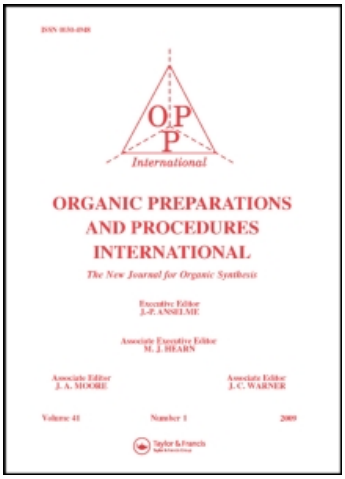

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PREPARATION OF 2-PHENYL-4-(1*H*-PYRAZOL-5-YL)QUINOLINES

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PREPARATION OF 2-PHENYL-4-(1*H*-PYRAZOL-5-YL)QUINOLINES

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(08/30/00)

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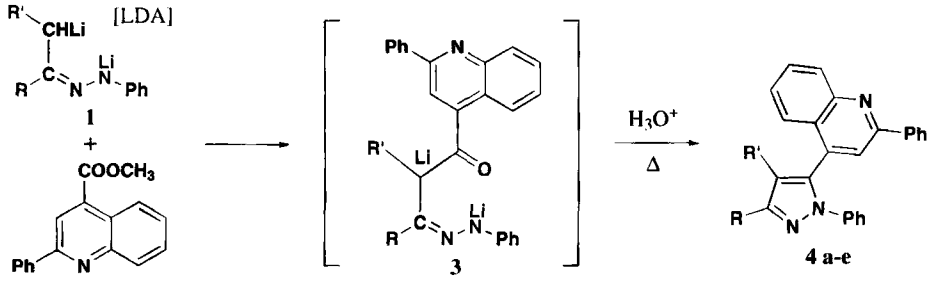
Although the synthesis and uses of 1*H*-pyrazoles are well documented[1], the study of unsymmetrical pyrazoles with heteroaromatic groups at the 3- or 5- position such as pyridinyl[2-11] or quinolinyl[12-17], imidazolyl[18] and others[19,20] has received only limited attention. The preparation of unsymmetrical pyrazoles, from the reactions of polylithiated hydrazones with esters[21] or related electrophilic reagents[22], has been the subject of continuing investigation in our group in order to explore the versatility of this method. The lithiated hydrazones have been condensed and cyclized with a variety of esters ranging from methyl benzoate[21] to lithiated ethyl benzoylacetate[22]. In each case, the *C*-acylated intermediates could be easily cyclized with aqueous hydrochloric acid. One of the major challenges that can be encountered in the one-pot synthesis procedure [3, 22, 23] is the cyclization of a *C*-acylated quinolinoyl intermediate **3** with an electron-withdrawing group conjugated with the carbonyl carbon; it has the potential of hindering the cyclization step. This problem is dealt with in this communication.

In the present study, the phenylhydrazones of 4-fluoro-, 4-chloro-, 4-bromo-, 4-methoxyacetophenone, and deoxybenzoin were dilithiated to **1** with excess LDA and condensed with methyl 2-phenyl-4-quinolinecarboxylate (**2**). This was followed by an acid-catalyzed cyclization to the desired substituted 1*H*-pyrazoles [2-phenyl-4(1*H*-pyrazol-5- yl)quinolines] **4a-e** in moderate to good yields.



a. R = 4-FC_6H_4; R' = H **b.** R = 4-ClC_6H_4; R' = H
c. R = 4-BrC_6H_4; R' = H **d.** R = 4-$CH_3OC_6H_4$; R' = H
e. R = C_6H_5; R' = C_6H_5

The most important experimental parameter was in the cyclization step (100 mL of aqueous hydrochloric acid was followed by an addition of another 100 mL of solvent grade tetrahydrofuran), where vigorous stirring of the two-phase system was essential. Thus the presence of the electron-withdrawing goup does not prevent reaction, and control can be exercised over the substituents at positions 1-, 3-, 4-, and 5- in the pyrazole by careful choice of reactants. In contrast, when dilithiated oximes[21] and carboalkoxyhydrazones[23] were treated with ester, only *C*-acylation occurred without cyclization.

EXPERIMENTAL SECTION

Melting points were obtained with a Mel-Temp II melting point apparatus in open capillary tubes and are uncorrected. Infrared spectra were obtained with a Nicolet Impact 410 FT-IR or a Mattson Genesis II FT-IR with Specac Golden Gate Accessory. Proton, ^{13}C, and ^{19}F NMR spectra were obtained with a Varian Associates Mercury Oxford 300 MHz, nuclear magnetic resonance spectrometer, and chemical shifts are recorded in δ ppm downfield from an internal tetramethylsilane (TMS) standard. Combustion analyses were performed by Quantitative Technologies, Inc., P.O. Box 470, Whitehouse, NJ 08888.

General Procedure for the Preparation of 2-Phenyl-4(1*H*-pyrazol-5-yl)quinolines (4).- To a three-neck round-bottomed flask (*e.g.*, 500 mL), equipped with a nitrogen inlet tube, a side-arm addition funnel (*e.g.*, 125 mL), and a magnetic stir bar, was added 20 mL of 1.6*M* *n*-butyllithium (31.5 mmol) in hexanes (0°) under N_2. The flask was cooled in an ice water bath and a solution of 3.20 g (31.5 mmol) of diisopropylamine [99.5% - Aldrich Chem. Co.], in 25-30 mL of dry THF freshly distilled from sodium, was added over a 5 min (0°, N_2) period. The solution was stirred for an additional 15-20 min, and then treated *via* the addition funnel, during 5 min, with the phenylhydrazone[24] (10 mmol) dissolved in 35-45 mL of THF. After 45-60 min, a solution of 2.91 g (10.5 mmol - 5% molar excess) of methyl 2-phenyl-4-quinolinecarboxylate [95% - Aldrich Chem. Co.] in 25-35 mL of THF, was added, during 5 min, to the dilithiated intermediate, and the solution was stirred for 45-60 min (0°, N_2). Finally, 100 mL of 3*N* hydrochloric acid was added all at once, followed by an additional 100 mL of solvent grade THF, and the two-phase mixture was stirred and heated under reflux for approximately 45-60 min. At the end of this period, the mixture was usually poured into a large flask (*ca.*, 1 or 2L) containing ice (*ca.*, 100 g), followed by the addition of 100 mL of solvent grade ether. The mixture was then rapidly and completely neutralized with solid sodium bicarbonate, and the layers were separated. The aqueous layer was extracted with ether (2x75 mL), and the organic fractions were combined, dried, filtered, evaporated, and the residue was recrystallized.

4-[3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazol-5-yl]-2-phenylquinoline (4a).- was obtained as pale yellow crystals, mp. 205-208° (methanol/benzene) in 45% yield [1.98g] using the general procedure from the condensation-cyclization of dilithiated 4-fluoroacetophenone phenylhydrazone and methyl 2-phenyl-4-quinolinecarboxylate. IR: 1596 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.21-7.53, 7.73-7.78, 8.01-8.19 (m, 20H, C_4-H, and ArH); ^{13}C NMR (DMSO- d_6): δ 108.0, 115.6, 115.9, 120.4, 124.3, 124.7, 127.2, 127.3, 127.5, 127.6 (2), 127.7, 128.3, 128.9, 129.0, 129.1, 129.6, 129.9, 130.3, 137.4, 138.0, 139.4, 140.0, 147.8, 150.4, 155.5, and 160.5 ppm. ^{19}F NMR (DMSO-d_6): δ -113.9 ppm.

Anal. Calcd for $C_{30}H_{20}FN_3$: C, 81.61; H, 4.57; N, 9.52. Found: C, 81.37; H, 4.53; N, 9.20

4-[3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-5-yl]-2-phenylquinoline (4b).- was obtained as pale yellow crystals, mp. 210-212° (methanol/benzene) in 48% yield [2.20g] using the general procedure from the condensation-cyclization of dilithiated 4-chloroacetophenone phenylhydrazone and methyl 2-phenyl-4-quinolinecarboxylate. IR: 1595 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.21-8.22 (m, ArH); ^{13}C NMR (DMSO-d_6): δ 108.2, 120.4, 124.3, 124.7, 125.0, 127.16, 127.20, 127.3, 127.8, 128.28, 128.91,

129.0, 129.7, 129.9, 130.3, 131.3, 132.8, 137.3, 138.0, 139.3, 140.1, 147.8, 150.2, and 155.5 ppm.

Anal. Calcd for $C_{30}H_{20}ClN_3$: C, 78.68; H, 4.40; N, 9.18. Found: C, 78.65; H, 4.64; N, 9.00

4-[3-(4-Bromophenyl)-1-phenyl-1*H*-pyrazol-5-yl]-2-phenylquinoline (4c).- was obtained as pale yellow crystals, mp. 204-207° (ethanol/benzene) in 60% yield [3.01 g] using the general procedure from the condensation-cyclization of dilithiated 4-bromoacetophenone phenylhydrazone and methyl 2-phenyl-4-quinolinecarboxylate. IR: 1595 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.21-8.19 (m, ArH); ^{13}C NMR (DMSO-d_6): δ 108.2, 120.5, 121.4, 124.3, 124.7, 127.18, 127.2, 127.3, 127.5, 127.8, 128.3, 128.9, 129.1, 129.7, 129.9, 130.3, 131.7, 131.8, 137.3, 138.0, 139.3, 140.1, 147.8, 150.3, and 155.6 ppm.

Anal. Calcd for $C_{30}H_{20}BrN_3$: C, 71.72; H, 4.01; N, 8.36. Found: C, 71.96; H, 3.78; N, 8.24

4-[3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-5-yl]-2-phenylquinoline (4d).- was obtained as pale yellow crystals, mp. 172-174° (methanol/benzene) in 58% yield [2.63 g] using the general procedure from the condensation-cyclization of dilithiated 4-methoxyacetophenone phenylhydrazone and methyl 2-phenyl-4-quinolinecarboxylate. IR: 1595 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.82 (s, 3H, OCH_3), 7.04-7.07, 7.21-7.37, 7.48-7.56, 7.74-7.79, 7.94-8.22 (m, 20H, C_4-H and ArH); ^{13}C NMR (DMSO-d_6): δ 55.2, 107.6, 114.2, 120.3, 124.1, 124.8, 124.99, 125.04, 126.9, 127.17, 127.23, 127.5, 128.9, 129.0, 129.6, 129.9, 130.2, 137.6, 138.1, 139.5, 139.7, 147.8, 151.2, 155.5, and 159.3 ppm.

Anal. Calcd for $C_{31}H_{23}N_3O$: C, 82.10; H, 5.11; N, 9.26. Found: C, 82.02; H, 5.36; N, 9.02

2-Phenyl-4-(1,3,4-triphenyl-1*H*-pyrazol-5-yl)quinoline (4e).- was obtained as pale yellow crystals, mp. 192-194° (ethanol/benzene) in 72% yield [3.59 g] using the general procedure from the condensation-cyclization of dilithiated deoxybenzoin phenylhydrazone and methyl 2-phenyl-4-quinolinecarboxylate. IR: 1596 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.14-7.70, 8.00- 8.31 (m, ArH); ^{13}C NMR (DMSO-d_6): δ 121.9, 122.3, 124.3, 124.9, 125.3, 127.16, 127.22, 127.3, 127.7, 127.8, 128.0, 128.3, 128.4, 128.90, 128.95, 129.5, 129.8, 129.9, 130.2, 132.2, 132.5, 137.2, 137.8, 137.9, 139.3, 147.4, 149.1, and 155.4 ppm.

Anal. Calcd for $C_{36}H_{25}N_3$: C, 86.55; H, 5.04; N, 8.41. Found: C, 86.26; H, 4.93; N, 8.37

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A PRACTICAL METHOD FOR THE SYNTHESIS OF PHENOPHTHALEIN SPIROLACTAMS

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(7/12/2000)

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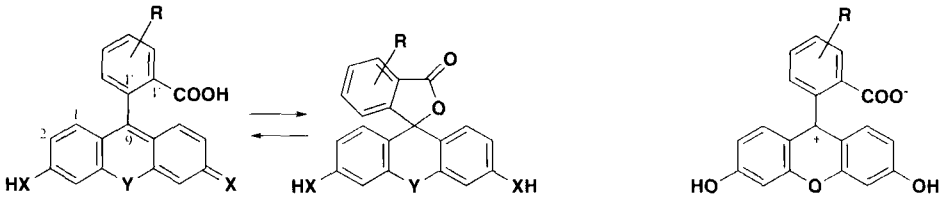
Since their synthesis in the late 1800s, various dyes have been utilized in many biotechnological applications.[1] Of these dyes, the fluoresceins are the most commonly used labels due to their solubility in aqueous buffers and high fluorescence quantum yield at physiological pH,[2] although the rhodamines are prized for their great photostability, pH insensitivity over a broad range (low to neutral pH), and the ability of their fluorescence characteristics to be tailored for a particular application by changing ring and nitrogen substituents.[2] Traditionally, these dyes have been viewed to exist in two pH dependent forms: a highly colored open, quinone form and a nearly colorless, closed, spirolactone form (see below),[3] although more recently a third zwitterionic structure has been postulated for fluorescein in aqueous solution.[4,5]



(rhodamine: X = NH, RN, Y = O; fluorescein: X = Y = O