

Heterocyclic synthesis using nitrilimines: part 14. Synthesis of new pyrazole derivatives

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Received 12.10.2009

A new series of 1,3,4,5-tetrasubstituted pyrazoles have been synthesized by the 1,3-dipolar cycloaddition of suitable nitrilimines to 3-propylidene and 3-benzylidene-phthalide. Both analytical and spectroscopic data of all the synthesized compounds are in full agreement with the proposed structures.

Key Words: Nitrilimines, 1,3-dipolar cycloaddition, phthalides, pyrazoles

Introduction

In recent years, 1,3-dipolar cycloaddition reactions have received considerable attention because they have been shown to be an efficient synthetic tool for the preparation of a wide variety of heterocyclic compounds.¹ The reactions of nitrilimine 1,3-dipoles with dipolarophiles provide an option for the construction of substituted pyrazoles.^{1,2} The stereochemistry of the formation of pyrazoles from nitrilimines was reported in many studies.^{3–9} The pyrazole ring comprises the core structure of a number of drugs,^{10–13} including the widely prescribed Celebrex (Celecoxib),¹⁴ Viagra,¹⁵ and Rimonabant (Acomplia® or Zimulti®), a high-potency cannabinoid type-1 (CB₁) receptor inverse agonist that has recently been approved in the European Union as a treatment for obesity.⁵ Furthermore, recent reports indicate the pyrazole chemotype as the structural motif of a number of highly potent inhibitors of coagulation factor Xa.¹³ Among them, Rivaroxaban and Apixaban were selected for clinical development for the prevention and treatment of thrombotic diseases.¹⁶ A huge number of pyrazole derivatives have antimicrobial,¹⁷ antiviral,^{17,18} herbicidal,¹⁹ hypoglycemic,²⁰ hypolipidemic,^{19,21} and anticancer^{21,22} activities. Some of them were identified as selective antagonists of subtype 1 PGE₂ receptors (EPI),^{22,23} and showed efficacy in numerous preclinical models of pain, including allodynia and neuropathic pain, and are expected to be devoid of the gastrointestinal effects associated with non-steroidal anti-inflammatory drugs (NSAIDs)²⁴ and the cardiovascular side effects typical of COX-2 selective inhibitors.²⁵ In view of these

facts and in continuation of our studies on the use of hydrazonoyl halides as useful precursors for the synthesis of various heterocycles,²⁶ we report here the synthesis of new pyrazole derivatives via reaction of nitrilimines with 3-propylidenephthalide and 3-benzylidenephthalide.

Experimental

Melting points were determined on an A. Krüss Melting Point Meter and are uncorrected. The IR spectra were measured as potassium bromide pellets using a Satellite 3000 Mid infrared spectrophotometer. The ¹H-NMR and ¹³C-NMR spectra were recorded on a Bruker AM 300 MHz spectrometer at room temperature in DMSO-d₆ solution using tetramethylsilane (TMS) as internal reference. Chemical shifts were recorded as δ values in parts per million (ppm) downfield from internal TMS. Electron impact (EI) mass spectra were run on a Shimadzu GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were performed at the Microanalytical Center of Cairo University, Egypt. The hydrazonoyl halides **1**^{27–29} and 3-benzylidenephthalide³⁰ were prepared according to literature procedures. 3-Propylidenephthalide, benzene, and triethylamine were purchased from Avocado Research Chemicals, England, and used without further purification.

General procedure for synthesis of pyrazole derivatives 5a-p.

Triethylamine (10 mmol) was added to a stirred mixture of phthalides **3** (5 mmol) and the appropriate hydrazonoyl halides **1** (5 mmol) in benzene (50 mL) and the reaction mixture was heated under refluxing condition. The reaction was controlled by TLC and continued until the starting substrates were completely consumed (10–12 h); it was then left to cool to room temperature. The solvent was then evaporated under reduced pressure and the residual solid was washed with water (2 × 25 mL) and in a few cases the gummy products were triturated with ethanol or methanol (10 mL). The crude solid product was collected and recrystallized from ethanol to give the desired compounds.

The following compounds were synthesized using this method:

2-[3-Acetyl-1-(4-chlorophenyl)-4-ethyl-1H-pyrazol-5-yl]benzoic acid (5a): Yield 54%; mp 176–178 °C; ¹H-NMR (DMSO-d₆) δ 12.45 (1H, s, OH), 7.76–7.21 (8H, m, arom. H), 2.69 (2H, q, *J* 7.5, CH₂), 2.56 (3H, s, COCH₃), 1.09 (3H, t, *J* 7.5, CH₃); ¹³C-NMR (DMSO-d₆) δ 192.3, 166.7, 147.6, 146.3, 142.2, 137.9, 135.3, 133.1, 131.8, 129.8, 129.4, 128.9, 128.2, 124.3, 118.7, 25.6, 16.8, 13.6; IR (KBr) ν 2525 (br OH), 1720 (C=O acid), 1690 (C=O acetyl), 1621 (C=N) cm^{–1}; MS: *m/z* = 368/370 [M⁺]; Analysis (% Calculated/found) for C₂₀H₁₇ClN₂O₃ (Mw 368.82) C: 65.13/65.45, H: 4.65/4.50, N: 7.60/7.45.

2-[3-Acetyl-4-ethyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]benzoic acid (5b): Yield 56%; mp 156–158 °C; ¹H-NMR (DMSO-d₆) δ 12.50 (s, 1H, OH), 7.75–7.23 (8H, m, arom. H), 2.73 (3H, s, p-CH₃), 2.66 (2H, q, *J* 7.5, CH₂), 2.54 (3H, s, COCH₃), 1.10 (3H, t, *J* 7.5, CH₃); ¹³C-NMR (DMSO-d₆) δ 192.3, 166.7, 147.8, 146.3, 142.2, 136.9, 135.4, 133.0, 130.8, 129.3, 128.6, 128.3, 125.3, 123.2, 118.7, 25.6, 21.7, 16.8, 13.6; IR (KBr) ν 2520 (br OH), 1720 (C=O acid), 1692 (C=O acetyl), 1622 (C=N) cm^{–1}; MS: *m/z* = 348 [M⁺]; Analysis (% Calculated/found) for C₂₁H₂₀N₂O₃ (Mw 348.41) C: 72.40/72.15, H: 5.79/5.90, N: 8.04/7.95.

2-[3-Acetyl-1,4-diphenyl-1H-pyrazol-5-yl]benzoic acid (5c): Yield: 57%; mp 160–162 °C; ¹H-NMR (DMSO-d₆) δ 12.50 (s, 1H, OH), 7.75–7.21 (14H, m, arom. H), 2.54 (3H, s, COCH₃); ¹³C-NMR (DMSO-

δ 192.1, 166.7, 147.6, 146.3, 142.3, 139.7, 136.4, 134.8, 133.3, 129.8, 129.2, 128.8, 128.5, 128.3, 127.2, 126.3, 124.8, 123.7, 118.7, 25.6; IR (KBr) ν 2525 (br OH), 1718 (C=O acid), 1690 (C=O acetyl), 1620 (C=N) cm^{-1} ; MS: $m/z = 382$ [M^+]; Analysis (% Calculated/found) for $\text{C}_{24}\text{H}_{18}\text{N}_2\text{O}_3$ (Mw 382.42) C: 75.38/75.65, H: 4.74/4.60, N: 7.33/7.21.

2-[1-(4-Chlorophenyl)-4-ethyl-3-methoxycarbonyl-1H-pyrazol-5-yl]benzoic acid (5d): Yield: 51%; mp 171-173 °C; $^1\text{H-NMR}$ (DMSO-d_6) δ 12.51 (1H, s, OH), 7.72-7.28 (8H, m, arom. H), 3.75 (3H, s, OCH_3), 2.67 (2H, q, J 7.5, CH_2), 1.12 (3H, t, J 7.5, CH_3); $^{13}\text{C-NMR}$ (DMSO-d_6) δ 166.7, 164.3, 147.1, 146.3, 142.2, 137.9, 134.9, 133.0, 131.8, 130.4, 129.7, 128.7, 128.2, 124.8, 118.7, 47.9, 16.8, 13.6; IR (KBr) ν 2530 (br OH), 1712 (C=O acid), 1705 (C=O ester), 1624 (C=N) cm^{-1} ; MS: $m/z = 384/386$ [M^+]; Analysis (% Calculated/found) for $\text{C}_{20}\text{H}_{17}\text{ClN}_2\text{O}_4$ (Mw 384.82) C: 62.42/62.20, H: 4.45/4.55, N: 7.28/7.40.

2-[3-Benzoyl-1-(4-chlorophenyl)-4-ethyl-1H-pyrazol-5-yl]benzoic acid (5e): Yield: 47%; mp 196-198 °C; $^1\text{H-NMR}$ (DMSO-d_6) δ 12.52 (1H, s, OH), 7.77-7.26 (13H, m, arom. H), 2.61 (2H, q, J 7.5, CH_2), 1.10 (3H, t, J 7.5, CH_3); $^{13}\text{C-NMR}$ (DMSO-d_6) δ 185.3, 166.7, 147.8, 146.3, 144.3, 142.2, 137.8, 134.9, 133.1, 132.2, 131.6, 129.9, 129.7, 129.1, 128.8, 128.5, 127.9, 124.6, 118.7, 16.8, 13.6; IR (KBr) ν 2520 (br OH), 1714 (C=O acid), 1654 (Ar-C=O), 1619 (C=N) cm^{-1} ; MS: $m/z = 430/430$ [M^+]; Analysis (% Calculated/found) for $\text{C}_{25}\text{H}_{19}\text{ClN}_2\text{O}_3$ (Mw 430.89) C: 69.69/69.45, H: 4.44/4.60, N: 6.50/6.65.

2-[3-Benzoyl-1-(4-chlorophenyl)-4-phenyl-1H-pyrazol-5-yl]benzoic acid (5f): Yield: 44%; mp 189-191 °C; $^1\text{H-NMR}$ (DMSO-d_6) δ 12.52 (1H, s, OH), 7.71-7.26 (18H, m, arom. H); $^{13}\text{C-NMR}$ (DMSO-d_6) δ 185.2, 166.7, 147.8, 146.3, 143.6, 141.9, 137.8, 136.9, 134.6, 133.4, 132.6, 131.8, 130.7, 129.7, 129.4, 129.1, 128.8, 128.6, 128.2, 127.6, 124.6, 123.7, 118.7; IR (KBr) ν 2527 (br OH), 1715 (C=O acid), 1656 (Ar-C=O), 1620 (C=N) cm^{-1} ; MS: $m/z = 478/480$ [M^+]; Analysis (% Calculated/found) for $\text{C}_{29}\text{H}_{19}\text{ClN}_2\text{O}_3$ (Mw 478.94) C: 72.73/72.95, H: 4.00/3.85, N: 5.85/5.71.

2-[4-Ethyl-1-phenyl-3-phenylcarbamoyl-1H-pyrazol-5-yl]benzoic acid (5g): Yield: 49%; mp 165-167 °C; $^1\text{H-NMR}$ (DMSO-d_6) δ 12.50 (1H, s, OH), 9.80 (1H, s, NH), 7.76-7.17 (14H, m, arom. H), 2.60 (2H, q, J 7.5, CH_2), 1.09 (3H, t, J 7.5, CH_3); $^{13}\text{C-NMR}$ (DMSO-d_6) δ 159.5, 166.7, 146.8, 145.7, 142.2, 139.8, 138.1, 134.4, 133.1, 130.2, 129.6, 129.0, 128.7, 128.1, 127.7, 126.6, 124.6, 123.4, 121.8, 16.8, 13.6; IR (KBr) ν 2525 (br OH), 1710 (C=O acid), 1665 (Ar-C=O), 1613 (C=N) cm^{-1} ; MS: $m/z = 411$ [M^+]; Analysis (% Calculated/found) for $\text{C}_{25}\text{H}_{21}\text{N}_3\text{O}_3$ (Mw 411.46) C: 72.98/73.25, H: 5.14/4.92, N: 10.21/10.05.

2-[1-(4-Chlorophenyl)-4-ethyl-3-phenylcarbamoyl-1H-pyrazol-5-yl]benzoic acid (5h): Yield: 47%; mp 157-158 °C; $^1\text{H-NMR}$ (DMSO-d_6) δ 12.51 (1H, s, OH), 9.85 (1H, s, NH), 7.79-7.16 (13H, m, arom. H), 2.63 (2H, q, J 7.5, CH_2), 1.11 (3H, t, J 7.5, CH_3); $^{13}\text{C-NMR}$ (DMSO-d_6) δ 159.2, 166.7, 147.1, 145.9, 142.2, 138.2, 137.6, 134.1, 133.0, 131.8, 130.2, 129.7, 128.6, 128.4, 127.8, 124.6, 123.6, 121.6, 118.7, 16.8, 13.6; IR (KBr) ν 2525 (br OH), 1712 (C=O acid), 1662 (Ar-C=O), 1616 (C=N) cm^{-1} ; MS: $m/z = 445/447$ [M^+]; Analysis (% Calculated/found) for $\text{C}_{25}\text{H}_{20}\text{ClN}_3\text{O}_3$ (Mw 445.91) C: 67.34/67.11, H: 4.52/4.70, N: 9.42/9.55.

2-[1-(4-Chlorophenyl)-4-phenyl-3-phenylcarbamoyl-1H-pyrazol-5-yl]benzoic acid (5i): Yield: 45%; mp 171-173 °C; $^1\text{H-NMR}$ (DMSO-d_6) δ 12.51 (1H, s, OH), 9.85 (1H, s, NH), 7.74-7.18 (13H, m, arom. H); $^{13}\text{C-NMR}$ (DMSO-d_6) δ 166.7, 159.4, 147.1, 146.3, 142.3, 141.2, 137.9, 137.5, 136.4, 134.6, 133.4, 131.8, 129.8, 129.4, 129.2, 128.9, 128.6, 128.4, 127.9, 127.3, 124.8, 123.7, 121.6; IR (KBr) ν 2525 (br OH), 1714 (C=O acid), 1660 (Ar-C=O), 1613 (C=N) cm^{-1} ; MS: $m/z = 493/495$ [M^+]; Analysis (% Calculated/found)

for $C_{29}H_{20}ClN_3O_3$ (Mw 493.95) C: 70.52/70.85, H: 4.08/3.90, N: 8.51/8.40.

2-[4-Ethyl-1-(4-fluorophenyl)-3-phenylcarbamoyl-1H-pyrazol-5-yl]benzoic acid (5j): Yield: 43%; mp 181-183 °C; 1H -NMR (DMSO- d_6) δ 12.50 (1H, s, OH), 9.75 (1H, s, NH), 7.76-7.22 (13H, m, arom. H), 2.60 (2H, q, J 7.5, CH_2), 1.10 (3H, t, J 7.5, CH_3); ^{13}C -NMR (DMSO- d_6) δ 159.2, 166.7, 160.9, 147.4, 146.5, 142.2, 138.1, 135.8, 134.7, 133.2, 130.5, 129.1, 128.8, 128.6, 127.9, 123.8, 121.7, 116.8, 115.7, 16.8, 13.6; IR (KBr) ν 2525 (br OH), 1713 (C=O acid), 1665 (Ar-C=O), 1618 (C=N) cm^{-1} ; MS: m/z = 429 [M^+]; Analysis (% Calculated/found) for $C_{25}H_{20}FN_3O_3$ (Mw 429.45) C: 69.92/70.28, H: 4.69/4.55, N: 9.78/9.65.

2-[1-(4-Methylphenyl)-4-phenyl-3-phenylcarbamoyl-1H-pyrazol-5-yl]benzoic acid (5k): Yield: 46%; mp 193-195 °C; 1H -NMR (DMSO- d_6) δ 12.51 (1H, s, OH), 9.68 (1H, s, NH), 7.72-7.10 (18H, m, arom. H), 2.73 (3H, s, p- CH_3); ^{13}C -NMR (DMSO- d_6) δ 159.5, 166.7, 147.4, 146.7, 142.3, 138.4, 137.1, 136.6, 136.2, 135.7, 134.4, 133.0, 130.4, 129.8, 129.4, 128.7, 128.5, 128.1, 127.8, 127.3, 125.7, 123.7, 121.6, 21.6; IR (KBr) ν 2525 (br OH), 1711 (C=O acid), 1660 (Ar-C=O), 1615 (C=N) cm^{-1} ; MS: m/z = 473 [M^+]; Analysis (% Calculated/found) for $C_{30}H_{23}N_3O_3$ (Mw 473.54) C: 76.09/75.81, H: 4.90/5.10, N: 8.87/9.05.

2-[1-(4-Chlorophenyl)-4-ethyl-3-(furan-2-yl)-1H-pyrazol-5-yl]benzoic acid (5l): Yield: 51%; mp 172-173 °C; 1H -NMR (DMSO- d_6) δ 12.53 (1H, s, OH), 8.12-7.28 (11H, m, arom. H), 2.67 (2H, q, J 7.5, CH_2), 1.11 (3H, t, J 7.5, CH_3); ^{13}C -NMR (DMSO- d_6) δ 173.4, 166.7, 149.5, 147.1, 146.6, 143.7, 142.2, 137.8, 134.1, 132.9, 131.2, 130.9, 129.7, 128.7, 128.3, 124.8, 123.5, 121.2, 115.7, 16.8, 13.6; IR (KBr) ν 2525 (br OH), 1715 (C=O acid), 1655 (Ar-C=O), 1622 (C=N) cm^{-1} ; MS: m/z = 420/422 [M^+]; Analysis (% Calculated/found) for $C_{23}H_{17}ClN_2O_4$ (Mw 420.86) C: 65.64/65.45, H: 4.07/3.90, N: 6.66/6.85.

2-[1-(4-Chlorophenyl)-4-ethyl-3-(thiophen-2-yl)-1H-pyrazol-5-yl]benzoic acid (5m): Yield: 53%; mp 167-169 °C; 1H -NMR (DMSO- d_6) δ 12.52 (1H, s, OH), 8.21-7.27 (11H, m, arom. H), 2.69 (2H, q, J 7.5, CH_2), 1.12 (3H, t, J 7.5, CH_3); ^{13}C -NMR (DMSO- d_6) δ 176.6, 166.7, 147.8, 146.3, 144.3, 142.0, 137.6, 135.9, 134.4, 133.7, 133.2, 131.4, 130.2, 129.6, 129.2, 128.7, 128.4, 124.3, 123.6, 16.8, 13.6; IR (KBr) ν 2525 (br OH), 1715 (C=O acid), 1665 (Ar-C=O), 1624 (C=N) cm^{-1} ; MS: m/z = 436/438 [M^+]; Analysis (% Calculated/found) for $C_{23}H_{17}ClN_2O_3S$ (Mw 436.92) C: 63.23/63.50, H: 3.92/4.10, N: 6.41/6.25.

2-[1-(4-Chlorophenyl)-4-ethyl-3-(2-naphthoyl)-1H-pyrazol-5-yl]benzoic acid (5n): Yield: 47%; mp 197-199 °C; 1H -NMR (DMSO- d_6) δ 12.45 (1H, s, OH), 8.41-7.22 (15H, m, arom. H), 2.56 (2H, q, J 7.5, CH_2), 1.08 (3H, t, J 7.5, CH_3); ^{13}C -NMR (DMSO- d_6) δ 183.5, 166.7, 147.3, 146.1, 142.2, 139.1, 137.9, 134.7, 133.1, 132.6, 132.3, 131.7, 131.0, 130.6, 129.7, 129.1, 128.8, 128.3, 128.1, 127.9, 127.5, 126.9, 125.1, 124.6, 123.4, 16.8, 13.6; IR (KBr) ν 2525 (br OH), 1710 (C=O acid), 1645 (Ar-C=O), 1610 (C=N) cm^{-1} ; MS: m/z = 481/483 [M^+]; Analysis (% Calculated/found) for $C_{29}H_{22}ClN_2O_3$ (Mw 481.96) C: 72.27/72.56, H: 4.60/4.50, N: 5.81/5.66.

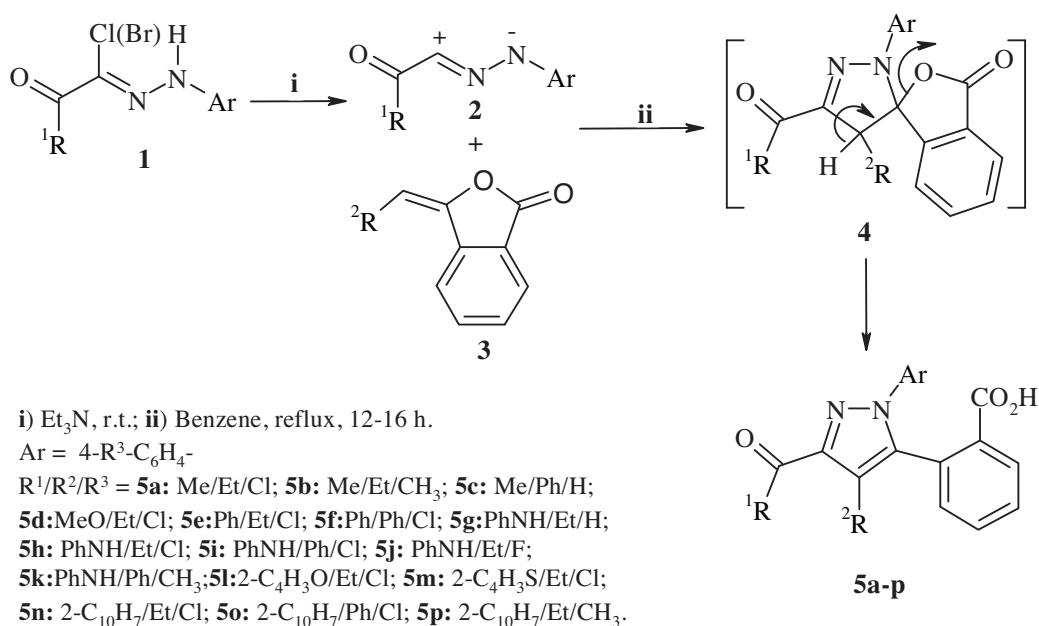
2-[1-(4-Chlorophenyl)-3-(2-naphthoyl)-4-phenyl-1H-pyrazol-5-yl]benzoic acid (5o): Yield: 49%; mp 170-172 °C; 1H -NMR (DMSO- d_6) δ 12.45 (1H, s, OH), 8.45-7.24 (20H, m, arom. H); ^{13}C -NMR (DMSO- d_6) δ 183.6, 166.7, 147.1, 146.3, 141.7, 139.0, 137.8, 136.6, 134.3, 133.2, 132.8, 132.6, 131.8, 130.9, 130.2, 129.6, 129.3, 129.1, 128.8, 128.6, 128.4, 128.2, 127.9, 127.7, 127.3, 126.7, 124.6, 124.2, 123.4; IR (KBr) ν 2525 (br OH), 1712 (C=O acid), 1647 (Ar-C=O), 1615 (C=N) cm^{-1} ; MS: m/z = 528/530 [M^+]; Analysis (% Calculated/found) for $C_{33}H_{21}ClN_2O_3$ (Mw 529.00) C: 74.93/75.25, H: 4.00/3.85, N: 5.30/5.43.

2-[4-Ethyl-1-(4-methylphenyl)-3-(2-naphthoyl)-1H-pyrazol-5-yl]benzoic acid (5p): Yield: 45%;

mp 184-186 °C; $^1\text{H-NMR}$ (DMSO-d_6) δ 12.46 (1H, s, OH), 8.43-7.26 (15H, m, arom. H), 2.72 (3H, s, p- CH_3), 2.58 (2H, q, J 7.5, CH_2), 1.09 (3H, t, J 7.5, CH_3); $^{13}\text{C-NMR}$ (DMSO-d_6) δ 183.4, 166.7, 146.5, 145.7, 140.8, 139.0, 136.8, 135.7, 134.5, 133.0, 132.4, 132.1, 130.8, 130.2, 129.7, 129.3, 128.6, 128.5, 128.3, 128.1, 127.7, 126.9, 124.6, 123.2, 21.7, 16.8, 13.6; IR (KBr) ν 2525 (br OH), 1710 (C=O acid), 1645 (Ar-C=O), 1612 (C=N) cm^{-1} ; MS: m/z = 460 [M^+]; Analysis (% Calculated/found) for $\text{C}_{30}\text{H}_{24}\text{N}_2\text{O}_3$ (Mw 460.54) C: 78.24/77.90, H: 5.25/5.42, N: 6.08/5.96.

Results and discussion

The required nitrilimines **2** were generated in situ by base-promoted dehydrohalogenation of the corresponding hydrazonoyl halides **1**. Treatment of the resulting non-isolable nitrilimines **2**, 1,3-dipole, with phthalides **3** in refluxing benzene gave in each case a single product that proved to be the respective 1,3,4,5-tetrasubstituted pyrazoles **5a-p** instead of spiropyrazoline derivatives **4**. The proposed mechanism involved initial formation of the spiro intermediates **4** via 1,3-dipolar cycloaddition of nitrilimines **2** to the exocyclic double bond of compound **3**. The latter intermediates, which cannot be isolated nor observed by TLC, ultimately underwent ring opening via 1,3-hydrogen shift to aromatic pyrazole derivatives **5a-p** as outlined in the Scheme. It is worth mentioning that the nitrile oxides generated in situ from the respective hydroxamoyl chlorides with triethylamine as a base react with 3-benzylidenephthalides to afford isoxazoles.³¹ The purity of obtained compounds was controlled by TLC and elemental analysis. Both the analytical and spectral data (IR, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, and mass spectra) of the synthesized pyrazoles were in full agreement with the proposed structures.



Scheme. Synthetic pathway for the preparation of pyrazoles **5a-p**.

The characterization data of the synthesized compounds **5a-p** are given in the Experimental section. The electron impact (EI) mass spectra displayed the correct molecular ions ($\text{M}^{+\cdot}$) in accordance with the suggested

structures. The IR spectra of compounds **5a-p** revealed 2 strong absorption bands in the regions 1720-1710 cm^{-1} (COOH) and 1690-1640 cm^{-1} (C=O aroyl). The stretching band for C=N of the pyrazole ring appeared in the region 1620-1610 cm^{-1} . All these products gave a singlet signal at 12.5 ppm in their ^1H -NMR spectra assignable to benzoic acid moiety. Their ^{13}C -NMR spectra showed all the signals of the proposed structures; in particular the carbon of the carboxyl group was found to resonate at about 167 ppm and the signal at about 147-145 ppm was attributed to C=N of the pyrazole ring. The complete ^{13}C -NMR data are presented in the Experimental section.

In conclusion, we described the 1,3-dipolar cycloadditions of nitrilimines to some exocyclic olefins and the results demonstrated that the aromatization was the driving force for the formation of aromatic pyrazole derivatives.

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