of the reaction was monitored by thin layer chromatography (TLC) until complete consumption of the starting materials was observed. The structures of products **3** were confirmed by elemental analysis, IR and ^{1}H and ^{13}C NMR spectroscopic techniques.

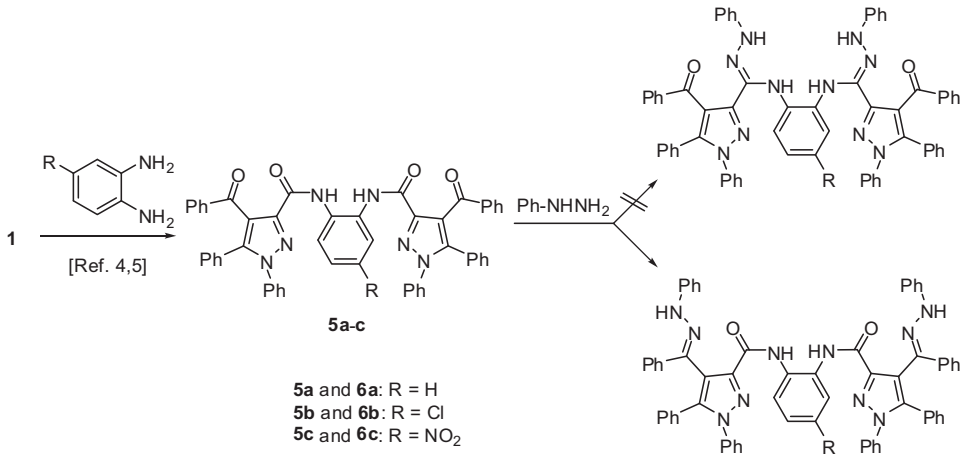
Friedel-Crafts acylation of selected arenes with the 1*H*-pyrazole-3-carboxylic acid chloride **1** in the presence



2a and **3a**: $R^1 = NMe_2$
2b and **3b**: $R^1 = NPh_2$
2c and **3c**: R^1 = NHPh-4-Me

4a: R^2 = Me
4b: R^2 = Cl
4c: R^2 = Br

Scheme 1



Scheme 2

of anhydrous aluminum chloride to afford **4a–c** is also presented in Scheme 1. Recently, an analogous reaction of **1** with benzene was reported by Şener and co-workers [9]. The formation of products **4a–c** is strongly supported by the results of elemental analyses and spectroscopic measurements. The reactions of compound **1** with some aromatic diamines to give the corresponding dicarboxamide derivatives **5a–c** have recently been reported (Scheme 2) [4, 5]. Compounds **5a–c** were allowed to react with phenylhydrazine to give new hydrazone derivatives **6a–c**.

In vitro antimicrobial activity

All new compounds were evaluated against eight Gram (-), five Gram (+) and two yeasts. The results with the active compounds **3a**, **3c**, **4b** and **6b** are shown in Table 1. The antibacterial antibiotics ampicillin (AMP) and chloramphenicol (C) were used as controls. Compounds **3b, 4a**, **4c, 6a** and **6c** were practically inactive against the tested microorganisms. All compounds had no inhibitory effects on yeasts tested in the present study. Compound **5c**

Table 1 Screening for antimicrobial activity of selected compounds **3a**, **3c**, **4b** and **6b**[a].

Microorganisms	3a	3c	4b	6b	AMP[c]	C[c]
Gram (-)						
Aeromonas hydrophila ATCC 7965	8.75±0.4[b]	–	–	–	27.0±0.0	18.0±0.0
Escherichia coli ATCC 25922	8.5±0.7	–	–	–	6.5±0.0	17.0±0.0
Klebsiella pneumoniae FMC 5	10.0±0.0	–	–	–	14.0±0.0	13.0±0.0
Morganella morganii	9.5±0.7	–	–	–	–	11.0±0.0
Salmonella typhimurium NRRLE 4463	8.25±0.4	–	–	–	24.0±0.0	22.0±0.0
Proteus mirabilis BC 3624	–	–	–	–	26.0±0.0	19.0±0.0
Pseudomonas aeruginosa ATCC 27853	6.5±0.0	–	–	–	25.0±0.0	15.0±0.0
Yersinia enterocolitica ATCC 1501	–	–	–	–	8.0±0.0	17.0±0.0
Gram (+)						
Bacillus brevis FMC 3	9.0±0.0	–	7.0±0.0	–	8.0±0.0	20.0±0.0
B. cereus RSKK 863	7.25±0.4	–	–	–	31.0±0.0	21.0±0.0
B. subtilis ATCC 6633	8.5±0.0	–	–	–	24.0±0.0	25.0±0.0
Mycobacterium smegmatis RUT	8.5±0.7	6.75±0.4	–	7.0±0.0	25.0±0.0	17.0±0.0
Staphylococcus aureus ATCC 29213	8.5±0.0	–	–	–	16.0±0.0	15.0±0.0
Yeast						
Candida albicans ATCC 1223	–	–	–	–	–	–
Saccharomyces cerevisiae BC 5461	–	–	–	–	–	–

[a]The inhibition zones (mm) are shown.
[b]Inhibition zones include diameter of disc (6 mm).
[c]Ampicillin (AMP, 10 μg); chloramphenicol (C, 30 μg). –, not detected.

was slightly effective against *Mycobacterium smegmatis* among the tested microorganisms.

The strongest activity was displayed by compound **3a**.

Experimental

Solvents were dried by heating under reflux with appropriate drying agents and distilled before use. Melting points were determined on an Electrothermal 9200 apparatus and are uncorrected. Microanalyses were performed on a Carlo Erba Elemental Analyzer, model 1108. The IR spectra were recorded on a Shimadzu Model 8400 FT IR spectrophometer. The ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were recorded on a Bruker-400 Ultra Shield instrument. All experiments were followed by TLC using a DC Alufolien Kieselgel 60 F_{254} Merck and Camag TLC lamp (254/366 nm).

Antimicrobial assay

Bacterial strains used in the present study were obtained from the Department of Biology, Faculty of Science, Erciyes University, Kayseri, Turkey. The bacterial strains were *Aeromonas hydrophila* ATCC 7965, *Bacillus brevis* FMC 3, *Bacillus cereus* RSKK 863, *Bacillus subtilis* ATCC 6633, *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 27736, *Morganella morganii, Mycobacterium smegmatis* RUT, *Proteus mirabilis* BC 3624, *Pseudomonas aeruginosa* ATCC 27853, *Salmonella typhimurium* NRRLE 4463, *Staphylococcus aureus* ATCC 29213 and *Yersinia enterocolitica* ATCC 1501. The yeasts were *Candida albicans* ATCC 1223 and *Saccharomyces cerevisiae* BC 5461 (Table 1). Antimicrobial activity testing was carried out by disc diffusion methods [21] using 100 µL of suspension containing 10^6–10^7 colony forming units (cfu)/mL of bacteria and yeasts spread on nutrient agar (NA) and sabouraud dextrose agar (SDA). The sterile discs (6 mm) were impregnated with 10 µL of compounds in dimethyl sulfoxide (DMSO; 500 mg/disc) placed in the middle of inoculated agar plates. DMSO was added on the disc to provide negative control. Ampicillin (AMP, 10 µg) and chloramphenicol (C, 30 µg) were used as positive controls. Yeasts *C. albicans* and *S. cerevisiae* were incubated at 25°C for 24–48 h in the inverted position. Other microorganisms were incubated at 37°C for 18–24 h. At the end of the period, antimicrobial activity was evaluated by measuring the zone of inhibition (mm), and experiments were repeated twice.

General procedure for 3a–c

A solution of acid chloride **1** (0.20 g), *N,N*-disubstituted hydrazine **2a–c** (0.04 mL) (molar ratio 1:1) and a catalytic amount of pyridine in xylene was heated under reflux for 2 h. Then the solvent was removed and the remaining oily residue was treated with dry diethyl ether and the mixture was stirred for 1 h. The resultant solid product **3** was crystallized from toluene or cyclohexane and dried over P_2O_5.

4-Benzoyl-3-[(*N′*,*N′*-dimethylhydrazino)carbonyl]-1,5-diphenyl-1*H*-pyrazole (3a) White powder; mp 148–149°C; IR: υ 3209 (N-H), 2959 (aliph. C-H), 1670, 1650 cm^{-1} (C=O); ^{1}H NMR: δ 3.00 (s, 6H, CH_3) 7.12–7.90 (m, 15H, ArH), 9.30 (s, 1H, NH); ^{13}C NMR: δ 46.6, 122.1, 125.4, 127.7, 128.3, 128.5, 128.6, 129.1, 129.4, 129.5, 129.8, 133.2, 137.8, 138.6, 143.4, 144.2, 158.7, 191.3. Anal. Calcd for $C_{25}H_{22}N_4O_2$: C, 73.15; H, 5.40; N, 13.65. Found: C, 72.80; H, 5.67; N, 13.96.

4-Benzoyl-1,5-diphenyl-3-[(*N′*,*N′*-diphenylhydrazino) carbonyl]-1*H*-pyrazole (3b) White powder; mp 207–208°C; IR: υ 3284 (N-H), 1686, 1662 cm^{-1} (C=O); ^{1}H NMR: δ 7.00–7.90 (m, 25H, ArH), 9.18 (s, 1H, NH); ^{13}C NMR: δ 119.7, 120.2, 120.4, 122.4, 123.0, 125.4, 127.8, 128.2, 128.5, 128.6, 128.9, 129.1, 129.1, 129.3, 129.5, 129.9, 133.1, 138.0, 138.8, 144.1, 144.2, 145.9, 159.7, 191.2. Anal. Calcd for $C_{35}H_{26}N_4O_2$: C, 78.63; H, 5.90; N, 10.48. Found: C, 78.54; H, 5.43; N, 10.73.

4-Benzoyl-1,5-diphenyl-3-{*N′*-[(4-methylphenyl)hydrazino] carbonyl}-1*H*-pyrazole (3c) White powder; mp 175–176°C; IR: υ 3269 (N-H), 2920 (aliph. C-H), 1678, 1662 cm^{-1} (C=O); ^{1}H NMR: δ 3.02 (s, 3H, CH_3) 6.70–7.85 (m, 20H, ArH), 8.75 (s, 1H, NH); ^{13}C NMR: δ 40.8, 113.1, 113.4, 119.7, 122.3, 125.4, 127.9, 128.2, 128.5, 128.5, 128.6, 129.0, 129.1, 129.3, 129.5, 129.9, 133.1, 138.0, 138.8, 144.1, 144.3, 149.3, 159.5, 191.4. Anal. Calcd for $C_{30}H_{24}N_4O_2$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.05; H, 5.65; N, 11.30.

General procedure for 4a–c

A mixture of acid chloride **1** (0.40 g) anhydrous $AlCl_3$ (0.70 g) and an aromatic compound (molar ratio 1:5:25) was heated at 100–140°C for 1–3 h in a calcium chloride guard tube fitted round bottom flask of 50 mL. Then, the mixture was poured onto HCl/ice-water for hydrolysis and extracted with diethyl ether. Then, petroleum ether was added and the resulting solid was collected and crystallized from ethanol.

4-Benzoyl-1,5-diphenyl-3-(4-methylbenzoyl)-1*H*-pyrazole (4a) Compound **4a** was prepared from toluene with heating for 1 h at 120°C; yield 61% (0.28 g); white powder; mp 192–193°C; IR: υ 1666, 1639 cm^{-1} (C=O); ^{1}H NMR: δ 2.45 (s, 3H, CH_3), 7.25–8.30 (m, 19H, Ar-H); ^{13}C NMR: δ 21.7, 124.2, 125.4, 128.1, 128.3, 128.4, 128.5, 128.9, 129.0, 129.2, 129.9, 130.7, 132.9, 134.0, 138.1, 139.1, 143.3, 143.9, 150.2, 186.4, 191.5. Anal. Calcd for $C_{30}H_{22}N_2O_2$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.18; H, 5.00; N, 5.99.

4-Benzoyl-1,5-diphenyl-3-(4-chlorobenzoyl)-1*H*-pyrazole (4b) Compound **4b** was prepared from chlorobenzene with heating for 2 h at 100°C; yield 42% (0.20 g); white powder; mp 180–181°C; IR: υ 1666, 1639 cm^{-1} (C=O); ^{1}H NMR: δ 7.20–8.35 (m, 19H, Ar-H); ^{13}C NMR: δ 124.4, 125.4, 127.8, 128.4, 128.5, 129.1, 129.2, 129.3, 129.9, 132.1, 133.1, 134.8, 137.3, 139.0, 139.6, 143.4, 149.6, 185.3, 191.4. Anal. Calcd for $C_{29}H_{19}N_2O_2Cl$: C, 75.24; H, 4.14; N, 6.05. Found: C, 75.28; H, 4.17; N, 5.57.

4-Benzoyl-1,5-diphenyl-3-(4-bromobenzoyl)-1*H*-pyrazole (4c) Compound **4c** was prepared from bromobenzene with heating for 2 h at 140°C; yield 56% (0.28 g); white powder; mp 172–173°C; IR: υ 1660, 1649 cm^{-1} (C=O);^{1}H NMR: δ 7.25–8.30 (m, 19H, Ar-H); ^{13}C NMR: δ 124.4, 125.4, 125.4, 127.8, 127.9, 128.2, 128.4, 128.4, 128.4, 128.5, 128.6, 129.1, 129.1, 129.2, 129.3, 129.4, 129.8, 129.9, 130.6, 131.6, 132.2, 133.0, 133.1, 135.2, 136.5, 137.9, 138.1, 138.9, 143.5, 149.6, 185.5, 191.4. Anal. Calcd for $C_{29}H_{19}N_2O_2Br$: C, 68.65; H, 3.77; N, 5.52. Found: C, 68.27; H, 4.12; N, 5.37.

General procedure for 6a–c

A solution of compound **5a–c** (0.30 g), phenylhydrazine (0.50 mL) (molar ratio 1:13) and a catalytic amount of acetic acid in *n*-butanol (10 mL) was heated under reflux for 15 h. The solvent was removed and the remaining oily residue was treated with dry diethyl ether and the mixture stirred for 1 h. The yellow solid product was crystallized from benzene or xylene.

***N,N′*-Bis{4-[α-(phenylhydrazono)benzyl]-1,5-diphenyl-1*H*-pyrazol-3-yl-carbonyl}-1,2-phenylendiamine (6a)** Yellow powder; mp 198–199°C. IR: υ 3225 (N-H), 1659 cm^{-1} (C=O); ^{1}H NMR: δ 6.72–7.54 (m, 44H, ArH), 9.34 and 9.37 (2s, 2H, NH), 10.11 and 10.13 (2s, 2H, Ph-NH); ^{13}C NMR: δ 113.1, 120.2, 124.8, 125.0, 125.3, 125.9, 126.0, 126.1, 127.6, 128.0, 128.1, 128.3, 128.8, 129.0, 129.1, 129.3, 129.4, 129.7, 129.9, 136.3, 138.4, 143.8, 144.8, 145.1, 159.3, 170.0. Anal. Calcd for $C_{64}H_{48}N_{10}O_2$: C, 77.71; H, 4.98; N, 14.16. Found: C, 77.32; H, 4.91; N, 13.99.

***N,N′*-Bis{4-[α-(phenylhydrazono)benzyl]-1,5-diphenyl-1*H*-pyrazol-3-yl-carbonyl}-4-chloro-1,2-phenylendiamine (6b)** Yellow powder; mp 239–240°C; IR: υ 3232, 3163 (N-H), 1662 cm^{-1} (C=O); ^{1}H NMR: δ 6.73–7.73 (m, 43H, ArH), 9.33 and 9.38 (2s, 2H, NH), 10.15, 10.19, 10.21 and 10.24 (4s, 4H, Ph-NH); ^{13}C NMR: δ 113.4, 125.5, 125.5, 125.5, 125.6, 128.9, 129.3, 129.3, 129.4, 144.5, 159.8, 178.1. Anal. Calcd for $C_{64}H_{47}N_{10}O_2Cl$: C, 75.10; H, 4.63; N, 13.68. Found: C, 74.87; H, 4.80; N, 13.15.

***N,N′*-Bis{4-[α-(phenylhydrazono)benzyl]-1,5-diphenyl-1*H*-pyrazol-3-yl-carbonyl}-4-nitro-1,2-phenylendiamine (6c)** Yellow powder; mp 257–258°C; IR: υ 3315 (N-H), 1678 cm^{-1} (C=O); ^{1}H NMR: δ 6.74–8.32 (m, 43H, ArH), 9.38 and 9.40 (2s, 2H, NH), 10.40, 10.45, 10.54 and 10.56 (4s, 4H, Ph-NH); ^{13}C NMR: δ 113.5, 125.5, 126.4, 128.5, 128.7, 129.0, 129.3, 129.5, 130.1, 159.8, 161.18, 170.9. Anal. Calcd for $C_{64}H_{47}N_{11}O_4$: C, 73.79; H, 4.38; N, 13.35. Found: C, 73.70; H, 4.66; N, 13.85.

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