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NOVEL PROCESS TO 4,4-DIALKYL-1,4-DIHYDRO-6-METHOXY-3-PHENYLCINNOLINES *VIA* GRIGNARD REACTION

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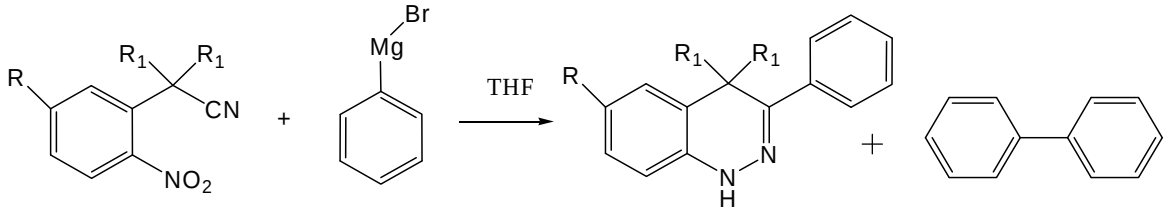
Abstract – 4,4-Dialkyl-1,4-dihydro-6-methoxy-3-phenylcinnolines were obtained from 2-(5-methoxy-2-nitrophenyl)acetonitrile analogues and phenylmagnesium bromide by one step, and the possible mechanism was speculated.

Cinnolines have been used as Liver-X receptor modulators, cell proliferation inhibitors, antitumor agents, and anti-inflammatory agents recently.[1] H. S. Lowrie synthesized 3-phenylcinnoline-4-carboxylic acids *via* Stolle-Becker cinnoline synthesis.[2] Yoshio Matsubara synthesized cyanocinnolines from aromatic hydrazones and TCNE,[3] and 4(1*H*)-cinnolones from 4-cyancinnolines,[4] as well as some other processes to synthesize cinnolines.[5-8] To the best of our knowledge, there are very limited reports describing the preparation of dihydrocinnolines.[9,10]

In our estrogen receptor β ligands research, we found a new method to synthesis 4,4-dialkyl-1,4-dihydro-6-methoxy-3-phenylcinnoline with the biphenyl as the byproduct from 2-(5-methoxy-2-nitrophenyl)acetonitrile analogues with the phenylmagnesium bromide in THF solution at ice bath, When we used alkylmagnesium bromide or benzylmagnesium bromide instead of phenylmagnesium bromide, we didn't get the object 1,4-dihydro-3-substituted-cinnoline.

The results were summarized in Table 1. It appears that several important factors are involved in this reaction. 1) One opposite methoxy to the nitro group on the benzene ring is important, which is supposed as an electron donor that makes nitro's eletrophilic ability weaker than the nitrile. 2) The dialkyl substitutes of the o-nitro phenylacetonitrile are important, which enlarge the steric hindrance to reduce the free rotation of nitrile to force the reaction between the nitrile and nitro groups. And the bulky groups are preferable. 3) A proper temperature is also important to get a higher yield.

This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.



1a-9a **1b-9b**

Table 1. Reaction conditions of *o*-nitro phenylacetonitriles and phenylmagnesium bromide

	R	R_1	Centigrade(^{0}C)	Time	Yield(%)
1	H	H	0	2	0
2	H	-CH_2-	0	2	0
			-78	2	0
3	OMe	-CH_2-	0	2	34
			-78	2	30
			20	2	10
4	OMe	Me	0	1.5	20
5	OMe	Et	0	2	62
6	OMe	*n*-Bu	0	2	50
7	OMe	*n*-Oct	0	2	58
8	OMe	benzyl	0	3	12
			-78	4	trace
9	OMe	allyl	0	3	trace
			-78	3	0

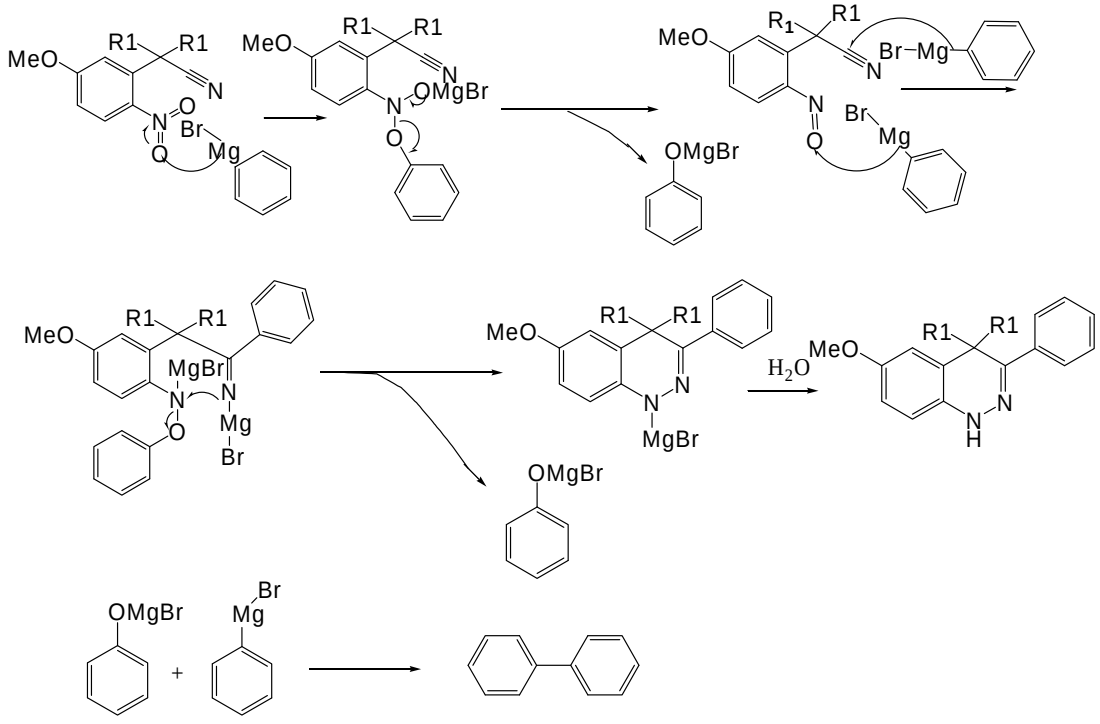


Figure 1. Possible mechanism to 4,4-dialkyl-1,4-dihydro-3-phenylcinnolines

We also evaluated their anti-cancer activities. The cytotoxicity of these cinnolines was conveniently determined by the conventional MTT assay against HL-60 cell line and sulforhodamine B (SRB)-assay against A-549 (human lung carcinoma). Compound 6b, 7b and 8b showed moderate inhibition to HL-60 cell line.

EXPERIMENTAL

GENERAL PROCEDURE

To the solution of phenylmagneium bromide (8 mmol) in THF (20 mL) in ice bath, the solution of 1-(5-methoxy-2-nitrophenyl)cyclopropanecarbonitrile (**3a**) (218mg, 1 mmol) in THF (20 mL) was added drop by drop at stirring for 5-10 min. The mixture was stirred for additional 2 h and then poured into water (20 mL). The organic phase was separated, and the water phase was extracted with EtOAc (20 mL $\times$2). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated. Purification of the residue by column chromatography (silica gel CH_2Cl_2 : MeOH 15:1) and get (**3b**) 90 mg, yield 34%.

6-Methoxy-3-phenyl-1*H*-spiro[cinnoline-4,1'-cyclopropane] (3b)

^{1}H NMR (CD_3OD) δ_H: 1.66 (sym, 4H), 3.69 (s, 3H), 6.45 (d, 1H, J = 8.6Hz), 6.54 (d, 1H, J = 2.4Hz), 6.60 (dd, 1H, J = 8.5 Hz, J = 2.4Hz), 7.31 (m, 2H), 7.43 (m, 1H), 7.55 (m, 2H); ^{13}C NMR (CD_3OD)δ_C: 21.592, 22.272, 55.722, 105.518, 107.769, 110.738, 124.348, 127.867, 130.039, 133.022, 135.550, 138.897, 155.243, 169.753; IR 3293.9 (NH), 2933.2 (CH_3), 1650.8 (C = N), 1598.7 (Ph), 1484.9 (Ph), 1388.5, 1292.1, 1201.5, 1033.7, 757.9, 698.7 (Ph); MS (EI): 57(10) 77(11) 107(30) 221(18.8) 249(16) 263(46) 264(100) 265(18).

1,4-Dihydro-6-methoxy-4,4-dimethyl-3-phenylcinnoline (4b)

^{1}H NMR (CD_3OD) δ_H:1.50 (s, 6H), 3.75 (s, 3H), 6.45 (d, 1H, J = 8.6Hz), 6.70 (dd, 1H, J = 8.5Hz, J = 2.4Hz), 6.95 (d, 1H, 2.4Hz), 7.39 (m, 2H), 7.50 (m, 1H), 7.60 (m, 2H); ^{13}C NMR (CD_3OD) δ_C: 27.462, 47.227, 56.782, 110.427, 111.279, 113.966, 129.241, 130.284, 132.019, 137.002, 139.163, 139.383, 158.206, 178.236; IR 3423.1 (NH), 2973.7, 2927.5, 1650.8 (C = N), 1598.7 (Ph), 1496.5(Ph), 1432.9, 1384.7, 1278.6. 1201.5, 1027.9, 808.1, 696.2; MS 77(8) 224(10) 236(12) 250(10) 251(85) 265(58) 266(100) 267(20); HRMS calculated for $C_{17}H_{18}ON_2$: 266.1419 and found $[M-H]^+$ 265.1345, M^+ 266.1408, $[M+H]^+$ 267.1424.

4,4-Diethyl-1,4-dihydro-6-methoxy-3-phenylcinnoline (5b)

^{1}H NMR (CD_3OD) δ_H: 0.7 (t, 3H, J = 7.4Hz), 1.95 (q, 2H, J = 7.3Hz), 3.75 (s, 3H), 6.45 (d, 1H, J = 8.5Hz), 6.70 (dd, 1H, J = 8.4Hz, J = 2.4Hz), 6.85 (d, 1H, 2.5Hz), 7.31 (m, 2H), 7.48 (m, 1H), 7.60 (m, 2H); ^{13}CNMR (CD_3OD) δ_C: 9.563, 34.462, 56.750, 57.174, 109.717, 111.470, 113.848, 129.318, 130.097, 131.987, 134.925, 137.375, 141.765, 158.011, 175.645; IR 3293.9 (NH), 2962.2, 2929.4, 1650.8 (C = N),

1598.7 (Ph), 1498.4 (Ph), 1272.8. 1201.5, 804.2, 694.3; MS 235(11) 249(12) 250(15) 251(99) 252(17) 265(69) 266(100) 267(17) 294 (75) 295(15); HRMS calculated for $C_{19}H_{22}ON_2$: 294.1732, found M^+294.1733, $[M+H]^+$ 295.1753.

4,4-Dibutyl-1,4-dihydro-6-methoxy-3-phenylcinnoline (6b)

^{1}H NMR (CD_3OD) δ_H: 0.7 (m, 8H), 1.2 (m, 6H), 1.9 (m, 4H), 3.75 (s, 3H), 6.45 (d, 1H, J = 8.8Hz), 6.50 (dd, 1H, J = 8.5Hz, J = 2.4Hz), 6.85 (d, 1H, J = 2.3Hz), 7.30 (m, 2H), 7.46 (m, 1H), 7.60 (m, 2H); ^{13}C NMR (CD_3OD) δ_C: 14.677, 24.237, 27.912, 41.129, 56.851, 111.007, 111.417, 114.227, 128.960, 131.123, 132.394, 135.755, 135.978, 140.555, 158.978, 176.380; IR 3293.9 (NH), 2929.4, 2871.5, 1648.9 (C = N), 1598.7(Ph), 1484.9(Ph), 1376.9, 1276.7, 1199.5, 802.3, 696.2, 609.4; MS 251(100) 252(18) 265(12) 294(49) 307(43) 350(27)351(7); HRMS calculated for $C_{23}H_{30}ON_2$: 350.2358, found M^+ 350.2353 $[M+H]^+$ 351.2393.

1,4-Dihydro-6-methoxy-4,4-dioctyl-3-phenylcinnoline (7b)

^{1}H NMR (CD_3OD) δ_H: 0.85 (t, 6H, J = 6.8Hz), 1.2 (m, 24H), 1.85 (t, 4H, J = 8.2Hz), 3.75 (s, 3H), 6.47 (d, 1H, J = 8.8Hz), 6.75 (dd. 1H, J = 8.5Hz, J = 2.7Hz), 6.9 (d, 1H, J = 2.5Hz), 7.31 (m, 2H, 7.50 (m, 1H), 7.62 (m, 2H); ^{13}C NMR (CD_3OD) δ_C: 14.913, 24.203, 25.719, 30.742, 30.806, 31.116, 33.406, 41.708, 56.231, 56.763, 110.135, 110.447, 113.829, 129.152, 130.405, 132.117, 135.810, 136.876, 141.152, 158.293, 176.226; IR 3291.9 (NH), 2960.2, 2925.5, 2854.2, 1650.8 (C = N), 1600.7 (Ph), 1484.9 (Ph), 1261.2, 1031.7, 800.3, 696.2; MS 59(12) 97(10) 251(100) 252(18) 294(23) 327(30) 350(48) 363(40) 462(17) 463(5); HRMS calculated for $C_{31}H_{47}ON_2$: 462.3610, found M^+ 462.3616 $[M+H]^+$ 463.3682.

4,4-Dibenzyl-1,4-dihydro-6-methoxy-3-phenylcinnoline (8b)

^{1}H NMR (CD_3OD) δ_H: 3.4 (sym, 4H) 3.80 (s, 3H), 5.86 (d, 1H, J = 8.4Hz), 6.46 (m, 2H), 6.55 (dd, 1H, J = 8.6Hz, J = 2.6Hz), 6.96 (m, 4H), 7.08 (m, 6H), 7.2 (d, 1H, J = 2.6Hz), 7.35 (m, 3H); IR 3432.7 (NH), 2919.7, 2850.3, 1645.0 (C = N), 1602.6 (Ph), 1496.5 (Ph), 1384.7, 1209.2, 1029.8, 698.1; MS 59(7) 295(5) 327(100) 328(24) 418(33) 419(10); HRMS calculated for $C_{29}H_{26}ON_2$: 428.2045, found M^+ 418.2056 $[M+H]^+$419.2078.

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