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Synthesis of 3,4-diaryl-1-phenyl-4,5-dihydro-1*H*-pyrazole-5-carbonitriles via 1,3-dipolar cycloaddition reactions

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Abstract: Nitrile imines generated by the oxidative dehydrogenation of aromatic aldehyde phenylhydrazones with chloramine-T as a catalytic dehydrogenating agent were trapped in situ by 4-methoxy cinnamonitrile to afford 3,4-diaryl-1-phenyl-4,5-dihydro-*1H*-pyrazole-5-carbonitrile in moderate to good yields. The structures of the cycloadducts were confirmed by spectral studies and elemental analysis.

Key words: Pyrazoles, nitrile imines, chloramine-T, dipolar, cycloaddition

1. Introduction

The pyrazoles constitute an interesting class of heterocyclic compounds as important building blocks in organic synthesis and more potent biologically active molecules in pharmaceutical and medicinal chemistry. The most convenient synthesis of pyrazole ring systems has been executed in the literature via 1,3-dipolar cycloaddition reactions of alkenes and alkynes with nitrile imines generated in situ from aldehyde phenylhydrazones.[1] The usual method of generation of nitrile imines involves the thermolysis of 2,5-diphenyl tetrazole,[2] catalytic oxidation of aldehyde hydrazones with lead tetraacetate,[3] chloramine-T,[4] and mercuric acetate.[5] Photolysis of 3,4-disubstituted sydnones and 2,4-disubstituted-1,3,4-oxadiazolin-5-ones[6] also provides nitrile imines. The pyrazoles act as selective inhibitors of tissue-nonspecific alkaline phosphatase,[7] also known to exhibit antimicrobial and antioxidant activities.[8–10] Pyrazole derivatives were reported to exhibit antiviral,[11] antitubercular,[12] antimicobacterial,[13] and antitumor and antiangiogenic properties.[14] A series of structurally related 1*H*-pyrazolyl derivative synthesized compounds were tested for their antiinflammatory activities, COX-1 and COX-2 inhibitory activities, ulcerogenic effects, and acute toxicity.[15]

In view of the enormous applications associated with pyrazole systems, the present study was undertaken with the hope of getting more biologically potent molecules. This paper describes the synthesis of a series of title compounds (**3**) that involve 1,3-dipolar cycloaddition reaction of 4-methoxy cinnamonitrile (**1**) and nitrile imines generated in situ from aldehyde phenylhydrazones (**2**) using chloramine-T as a catalytic dehydrogenating agent.

2. Experimental

The chemicals/reagents used were purchased from Sigma-Aldrich Chemicals (India) and Merck Chemicals (India). IR spectra were recorded on a Nujol mull on a Shimadzu 8300 spectrometer. The ^{1}H NMR and

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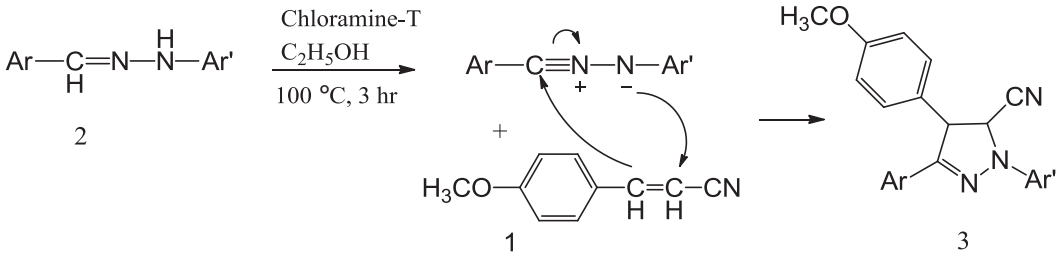
^{13}C NMR spectra were recorded on a Bruker Supercon 400 MHz spectrophotometer using $CDCl_3$ as solvent and TMS as an internal standard. The chemical shifts are expressed in ? ppm. Mass spectra were obtained on a Shimadzu LCMS-2010A spectrophotometer (chemical ionization) and the important fragments are given with the relative intensities in the bracket. Elemental analysis was obtained on a Thermo Finnigan Flash EA 1112 CHN analyzer. Thin layer chromatography (TLC) was performed on precoated silica gel sheets (HF 254, sd-fine) using benzene:ethyl acetate (7:2) eluent, and visualization of the spots was done in iodine vapor and UV light. Chromatographic separations were carried out on a silica gel column (70-230 mesh, Merck) using hexane:ethyl acetate (8:1) as the eluent.

In a typical 1,3-dipolar cycloaddition, the nitrile imines generated by the catalytic dehydrogenation of aromatic aldehyde phenylhydrazones **2** with chloramine-T were trapped in situ by 4-methoxy cinnamonitrile **1**, and the reaction afforded 3,4-diaryl-1-phenyl-4,5-dihydro-*1H*-pyrazole-5-carbonitriles **3** in 60%–76% yield (Scheme).



3 a) Ar = 4-FC_6H_4, Ar' = C_6H_5; b) Ar = 4-ClC_6H_4; Ar' = C_6H_5;
c) Ar = 4-BrC_6H_4; Ar' = C_6H_5; d) Ar = 4-CNC_6H_4; Ar' = C_6H_5;
e) Ar = C_6H_5; Ar' = C_6H_5; f) Ar = 4-$OCH_3C_6H_4$; Ar' = C_6H_5;
g) Ar = 3,4-$(OCH_3)_2C_6H_3$; Ar' = C_6H_5; h) Ar = Furan-2-yl, Ar' = C_6H_5.

Scheme.

Catalytic dehydrogenation of aromatic aldehyde phenylhydrazones with chloramine-T in ethyl alcohol generates nitrile imines. The nitrile imines generated in situ undergo 1,3-dipolar cycloaddition with an alkenyl moiety of 4-methoxy cinnamonitrile to produce the title compounds.

2.1. General procedure for the synthesis of 3,4-diaryl-1-phenyl-4,5-dihydro-*1H*-pyrazole-5-carbonitrile (3a–3h)

A mixture of 4-fluorobenzaldehyde phenylhydrazone **2** (4.0 mmol), 3-(4-methoxyphenyl) acrylonitrile **1** (4.0 mmol), and chloramine-T trihydrate (4.0 mmol) in ethanol was refluxed in a water bath for 3 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, the sodium chloride formed in the reaction mixture was filtered off and washed with ethanol (1 × 15 mL), and then the combined filtrate and washings were evaporated in vacuum. The residual part was extracted into ether (25 mL) and washed successively with water (2 × 15 mL), 10% sodium hydroxide (2 × 15 mL), and saturated brine solution (1 × 10 mL). The organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent yielded light brown oil, which gave 1 major spot corresponding to the product 3,4-diaryl-1-phenyl-4,5-dihydro-*1H*-pyrazole-5-carbonitrile **3** and 2 minor spots corresponding to the unreacted precursors in TLC. The product was purified by column chromatography using hexane:ethyl acetate (8:1 v/v) as an eluent. The products were obtained in relatively high yields. The same procedure was used in all cases.

2.2. 3-(4-Fluorophenyl)-4-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole-5-carbonitrile, 3a

Obtained as a light brown oil in 62% yield. IR (Nujol): 1675 (C=N str.), 2235 (C≡N str.) cm^{-1}. ^{1}H NMR ($CDCl_3$): 3.846 (s, 3H, OCH_3), 5.279 (d, 1H, C_4-H), 5.704 (d, 1H, C_5-H), 6.894–6.950 (m, 5H, Ar"-H), 7.025 (dd, 2H, Ar-H), 7.299 (dd, 2H, Ar'-H), 7.386 (dd, 2H, Ar-H), 7.785 (dd, 2H, Ar'-H). ^{13}C NMR ($CDCl_3$): 41.56 (1C, 4-C), 51.24 (1C, 5-C), 55.65 (1C, O<u>C</u>H_3), 114.16 (2C, Ar-C), 115.42 (2C, Ar-C), 116.32 (1C, <u>C</u>N), 116.64 (2C, Ar-C), 120.60 (1C, Ar-C), 128.56 (2C, Ar-C), 129.28 (2C, Ar-C), 129.42 (2C, Ar-C), 129.96 (1C, Ar-C), 132.75 (1C, Ar-C), 143.20 (1C, 3-C), 143.66 (1C, Ar-C), 156.36 (1C, Ar-C), 164.38 (1C, Ar-C). MS (relative abundance) m/z: 372 (MH^+, 100), 346 (11), 278 (18), 244 (06), 214 (16), 195 (14), 137(08). Anal. Calcd. for $C_{23}H_{18}FN_3O$: C, 74.38, H, 4.88, N, 11.31%; Found: C, 74.56, H, 4.79, N, 11.21%.

2.3. 3-(4-Chlorophenyl)-4-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole-5-carbonitrile, 3b

Obtained as a light brown oil in 70% yield. IR (Nujol): 1660 (C=N str.), 2233 (C≡N str.) cm^{-1}. ^{1}H NMR ($CDCl_3$): 3.838 (s, 3H, OCH_3), 5.221 (d, 1H, C_4-H), 5.674 (d, 1H, C_5-H), 6.904–6.952 (m, 5H, Ar"-H), 7.050 (dd, 2H, Ar-H), 7.300 (dd, 2H, Ar'-H), 7.398 (dd, 2H, Ar-H), 7.796 (dd, 2H, Ar'-H). ^{13}C NMR ($CDCl_3$): 41.62 (1C, 4-C), 51.34 (1C, 5-C), 55.55 (1C, O<u>C</u>H_3), 114.22 (2C, Ar-C), 116.12 (2C, Ar-C), 116.30 (1C, <u>C</u>N), 120.68 (1C, Ar-C), 128.12 (2C, Ar-C), 128.44 (2C, Ar-C), 128.80 (2C, Ar-C), 129.51 (2C, Ar-C), 131.71 (1C, Ar-C), 132.54 (1C, Ar-C), 136.80 (1C, Ar-C), 142.96 (1C, 3-C), 143.78 (1C, Ar-C), 157.06 (1C, Ar-C). MS (relative abundance) m/z: 389 (M^+, ^{37}Cl, 33), 387.11 (M^+, ^{35}Cl, 100), 361 (24), 294 (24), 260 (16), 230 (15), 211 (22), 153 (29). Anal. Calcd. for $C_{23}H_{18}ClN_3O$, C, 71.22, H, 4.68, N, 10.83%; Found: C, 71.20, H, 4.61, N, 10.74%.

2.4. 3-(4-Bromophenyl)-4-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole-5-carbonitrile, 3c

Obtained as a light brown oil in 60% yield. IR (Nujol): 1670 (C=N str.), 2240 (C≡N str.) cm^{-1}. ^{1}H NMR ($CDCl_3$): 3.842 (s, 3H, OCH_3), 5.218 (d, 1H, C_4-H), 5.644 (d, 1H, C_5-H), 6.920–6.945 (m, 5H, Ar"-H), 7.010 (dd, 2H, Ar-H), 7.308 (dd, 2H, Ar'-H), 7.412 (dd, 2H, Ar-H), 7.722 (dd, 2H, Ar'-H). ^{13}C NMR ($CDCl_3$): 41.68 (1C, 4-C), 51.54 (1C, 5-C), 55.50 (1C, O<u>C</u>H_3), 114.26 (2C, Ar-C), 116.50 (2C, Ar-C), 116.64 (1C, <u>C</u>N), 120.64 (1C, Ar-C), 125.24 (1C, Ar-C), 128.40 (2C, Ar-C), 128.78 (2C, Ar-C), 129.46 (2C, Ar-C), 131.52 (2C, Ar-C), 132.63 (1C, Ar-C), 133.02 (1C, Ar-C), 142.66 (1C, 3-C), 143.70 (1C, Ar-C), 156.70 (1C, Ar-C). Anal. Calcd. for $C_{23}H_{18}BrN_3O$: C, 63.90, H, 4.20, N, 9.72%; Found: C, 63.84, H, 4.12, N, 9.64%.

2.5. 3-(4-Cyanophenyl)-4-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole-5-carbonitrile, 3d

Obtained as a light brown oil in 64% yield. IR (Nujol): 1675 (C=N str.), 2230 (C≡N str.) cm^{-1}. ^{1}H NMR ($CDCl_3$): 3.832 (s, 3H, OCH_3), 5.186 (d, 1H, C_4-H), 5.626 (d, 1H, C_5-H), 6.090 (dd, 2H, Ar-H), 6.928–7.266 (m, 5H, Ar"-H), 7.300 (dd, 2H, Ar-H), 7.712 (dd, 2H, Ar'-H), 8.010 (dd, 2H, Ar'-H). ^{13}C NMR ($CDCl_3$): 41.76 (1C, 4-C), 52.32 (1C, 5-C), 55.96 (1C, O<u>C</u>H_3), 114.52 (2C, Ar-C), 114.84 (1C, Ar-C), 116.22 (2C, Ar-C), 116.58 (1C, <u>C</u>N), 118.12 (1C, <u>C</u>N), 120.26 (1C, Ar-C), 128.56 (2C, Ar-C), 129.46 (2C, Ar-C), 129.74 (2C, Ar-C), 132.66 (2C, Ar-C), 132.94 (1C, Ar-C), 138.12 (1C, Ar-C), 142.98 (1C, 3-C), 143.82 (1C, Ar-C),157.08 (1C, Ar-C). MS (relative abundance) m/z: 379 (MH^+, 100), 353 (20), 285 (14), 251 (26), 221 (19), 202 (32), 144 (30). Anal. Calcd. for $C_{24}H_{18}N_4O$: C, 76.17, H, 4.79, N, 14.81%; Found: C, 76.10, H, 4.73, N, 14.75%.

2.6. 4-(4-Methoxyphenyl)-1,3-diphenyl-4,5-dihydro-1*H*-pyrazole-5-carbonitrile, 3e

Obtained as light brown oil in 58% yield. IR (Nujol): 1672 (C=N str.), 2234 (C≡N str.) cm^{-1}. ^{1}H NMR ($CDCl_3$): 3.840 (s, 3H, OCH_3), 5.196 (d, 1H, C_4-H), 5.638 (d, 1H, C_5-H), 6.930 (dd, 2H, Ar-H), 6.998–7.544 (m, 10H, Ar', Ar"-H), 7.452 (dd, 2H, Ar-H). ^{13}C NMR ($CDCl_3$): 41.88 (1C, 4-C), 51.92 (1C, 5-C), 55.65 (1C, OCH$_3$), 114.20 (2C, Ar-C), 116.38 (2C, Ar-C), 116.80 (1C, CN), 120.42 (1C, Ar-C), 128.14 (2C, Ar-C), 128.56 (2C, Ar-C), 128.98 (2C, Ar-C), 129.64 (2C, Ar-C), 131.04 (1C, Ar-C), 131.32 (1C, Ar-C), 132.40 (1C, Ar-C), 143.48 (1C, Ar-C), 144.16 (1C, 3-C), 157.36 (1C, Ar-C). MS (relative abundance) m/z: 354 (MH^+, 100), 328 (24), 260 (24), 225 (16), 195 (21), 177 (32), 118 (24). Anal. Calcd. for $C_{23}H_{19}N_3O$: C, 78.16, H, 5.42, N, 11.89%; Found: C, 78.07, H, 5.34, N, 11.81%.

2.7. 3,4-Bis(4-methoxyphenyl)-1-diphenyl-4,5-dihydro-1*H*-pyrazole-5-carbonitrile, 3f

Obtained as a light brown oil in 65% yield. IR (Nujol): 1660 (C=N str.), 2235 (C≡N str.) cm^{-1}. ^{1}H NMR ($CDCl_3$): 3.854 (s, 6H, OCH_3), 5.166 (d, 1H, C_4-H), 5.526 (d, 1H, C_5-H), 6.890 (dd, 2H, Ar-H), 6.192-7.426 (m, 5H, Ar"-H), 7.010 (dd, 2H, Ar'-H), 7.542 (dd, 2H, Ar-H), 7.992 (dd, 2H, Ar'-H). ^{13}C NMR ($CDCl_3$): 41.68 (1C, 4-C), 51.54 (1C, 5-C), 55.50 (2C, OCH$_3$), 114.26 (2C, Ar-C), 116.50 (2C, Ar-C), 116.64 (1C, CN), 120.64 (1C, Ar-C), 125.24 (1C, Ar-C), 128.40 (2C, Ar-C), 128.78 (2C, Ar-C), 129.46 (2C, Ar-C), 131.52 (2C, Ar-C), 132.63 (1C, Ar-C), 133.02 (1C, Ar-C), 142.66 (1C, 3-C), 143.70 (1C, Ar-C), 156.70 (1C, Ar-C). MS (relative abundance) m/z: 384 (MH^+, 100), 358 (20), 290 (34), 256 (20), 226 (18), 207 (28), 149 (20). Anal. Calcd. for $C_{24}H_{21}N_3O_2$: C, 75.18, H, 5.52, N, 10.96%; Found: C, 75.11, H, 5.50, N, 10.91%.

2.8. 3-(3,4-Dimethoxyphenyl)-4-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole-5-carbonitrile, 3g

Obtained as a light brown oil in 61% yield. IR (Nujol): 1655 (C=N str.), 2238 (C≡N str.) cm^{-1}. 1650–1675 cm^{-1}, 2220-2240 cm^{-1}. ^{1}H NMR ($CDCl_3$): 3.848 (s, 9H, OCH_3), 5.102 (d, 1H, C_4-H), 5.485 (d, 1H, C_5-H), 6.882 (dd, 2H, Ar-H), 7.524 (dd, 2H, Ar-H), 6.998–7.510 (m, 8H, Ar', Ar"-H). ^{13}C NMR ($CDCl_3$): 41.68 (1C, 4-C), 51.54 (1C, 5-C), 55.50 (2C, OCH$_3$), 114.26 (2C, Ar-C), 116.50 (2C, Ar-C), 116.64 (1C, CN), 120.64 (1C, Ar-C), 125.24 (1C, Ar-C), 128.40 (2C, Ar-C), 128.78 (2C, Ar-C), 129.46 (2C, Ar-C), 131.52 (2C, Ar-C), 132.63 (1C, Ar-C), 133.02 (1C, Ar-C), 142.66 (1C, 3-C), 143.70 (1C, Ar-C), 156.70 (1C, Ar-C). Anal. Calcd. for $C_{25}H_{23}N_3O_3$: C, 72.62, H, 5.61, N, 10.16%; Found: C, 72.56, H, 5.54, N, 10.11%.

2.9. 3-(Furan-2-yl)-4-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole-5-carbonitrile, 3h

Obtained as a light brown oil in 67% yield. IR (Nujol): 1670 (C=N str.), 2240 (C≡N str.) cm^{-1}. ^{1}H NMR ($CDCl_3$): 3.852 (s, 3H, OCH_3), 5.110 (d, 1H, C_4-H), 5.502 (d, 1H, C_5-H), 6.513–6.728 (d, 2H, Ar'-H), 6.898 (dd, 2H, Ar-H), 7.080-7.344 (m, 5H, Ar"-H), 7.326 (dd, 2H, Ar-H), 7.752 (d, 1H, Ar'-H). Anal. Calcd. for $C_{21}H_{17}N_3O_2$ (m/z 343.13): C, 73.45, H, 4.99, N, 12.24%; Found: C, 73.36, H, 4.93, N, 12.16%.

3. Results and discussion

The structures of the cycloadducts were provided by IR, ^{1}H NMR, ^{13}C NMR, and MS studies and elemental analysis. For instance, in the IR spectra, the cycloadducts **3** gave absorptions bands in the region of 1650–1675 cm^{-1} for the C=N (str) group and strong and sharp absorption bands in the region of 2220–2240 cm^{-1}

for CN (str), which supports the fact that the C-N triple bond of the CN group is unaffected during the cycloaddition reaction. In ^{1}H NMR spectra, all substituted-4,5-dihydropyrazole-5-carbonitriles **3** showed peaks due to aromatic and substituent protons in the expected region. The consistent pattern signals due to C_4-H appeared as doublet in the region δ 5.102–5.279 ppm while signals due to C_5-H appeared as doublet in the region δ 5.704–5.485 ppm. The coupling constant (J) values calculated for C_4-H and C_5-H were in range of 7.0–9.6 Hz, these values indicating that both C_4-H and C_5-H are in *cis* orientation. The appearance of these proton signals in the downfield was expected due to the strong electron withdrawing –CN group and the aromatic ring bonded to C_4- and C_5- atoms, respectively.

In ^{13}C NMR, all products gave signals due to aromatic and substituent carbons in the expected region. The signals due to newly formed C_4-carbon appeared in the region δ_c 41.56–41.88 ppm, while C_5-carbon showed the signals in the region δ_c 51.24–51.92 ppm. The signals due to the CN group carbon appear in the region δ_c 116.2–118.0 ppm, which shows that the CN triple bond is unaffected during cycloaddition and is retained in the product. The new compounds (**3a**–**3h**) gave significantly stable molecular ion peaks with a relative abundance ranging up to 40% and a base peak at (MH^+). Furthermore, all showed satisfactory CHN analysis with a deviation of $\pm$0.02% from the theoretically calculated values. All these observations strongly favor the formation of the cycloadducts.

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