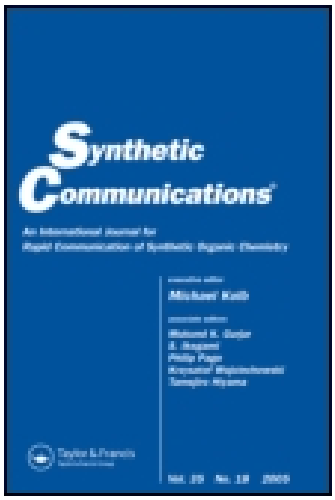


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

SYNTHESIS OF PYRAZOLE DERIVATIVES 4(1H)-QUINOLONE AND 4-CHLOROQUINOLINE BY THERMOLYSIS OF ARYLAMINOMETHYLENE MELDRUM's ACID DERIVATIVE

Lizeng Peng [a] , Tao Zhang [a] , Ying Li [a] & Yulin Li [a]

[a] National Laboratory of Applied Organic Chemistry , Institute of Organic Chemistry , Lanzhou University , Lanzhou, Gansu, 730000, P.R. China

Published online: 16 Aug 2006.

To cite this article: Lizeng Peng , Tao Zhang , Ying Li & Yulin Li (2002) SYNTHESIS OF PYRAZOLE DERIVATIVES 4(1H)-QUINOLONE AND 4-CHLOROQUINOLINE BY THERMOLYSIS OF ARYLAMINOMETHYLENE MELDRUM's ACID DERIVATIVE, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:5, 785-791, DOI: 10.1081/SCC-120002520

To link to this article: http://dx.doi.org/10.1081/SCC-120002520

SYNTHETIC COMMUNICATIONS, 32(5), 785–791 (2002)

SYNTHESIS OF PYRAZOLE DERIVATIVES 4(1H)-QUINOLONE AND 4-CHLOROQUINOLINE BY THERMOLYSIS OF ARYLAMINOMETHYLENE MELDRUM'S ACID DERIVATIVE

Lizeng Peng, Tao Zhang, Ying Li, and Yulin Li*

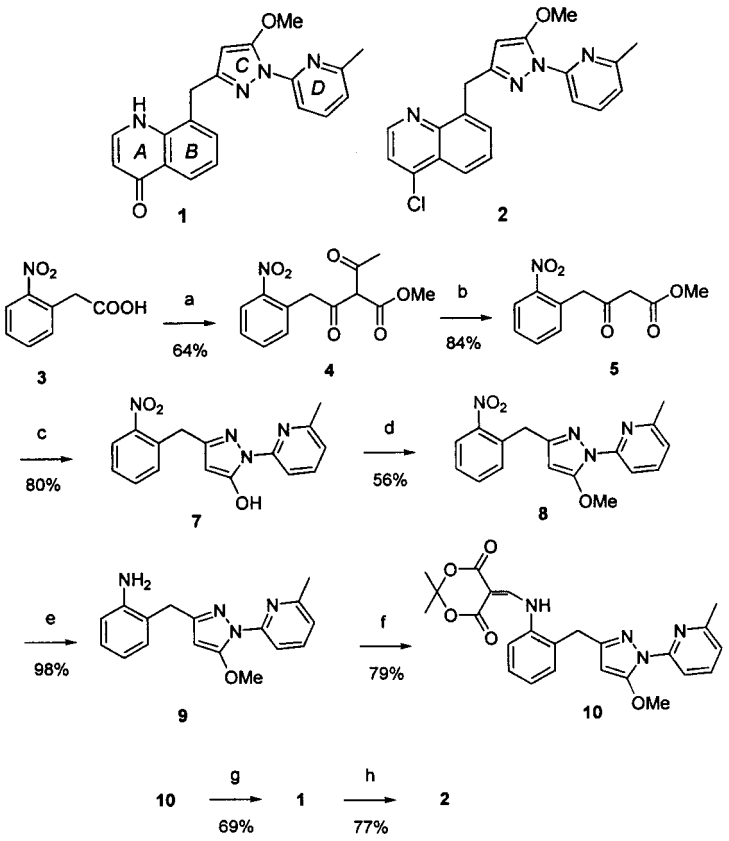
National Laboratory of Applied Organic Chemistry,
Institute of Organic Chemistry, Lanzhou University,
Lanzhou, Gansu 730000, P.R. China

ABSTRACT

Efficient syntheses of 4(1H)-quinolone **1** and 4-chloroquinoline **2** by thermolysis of arylaminomethylene Meldrum's acid derivative starting from 2-nitrophenyl acetic acid.

The search for new immunomodulating drugs is an active area of investigation in medicinal chemistry. Recently, the synthesis and immunomodulating effects of quinolines containing a pyrazole ring have been described.[1] Concerning our interest in the synthesis and chemistry of quinolones, we have finished the synthesis of a novel type of pyrazole derivatives 4(1H)-quinolone **1** and 4-chloroquinolone **2** that can be structurally compared to analogous compounds of known immunomodulatory activity.[1]

*Corresponding author. E-mail: liyl@lzu.edu.cn



Scheme 1. Reagents and conditions: a) 1. $SOCl_2$, toluene, r.t.; 2. methyl acetoacetate, NaH, THF, r.t. b) MeONa, MeOH, r.t.; c) 1. 2-(6-methyl)pyridyl hydrazine (**6**), MeOH, reflux; 2.MeONa, r.t.; d) 1. NaOH, H_2O, 0.5 h; 2) $AgNO_3$, 1 h; 3. MeI, THF, reflux, 3 h; e) H_2, Pd/C (10%), r.t.; f) Meldrum's acid, $CH(OMe)_3$, reflux; g) Ph_2O, reflux, 40 min; h) $POCl_3$, 80°C, 2 h.

The synthesis involves the construction of B-C-D ring system and subsequent quinolone cyclization as shown in Scheme 1. Condensation[2] of 2-nitrophenyl acetyl chloride derived from acid **3** with methyl acetoacetate was followed by deacetylation of resulting **4** with sodium methoxide to give the corresponding ketoester **5**, which was coupled[3] with 2-(6-methyl)pyridyl hydrazine **6**[4] in boiling MeOH to give the desired pyrazole **7**. Methylation[5] of silver alkoxide of **7** with methyl iodide afforded methoxy pyrazole **8** in 56% yield that was converted to amino compound **9** (98%) by catalytic

hydrogenation in methanol. Condensation[6] of **9** with one equivalent of methoxymethylene Meldrum's acid (prepared in situ by refluxing with methylorthoformate) to give the desired arylaminomethylene Meldrum's acid derivative **10**. Cyclization[7] of **10** in boiling diphenyl ether and subsequent recrystallization of the crude product from MeOH to afford quinolone **1**. Treatment[8] of **1** with $POCl_3$ at 80°C furnished chloride **2** in good yield (77%). The spectroscopic properties of synthetic products **1** and **2** were in good agreement with their assigned structures respectively.

EXPERIMENTAL

Melting points were measured on a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on a Nicolet 170 FT-IR spectrophotometer as a KBr discs. ^{1}H NMR spectra were recorded on a Bruker AM-400 instrument in a $CDCl_3$ solution with TMS as an internal standard. Low-resolution mass spectra were measured on an HP-5988 mass spectrometer and high-resolution mass spectra (HRMS) were determined on a Bruker Daltonics APEXII 47e Fourier Transfer spectrometer with any of EI, CI, FAB, SIMS or MALDI ionization methods. Purification of reagents and solvents was effected according to standard methods. Prior to concentration under reduced pressure, all extracts were dried over anhydrous Na_2SO_4. Flash column chromatography was performed on silica gel (200–300 mesh) purchased from Qing Dao Marine Chemical Co (Qingdao, China).

Methyl 2-Nitrophenylacetyl Acetoacetate (4)

Methyl acetoacetate (4.53 ml, 42 mmol) in dry THF (50 ml) was added dropwise to a stirred suspension of sodium hydride (60% suspension in oil, 1.96 g, 49 mmol) in THF (100 ml). The mixture was stirred for 2 h at room temperature and was treated with 2-nitrophenyl acetyl chloride prepared from 2-nitrophenyl acetic acid **3** (3.62 g, 20 mmol) and thionyl chloride (1.53 ml, 21 mmol) in 100 ml of anhydrous toluene. The resulting mixture was stirred for 16 h at room temperature. It was poured into water and extracted with ether (3×100 ml). The combined organic phases was dried and concentrated under reduced pressure. The residue was dissolved in 50 ml of methanol and allowed to stand in a freezer overnight to give **4** as yellow crystals (3.57 g, 64%), m.p. 74–75°C. IR (cm^{-1}): 2956, 2854, 1712, 1525, 1343, 1086, 790, 720; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H, $COCH_3$); 3.85 (s, 3H, $COOCH_3$); 4.52 (s, 2H, CH_2); 7.34 (d, $J = 7.4$ Hz,

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

1H, ArH); 7.50 (d, $J = 8.4$ Hz, 1H, ArH); 7.6 (d, $J = 7.4$ Hz, 1H, ArH); 8.12 (d, $J = 8.4$ Hz, 1H, ArH); EIMS (70 eV): m/z (%) 279 (27) [M^+].

Methyl 4-(2-Nitrophenyl)-3-oxobutyrate (5)

A solution of **4** (3.57 g, 12.8 mmol) in MeOH (30 ml) was treated with NaOMe (1.38 g, 25.6 mmol). After stirring for 2 h at r.t. the solvent was evaporated under vacuum and the residue was purified by column chromatography to give **5** (2.55 g, 84%). M.p. 54–55°C (MeOH). IR (cm^{-1}): 2954, 2850, 1710, 1525, 1353, 801, 732; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.66 (s, 2H, CH_2); 3.78 (s, 3H, $COOCH_3$): 4.25 (s, 2H, $ArCH_2$); 7.32 (d, $J = 7.2$ Hz, 1H, ArH); 7.48 (d, $J = 8.2$ Hz, 1H, ArH); 7.62 (d, $J = 7.2$ Hz, 1H, ArH); 8.14 (d, $J = 8.2$ Hz, 1H, ArH). EIMS (70 eV): m/z (%) 237 (40) [M^+].

1-(6-Methyl-2-pyridyl)-3-[(nitrophenyl)-methyl)]-1H-pyrazol-5-ol (7)

A mixture of **5** (2.55 g, 10.8 mmol), **6** (1.33 g, 10.8 mmol) in 20 ml of anhydrous MeOH was stirred under reflux at Ar atmosphere for 3 h. The oil bath was removed and MeONa (583 mg, 10.8 mmol) was added to the mixture and stirring continued for 3 h. At 0°C, AcOH (5 ml) was added slowly at 0°C and the precipitates was collected and dried to give **7** (2.68 g, 80%). M.p. 121–122°C. IR (cm^{-1}): 2867, 2697, 1602, 1525, 1479, 1398, 1353, 801, 753; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.53 (s, 3H, $COCH_3$); 4.28 (s, 2H, CH_2); 5.41 (s, 1H, CH); 6.97 (d, $J = 7.5$ Hz, 1H, ArH); 7.41 (d, $J = 8.0$ Hz, 1H, ArH); 7.44 (d, $J = 7.5$ Hz, 1H, ArH); 7.53 (t, $J = 7.5$ Hz, 1H, ArH); 7.62 (d, $J = 8.3$ Hz, 1H, ArH); 7.73 (t, $J = 8.0$ Hz, 1H, ArH); 7.96 (d, $J = 8.3$ Hz, 1H, ArH); EIMS (70 eV): m/z (%) 310 (100) [M^+].

2-[[5-Methoxy-3-(2-nitrophenyl)-1H-pyrazol-1-yl]-6-methyl]pyridine (8)

A mixture of **7** (2.68 g, 8.6 mmol) and NaOH (346 mg, 8.6 mmol) in H_2O (10 ml) was stirred for 0.5 h. The reaction mixture was treated with a solution of $AgNO_3$ (1.75 g, 10.3 mmol) in H_2O (10 ml), and the resulting mixture was stirred for 2 h at room temperature. After filtration of the reaction mixture, the resulting solid residue was taken up in 40 ml of dry THF and treated with 2 ml of MeI and brought to reflux for 3 h, filtered. The filtrate was concentrated and purified by column chromatography to give **8**

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

as foam (1.49 g, 56%). IR (cm^{-1}): 3410, 1601, 1574, 1526, 1456, 1350, 1101, 792; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.61 (s, 3H, CH_3; 3.89, (s, 3H, OCH_3; 4.32 (s, 2H, CH_2); 5.50 (s, 1H, CH); 7.07 (d, $J = 7.6$ Hz, 1H, ArH); 7.37 (t, $J = 8.0$ Hz, 1H, ArH); 7.40 (d, $J = 7.6$ Hz, 1H, ArH); 7.50 (t, $J = 7.6$ Hz, 1H, ArH); 7.52 (d, $J = 8.3$ Hz, 1H, ArH); 7.66 (t, $J = 8.0$ Hz, 1H, ArH); 7.96 (d, $J = 8.3$ Hz, 1H, ArH); EIMS (70 eV): m/z (%) 324 (18) [M^+].

2-[[5-Methoxy-1-(6-methyl-2-pyridyl)-1H-pyrazol-3-yl]methyl]benzenamine (9)

A mixture of the compound **8** (1.49 g, 4.6 mmol), Pd/C (10%, 345 mg) in MeOH (60 ml) was stirred with H_2 (1 atm.) at r.t. for 4 h. The mixture was filtered and the resulting filtrate was concentrated under reduced pressure to leave the product, compound **9** as foam (1.33 g, 98%). The crude amino product was used for the next operation without further purification. An analytical sample was obtained by column chromatography. IR (cm^{-1}): 3349, 1598, 1572, 1497, 1454, 1149, 1010, 794, 749; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.59 (s, 3H,CH_3); 3.82, (s, 3H, OCH_3; 3.88 (s, 2H, CH_2); 5.14 (br, 2H, CH_2); 5.42 (s, 1H, CH); 6.63 (d, $J = 7.2$ Hz, 1H, ArH); 6.72 (t, $J = 7.2$ Hz, 1H, ArH); 7.04 (d, $J = 7.5$ Hz, 1H, ArH); 7.06 (t, $J = 7.5$ Hz, 1H, ArH); 7.15 (d, $J = 7.5$ Hz, 1H, ArH); 7.39 (d, $J = 7.8$ Hz, 1H, ArH); 7.63 (t, $J = 7.5$ Hz, 1H, ArH); EIMS (70 eV) m/z (%): 294 (100) [M^+]. (Found (HRMS) (ESI): $M^+ + H$, 295.1549. $C_{17}H_{18}N_4O + H$ requires $M^+ + H$ 295.1553.)

1-[(4′,4′-Dimethyl-2′,6′-dioxo-3′,5′-dioxan-1′-yl)methylene amino]-2-[[5-methoxy-1-(6-methyl-2-pyridyl)-1H-pyrazol-3-yl]methyl]benezenamine 10

A mixture of 710 mg (5 mmol) of Meldrum's acid and methylorthoformate (20 ml) was refluxed for 2 h. The amino compound **9** (1.33 g, 4.5 mmol) was added and the heating continued for further 2 h. The solvent was evaporated under reduced pressure and the residue purified by column chromatography to give **10** (1.69 g, 79%). IR (cm^{-1}): 3161, 2991, 1729, 1682, 1622, 1594, 1438, 1271, 1202, 1144, 1012, 932, 797, 732; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73 (s, 6H, $2 \times OCH_3$); 2.59 (s, 3H, CH_3); 3.91 (s, 3H, OCH_3); 4.06 (s, 2H, CH_2); 5.53 (s, 1H, CH); 7.05 (d, $J = 7.6$ Hz, 1H, ArH); 7.27 (t, $J = 7.6$ Hz, 1H, ArH); 7.30 (d, $J = 7.6$ Hz, 1H, ArH); 7.34 (t, $J = 7.6$ Hz, 1H, ArH); 7.39 (d, $J = 7.6$ Hz, 1H, ArH); 7.50 (d, $J = 7.6$ Hz, 1H, ArH); 7.66 (t, $J = 7.6$ Hz, 1H, ArH); 8.54 (d, $J = 14.1$ Hz, 1H, NHC*H*);

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

11.49 (d, $J = 14.1$ Hz, 1H, N*H*CH); EIMS (70 eV) m/z (%): 476 (4) [M^+]. (Found (HRMS) (ESI): $M^+ + H$, 449.1818. $C_{24}H_{24}N_4O_5 + H$ requires $M^+ + H$ 449.1819).

8-[[5-Methoxy-1-(6-methyl-2-pyridyl)-1H-pyrazole-3-yl]methyl]-4(1H)-quinolone (1)

A suspension of the amino compound **10** (1.69 g, 3.56 mmol) in Ph_2O (20 ml) was heated under reflux for 40 min. After cooling, the mixture was diluted with 120 ml of light petroleum ether. The resulting precipitate was collected and recrystallized from MeOH to give **1** (690 mg, 69%). M.p. 223–224°C. IR (cm^{-1}): 3237, 2927, 1725, 1569, 1522, 1455, 1199, 1147, 1013, 792, 732; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.48 (s, 3H, CH_3); 3.83 (s, 3H, OCH_3); 4.16 (s, 2H, CH_2); 5.69 (s, 1H, CH); 6.06 (d, $J = 7.5$ Hz, 1H, ArH); 7.20 (t, $J = 7.5$ Hz, 1H, ArH); 7.26 (d, $J = 8.0$ Hz, 1H, ArH); 7.34 (d, $J = 8.0$ Hz, 1H, ArH); 7.51 (d, $J = 7.5$ Hz, 1H, ArH); 7.79 (t, $J = 7.5$ Hz, 1H, ArH); 7.85 (t, $J = 7.6$ Hz, 1H, ArH); 8.01 (d, $J = 7.6$ Hz, 1H, ArH); 11.27 (br, s, 1H, NH); EIMS (70 eV): m/z (%) 346 (100) [M^+]. (Found (HRMS) (ESI): $M^+ + H$, 347.1503. $C_{20}H_{18}N_4O_2 + H$ requires $M^+ + H$ 347.1503).

4-Chloro-8-[[5-methoxy-1-(6-methy-2-pyridyl)-1H-pyrazol-3-yl]-methyl]-quinoline (2)

A suspension of **1** (200 mg, 0.57 mmol) in $POCl_3$ (6 ml) was stirred under reflux for 3 h. The reaction mixture was cooled and poured onto ice (20 g), neutralized with sat aq. $NaHCO_3$ and extracted with CH_2Cl_2 (2×50 ml). The combined organic extracts were washed with sat aq. $NaHCO_3$, brine, and dried. The solvent was evaporated under reduced pressure and the residue purified by column chromatography to give **2** (120 mg, 77%). M.p. 127–128°C. IR (cm^{-1}): 3391, 2926, 1593, 1572, 1492, 1455, 1386, 1143, 1013, 794; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 (s, 3H, CH_3); 3.83 (s, 3H, OCH_3); 4.71 (s, 2H, CH_2); 5.43 (s, 1H, CH); 7.06 (d, $J = 7.5$ Hz, 1H, ArH); 7.44 (t, $J = 8.0$ Hz, 1H, ArH); 7.53 (d, $J = 4.8$ Hz, 1H, ArH); 7.57 (t, $J = 8.0$ Hz, 1H, ArH); 7.65 (t, $J = 8.0$ Hz, 1H, ArH); 7.74 (d, $J = 8.0$ Hz, 1H, ArH); 8.15 (t, $J = 8.0$ Hz, 1H, ArH); 8.86 (d, $J = 4.8$ Hz, 1H, ArH); EIMS (70 eV) m/z (%): 364 (100) [M^+], 366 (33) [$M^+ + 2$] (Found (HRMS) (ESI): $M^+ + H$, 365.1172. $C_{20}H_{17}ClN_4O_2 + H$ requires $M^+ + H$ 365.1164).

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

REFERENCES

1. Ismaili, L.; Refouvelet, B.; Robert, J.F. Synthesis of New Pyrazolo-[4,3-c]quinolin-3-one Derivatives and Some Oxazolo[4,5-c]quinoline-2,4-diones. J. Heterocycl. Chem. **1999**, *36*(3), 719–722 and references cited therein.
2. Somanathan, R.; Smith, K.M. Synthesis of Some 2-Alkyl-4-quinolone and 2-Alkyl-4-methoxyquinline Alkaloids. J. Heterocycl. Chem. **1981**, *18*(6), 1077–1079.
3. DeRuiter, J.; Carter, D.A.; Arledge, W.S.; Sullivan, P. Synthesis and Reactions of 4-Isopropylidene-1-aryl-3-methyl-2-pyrazolin-5-ones. J. Heterocycl. Chem. **1987**, *24*(1), 149–153.
4. Craig, L.C. A Study of the Preparation of Alpha-Pyridyl Halides from Alpha-Aminopyridyl by the Diazo Reaction. J. Am. Chem. Soc. **1934**, *56*(1), 231–232.
5. Kasahara, I.; Iihama, T.; Sugiura, T.; Hashimoto, S.; Sano, S.; Hosokawa, H.; Yokota, C. Preparation of Pyrazole Derivatives and Agrochemical Fungicides. Japanese Patent 93 07,138, April 15, 1993; Chem. Abstr. **1994**, *120*, 106997s.
6. Gomez-Bengoa, E.; Echavarren, A.M. Synthesis of Isoascididemin, A Regioisomer of the Marine Alkaloid Ascididemin. J. Org. Chem. **1991**, *56*(11), 3497–3501.
7. Cassis, R.; Tapia, R.; Valderrama, J.A. Syntheses of 4(1H)-Quinolone by Thermolysis of Arylaminomethylene Meldrum's Acid Derivatives. Synth. Commun. **1985**, *15*(2), 125–133.
8. Todter, C.; Lackner, H. Syntheses of Azabenzisochromanequinone Antibiotics, II: 9(6)-Hydroxy-6(9)-azabenzisochromanequinones via Aminoisochromanes and Meldrum's Acid. Synthesis **1997**, (*5*), 567–572.

Received in Japan November 17, 2000

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016