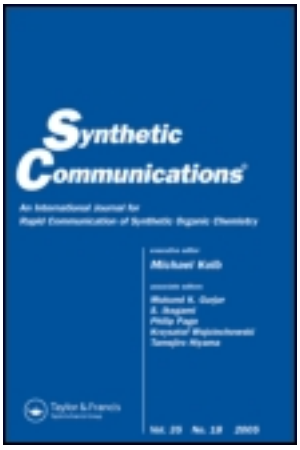

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Novel Methods for the Synthesis of 4-Arylisoquinolinium Perchlorates and 4-Arylisoquinolin-1-ones

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Novel Methods for the Synthesis of 4-Arylisoquinolinium Perchlorates and 4-Arylisoquinolin-1-ones

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Abstract: 2-Benzylamino-1-phenyl-ethanones **1** were converted to the corresponding isoquinolinium perchlorates **2** in high yields using 70% $HClO_4$-$FeCl_3$ mixture as a cyclization and oxidation reagent. A mild and high yielding method for the oxidation of perchlorates **2** to isoquinolin-1-ones **3** involving the treatment of **2** with KOH and $K_3[Fe(CN)_6]$ in THF-H_2O two-phase system at room temperature was developed. Compounds **2a–g** were shown to be disproportionate to **3** and the corresponding 1,2-dihydroisoquinoline **4** in the presence of base, which in turn is oxidized by $K_3[Fe(CN)_6]$ to **2**.

Keywords: 4-Aryldihydroisoquinolines, 4-arylisoquinolin-1-ones, 4-arylisoquinolines, disproportionation, isoquinolines, isoquinolinium perchlorates, isoquinolinones, oxidation with Fe(III), oxidative cyclization

INTRODUCTION

Isoquinolines have been extensively studied because of their interesting pharmacological properties. In particular, 4-aryltetrahydroisoquinolines are of considerable interest because compounds possessing this unit display biological activities of medicinal interest.[1a–e] Nomifensine[1f] and dichlofensine[1g] exhibit central nervous activity and inhibit serotonin- and dopamine-uptake mechanisms. The 4-aryltetrahydroisoquinoline unit also represents the basic skeleton of the naturally occurring alkaloids latifine and cherylline, which have been isolated from *Amaryllidaceae* plants.[2]

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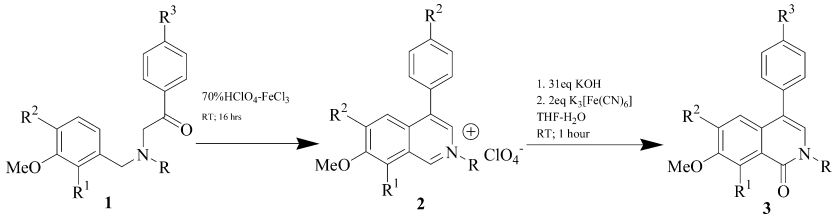
The 4-aryl-1(2*H*)-isoquinolone skeleton has previously been constructed starting from 3-aryl phtalides[3a] or trimethoxy-o-aroyldiphenylphosphoryl-methylbenzamide, which can be cyclized by treatment with KHMDS at −78°C.[3b,c] The appropriate 4-aryl-1(2*H*)-isoquinolones were converted to cherylline methyl ether.[3] The 1(2*H*)-isoquinolone skeleton constitutes the framework of plant alkaloids.[4] Doryanine was prepared in poor yield by subjecting the water-soluble 6,7-methylenedioxyisoquinoline methiodide to alkaline ferricyanide oxidation under reflux conditions.[5] Some 4-aryl-1-isoquinolinone derivatives have been reported to be potent and selective phosphodiesterase-5 inhibitors.[6]

RESULTS AND DISCUSSION

Previously we have reported the oxidative cyclization of *N*-benzyl-*N*-alkylarylacetamides with lead tetracetate in acetic acid/trifluoroacetic acid to give 4-aryl-1,4-dihydro-3(2*H*)-isoquinolinones.[7a,b] We have also reported high-yielding methods for the synthesis of 4-aryl-tetrahydroisoquinolines based on the cyclization of *N*-substituted benzylaminoacetophenones in the presence of different acids.[8a–c] *N,N*-Dibenzylphenacylamines were prepared in high yields by a one-pot cyclization procedure at room temperature to give 7,12-dihydro-l2-phenyl-5*H*-6,12-methanodibenz[c,f]azocines (95% H_2SO_4 or 70% $HClO_4$) in high yields.[9]

We herein report the first use of $HClO_4$-$FeCl_3$ system as a cyclization catalyst and oxidation reagent in the conversion of aminoketones **1** to 4-arylisoquinolinium perchlorates **2**. Compounds **2** were shown to disproportionate to 4-arylisoquinolin-1-ones **3** and dihydroisoquinolines **4** in the presence of KOH in THF-H_2O. The addition of $K_3[Fe(CN)]_6$ to the mixture led to the formation of only **3** at room temperature for a short time in excellent yields.

The aromatic aldehydes were treated with the corresponding alkyl or benzylamines in the presence of $NaBH_4$ to give the corresponding aminoketones **1** in high yields.[7,8] Compounds **1** were converted to their maleates and were treated for 16 h with two equivalents of $FeCl_3 \cdot 6H_2O$ dissolved in 70% perchloric acid to give the corresponding isoquinolinium perchlorates, which were easily isolated by pouring the mixture into ice water where the compounds precipitated.[9] In the case of **1g** where an electron-donating group is present, the cyclization required a longer time (50 h), as expected. The compounds have characteristic singlets around 9.60 in the ^1H NMR spectra taken in $CDCl_3$, which was assigned to the C-1 hydrogen. The singlet corresponding to C-3 hydrogen is at approximately 8 ppm. The ^{13}C NMR spectra are consistent with the proposed structure. Isoquinolinium perchlorates **2** were treated with two equiv $K_3[Fe(CN)_6]$ in THF-H_2O (2 : 1 mL) at room temperature for a short time in the presence of KOH (31 equiv) to give in high yields the corresponding isoquinoline-1-ones **3**



Scheme 1.

(see Scheme 1 and Table 1). The elemental analysis, ^{1}H, ^{13}C NMR, and mass spectral data confirm the proposed structure. The compounds have characteristic peaks at 1648 cm^{-1} corresponding to the carbonyl group. The singlet in the ^{1}H NMR spectra of the compounds, corresponding to C-3 hydrogen, appears approximately at 7.85 ppm. The signal in the ^{13}C NMR spectra of compounds **3**, corresponding to C-1, appears at 161 ppm. All compounds have molecular ion peak in their mass spectra.

The treatment of compounds **2** with KOH in the THF/water (2 : 1 mL), two-phase system at room temperature led to the formation of a mixture of **3** and the corresponding 1,2-dihydroisoquinoline **4** (see Scheme 2). The latter was identical in its TLC with the 1,2-dihydroisoquinoline obtained from the treatment of corresponding **1** in methylene chloride for a short time with conc. H_2SO_4.[7] Compounds **4** were also identical with the product obtained by the reduction of **2** with $NaBH_4$ in MeOH at room temperature. The IR spectrum of the mixture obtained from the disproportionation of **2e** showed a second peak at 1650 cm^{-1} in addition to the peak for the

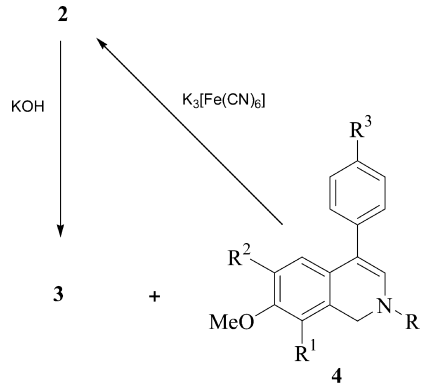
Table 1. Synthesis of compounds **2** and **3**

Entry	R	R^1	R^2	R^3	Yields **2**	Mp **2**	Yields **3**	Mp (°C) **3**
a	Me	H	MeO	H	82(22)[a]	257–259.5	98	180–181
b	Et	H	MeO	H	83(12)	212–214	97	174–176
c	n-Pr	H	MeO	H	73(28)	214–216	93	128–130
d	n-Bu	H	MeO	H	84(32)	198–199	94	104–107
e	Bn	H	MeO	H	62(17)	179–180[b]	98	142–143
f	Me	H	H	H	80(27)	169–170	94	165–166
g	Me	H	MeO	MeO	85	226–227	99	177–178[c]
h	Me	MeO	H	H	85(20)	180–182	24	146

[a]The yields in brackets are from the treatment of the aminoketones with $HClO_4$ without $FeCl_3$.

[b]Lit.[9] mp 180.2°C.

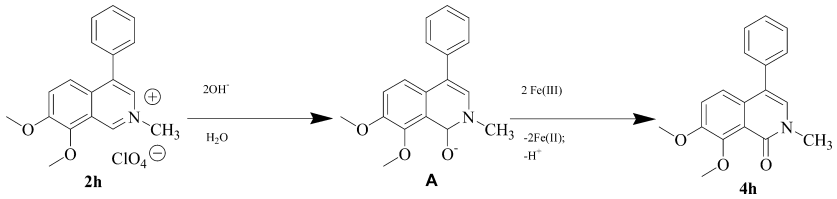
[c]Lit.[3b] mp 178–179°C.



Scheme 2.

carbonyl of **3e**. The OH-stretching region of the spectrum did not contain any peaks. Conversely, the treatment of this mixture with conc. H_2SO_4 led to the formation of a mixture, the main components of which were the corresponding 1,2,3,4-tetrahydroisoquinoline and isoquinolin-1-one. Traces of the corresponding 7,12-dihydro-l2-phenyl-5H-6,12-methanodibenz[c,f]azocine were detected by means of TLC. This undoubtedly proves the second disproportionation product to be the corresponding 1,2-dihydroisoquinoline. The addition of two equiv of $K_3[Fe(CN)_6]$ to the THF-H_2O-KOH solution of the disproportionation products gave again compound **3**. It is clear that at basic conditions the pseudobase alkoxide, formed from the nucleophilic addition of the hydroxide ion to C-1 and loss of hydrogen, transfers a hydride to the isoquinolinium ion, which is in equilibrium with the pseudobase. Thus, formed 1,2-dihydroisoquinoline is oxidized by $K_3[Fe(CN)_6]$ to the corresponding isoquinolinium cation. (The kinetics of the oxidation of isoquinolinium cations by ferricyanide ion in the range pH 11–14 in 20% CH_3CN–80% H_2O is discussed.[10] Although in this work a mechanism involving the formation of pseudobase and its oxidation with the ferricyanide ion is discussed, we have treated **2f** at pH 14 in 20% CH_3CN–80% H_2O mixture and found that the disproportionation process also occurs at these conditions.) However, compound **2h** does not undergo disproportionation, probably because of the steric hindrance of the methoxy group at position 8 when treated with KOH. To recover the unreacted isoquinolinium, the organic layer was separated, the solvent evaporated, and the residue treated with 70% $HClO_4$ and then poured onto ice water to give the starting **2h**. However, the treatment of starting material **2h** with 2 equiv of $K_3[Fe(CN)_6]$ according to the developed method produced **3h** and 6-benzoyl-2,3-dimethoxy-N-methylbenzamide both in 24% yields.

The mechanism for the oxidation of **2h** probably involves the pseudobase formation and its conversion to alkoxide **A** (see Scheme 3). The transfer of two



Scheme 3.

electrons from moiety **A** to 2 equiv of Fe(III) gives compound **3h**. The oxidation of in situ formed 1,2-dihydroisoquinolines to the corresponding **3** (Scheme 1) with $FeCl_3$ in acidic medium and with $K_3[Fe(CN)_6]$ in basic conditions requires 2 equiv of the oxidant (Attempts to perform the reaction with less than 2 equiv led to less satisfactory yields.)

The oxidation of compounds **4** at the mentioned conditions probably is also a two-electron transfer process similar to those in Scheme 3.

EXPERIMENTAL

Melting points were taken on an Electrothermal Digital melting-point apparatus. Infrared spectra were recorded on a Mattson 1000 FTIR. Proton and ^{13}C magnetic-resonance spectra were recorded on a Bruker Dpx 400-MHz spectrometer. Except **2a**, which is taken in DMSO-d_6, all spectra were taken in deuteriochloroform. The mass spectra were recorded on a Fisons VG Platform II instrument. Elemental analyses were performed on a EuroEA 3000 CHNS analyser.

4-Arylisoquinolinium Perchlorates, General Procedure

Compound **1** maleate (2 mmol) was dissolved in a mixture of $HClO_4$ (70%, 5 mL) and $FeCl_3 \cdot 6H_2O$ (4 mmol), and the mixture was stirred at room temperature for 16 h. The mixture was slowly poured into ice water (20 mL) with stirring. The amorphous solid formed was filtered and washed with water (2×5 mL) and dried under vacuum. The compound was recrystallized from ethanol. The crystals were collected by filtration and dried in air.

6,7-Dimethoxy-2-methyl-4-phenylisoquinolinium perchlorate 2a. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.40 (3H, s), 4.03 (3H, s), 4.50 (3H, s), 7.65 (5H, s), 7.70–8.13 (2H, m), 8.74 (1H, s), 10.02 (1H, s). Anal. calcd. for $C_{18}H_{18}ClNO_6$: C, 56.92; H, 4.78; N, 3.69. Found: C, 56.43; H, 4.74; N, 3.38.

2-Ethyl-6,7-dimethoxy-4-phenylisoquinolinium perchlorate 2b. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.67 (3H, t, $J = 7.0$), 3.87 (3H, s), 4.01 (3H, s),

4.69 (2H, q, $J = 7.0$), 7.17 (1H, s), 7.39–7.51 (5H, m), 7.88 (1H, s), 7.98 (1H, s), 9.61 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 17.06; 57.09; 57.14; 57.46; 103.73; 109.09; 125.78; 129.87; 129.94; 130.27; 131.48; 133.74; 134.50; 137.80; 144.58; 153.58; 158.91. Anal. calcd. for $C_{19}H_{20}ClNO_6$: C, 57.95; H, 5.12; N, 3.56. Found: C, 57.75; H, 5.24; N, 3.42.

6,7-Dimethoxy-4-phenyl-2-propylisoquinolinium perchlorate 2c. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.95 (3H, t, $J = 7.3$), 2.05 (2H, m, $J = 7.30$), 3.87 (3H, s), 4.02 (3H, s), 4.59 (2H, t, $J = 7.3$), 7.18 (1H, s), 7.44–7.55 (5H, m), 7.90 (1H, s), 7.97 (1H, s), 9.61 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 11.00; 25.21; 57.08; 57.45; 63.18; 103.70; 109.11; 125.64; 129.87; 129.92; 130.27; 131.72; 133.68; 134.44; 137.61; 144.89; 153.58; 158.93. Anal. calcd. for $C_{20}H_{22}ClNO_6$: C, 58.90; H, 5.44; N, 3.43. Found: C, 58.72; H, 5.50; N, 3.32.

2-Butyl-6,7-dimethoxy-4-phenylisoquinolinium perchlorate 2d. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.89 (3H, t, $J = 7.3$), 1.36 (2H, m, $J = 7.3$), 1.99 (2H, m, $J = 7.3$), 3.87 (3H, s), 4.02 (3H, s), 4.62 (2H, t, $J = 7.30$), 7.17 (1H, s), 7.48–7.55 (5H, m), 7.90 (1H, s), 7.95 (1H, s), 9.63 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 13.82; 19.87; 33.79; 57.08; 57.47; 61.69; 103.68; 109.15; 125.67; 129.88; 129.92; 130.28; 131.63; 133.70; 134.40; 137.61; 144.97; 153.58; 158.92. Anal. calcd. for $C_{21}H_{24}ClNO_6$: C, 59.79; H, 5.73; N, 3.32. Found: C, 59.66; H, 5.72; N, 3.12.

2-Benzyl-6,7-dimethoxy-4-phenylisoquinolinium perchlorate 2e. The compound was identical with those reported previously.[9] Anal. calcd. for $C_{24}H_{22}ClNO_6$: C, 63.23; H, 4.86; N, 3.07. Found: C, 63.47; H, 4.86; N, 3.00.

7-Methoxy-2-methyl-4-phenylisoquinolinium perchlorate 2f. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.00 (3H, s), 4.56 (3H, s), 6.71–8.00 (8H, m), 8.06 (1H, s), 9.67 (1H, s). Anal. calcd. for $C_{17}H_{16}ClNO_5$: C, 58.38; H, 4.61; N, 4.00. Found: C, 58.08; H, 4.54; N, 3.89.

6,7-Dimethoxy-4-(4-methoxy-phenyl)-2-methylisoquinolinium perchlorate 2g. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.85 (3H, s), 3.89 (3H, s), 4.03 (3H, s), 4.45 (3H, s), 7.05 (2H, d, $J = 8.6$), 7.40 (2H, d, $J = 8.6$), 7.8 (1H, s), 7.85 (1H, s), 9.58 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 48.25; 55.89; 57.07; 57.47; 103.83; 105.61; 111.95; 115.35; 125.64; 131.17; 132.30; 134.53; 137.54; 145.43; 153.65; 158.91; 161.25. Anal. calcd. for $C_{19}H_{20}ClNO_7$: C, 55.68; H, 4.92; N, 3.42. Found: C, 55.50; H, 4.71; N, 3.10.

7,8-Dimethoxy-2-methyl-4-phenylisoquinolinium perchlorate 2h. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.05 (3H, s), 4.23 (3H, s), 4.61 (3H, s), 7.54 (5H, s), 7.74–7.86 (2H, m), 8.05 (1H, s), 9.67 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ

ppm 51.05; 59.02; 64.56; 123.44; 126.41; 127.77; 131.19; 131.84; 132.59; 133.72; 134.85; 141.57; 146.60; 147.72; 153.14. Anal. calcd. for $C_{18}H_{18}ClNO_6$: C, 56.92; H, 4.78; N, 3.69. Found: C, 56.43; H, 4.74; N, 3.38.

4-Aryl-2H-isoquinolin-1-ones 4, General Procedure

Compound **2** (0.2 mmol) was suspended in a mixture of THF/H_2O (6 : 3 mL), and KOH (6.2 mmol) was added to the mixture. $K_3[Fe(CN)_6]$ (0.4 mmol) was added and the mixture stirred at room temperature for 1 h. The organic phase was separated and the solvent evaporated. The residue was extracted with chloroform (2 × 10 mL) and the solvent evaporated. The residue was recrystallized from MeOH.

6,7-Dimethoxy-2-methyl-4-phenyl-2H-isoquinolin-1-one 3a. FTIR (KBr) $\nu_{C=O}$ 1648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 3.66 (3H, s), 3.82 (3H, s), 4.04 (3H, s), 6.93 (1H, s), 6.98 (1H, s), 7.41–7.51 (5H, m), 7.93 (1H, s). MS m/z 295 (M^+). Anal. calcd. for $C_{18}H_{17}NO_3$ (295.34): C, 73.20; H, 5.80; N, 4.74. Found: C, 73.28; H, 5.64; N, 4.49.

2-Ethyl-6,7-dimethoxy-4-phenyl-2H-isoquinolin-1-one 3b. FTIR (KBr) $\nu_{C=O}$ 1648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.34 (3H, t, $J = 7.2$), 3.74 (3H, s), 3.95 (3H, s), 4.03 (2H, q, $J = 7.2$), 6.85 (1H, s), 6.90 (1H, s), 7.32–7.45 (5H, m), 7.85 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 15.10; 44.81; 56.28; 56.55; 105.32; 108.49; 119.72; 120.58; 128.01; 129.10; 129.41; 130.13; 131.96; 137.24; 149.54; 153.46; 161.15. MS m/z 309 (M^+). Anal. calcd. for $C_{19}H_{19}NO_3$ (309.37): C, 73.77; H, 6.19; N, 4.53. Found: C, 73.72; H, 6.40; N, 4.51.

6,7-Dimethoxy-4-phenyl-2-propyl-2H-isoquinolin-1-one 3c. FTIR (KBr) $\nu_{C=O}$ 1648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.93 (3H, t, $J = 7.3$), 1.77 (2H, m, $J = 7.3$), 3.73 (3H, s), 3.92 (2H, t, $J = 7.3$), 3.95 (3H, s), 6.85 (1H, s), 6.88 (1H, s), 7.32-7.45 (5H, m), 7.85 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 11.67; 23.08; 51.41; 56.29; 56.56; 105.34; 108.60; 119.36; 120.60; 128.01; 129.12; 130.03; 130.16; 131.95; 137.27; 149.55; 153.50; 161.40. MS m/z 323 (M^+). Anal. calcd. for $C_{20}H_{21}NO_3$ (323.40): C, 74.28; H, 6.55; N, 4.33. Found: C, 74.33; H, 6.69; N, 4.43.

2-Butyl-6,7-dimethoxy-4-phenyl-2H-isoquinolin-1-one 3d. FTIR (KBr) $\nu_{C=O}$ 1648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.89 (3H, t, $J = 7.3$), 1.34 (2H, m, $J = 7.4$), 1.73 (2H, m, $J = 7.4$), 3.73 (3H, s), 3.95 (3H, s), 3.98 (2H, t, $J = 7.4$), 6.86 (1H, s), 6.88 (1H, s), 7.32–7.45 (5H, m), 7.85 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 14.17; 20.45; 31.94; 49.65; 56.30; 56.55; 105.34; 108.60; 119.43; 120.60; 128.02; 129.12; 130.00; 130.16; 131.94; 137.26; 149.55; 153.50; 161.40. MS m/z 337 (M^+). Anal.

calcd. for $C_{21}H_{23}NO_3$ (337.42): C, 74.75; H, 6.87; N, 4.15. Found: C, 74.62; H, 6.96; N, 4.01.

2-Benzyl-6,7-dimethoxy-4-phenyl-2H-isoquinolin-1-one 3e. FTIR (KBr) $\nu_{C=O}$ 1648 cm^{-1}; [c1]H NMR (400 MHz, $CDCl_3$) δ ppm 3.73 (3H, s), 3.95 (3H, s), 5.19 (2H, s), 6.84 (1H, s), 6.92 (1H, s), 7.18–7.39 (5H, m), 7.88 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 52.38; 56.33; 56.60; 105.52; 108.85; 119.94; 120.56; 128.08; 128.20; 128.42; 129.11; 129.20; 129.55; 130.17; 132.05; 137.07; 137.44; 149.68; 153.66; 161.55. MS m/z 371 (M^+). Anal. calcd. for $C_{24}H_{21}NO_3$ (371.44): C, 77.61; H, 5.70; N, 3.77. Found: C, 77.65; H, 5.79; N, 3.82.

7-Methoxy-2-methyl-4-phenyl-2H-isoquinolin-1-one 3f. FTIR (KBr) $\nu_{C=O}$ 1648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 3.58 (3H, s), 3.86 (3H, s), 6.86 (1H, s), 7.12 (1H, dd, $J = 8.98, 2.8$), 7.31–7.41 (6H, m), 7.86 (1H, d, $J = 2.8$). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 37.48; 56.07; 108.49; 120.00; 122.78; 126.77; 127.59; 128.02; 129.02; 129.60; 130.28; 130.84; 136.91; 159.18.; 162.20. MS m/z 265 (M^+). Anal. calcd. for $C_{17}H_{15}NO_2$ (265.31): C, 76.96; H, 5.70; N, 5.28. Found: 76.66; H, 5.93; N, 5.07.

6,7-Dimethoxy-4-(4-methoxy-phenyl)-2-methyl-2H-isoquinolin-1-one 3g. FTIR (KBr) $\nu_{C=O}$ 1648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 3.57 (3H, s), 3.74 (3H, s), 3.80 (3H, s), 3.94 (3H, s), 6.82 (1H, s), 6.86 (1H, s), 6.93 (2H, d, $J = 8.57$), 7.26 (2H, d, $J = 8.57$), 7.85 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 37.39; 55.72; 56.28; 56.58; 105.45; 108.37; 114.52; 119.14; 120.35; 129.31; 130.43; 131.23; 132.48; 149.54; 153.46; 159.56;161.79. MS m/z 325 (M^+). Anal. calcd. for $C_{19}H_{19}NO_4$ (325.37): C, 70.14; H, 5.89; N, 4.31. Found: C, 70.19; H, 6.07; N, 4.24.

7,8-Dimethoxy-2-methyl-4-phenyl-2H-isoquinolin-1-one 3h. FTIR (KBr) $\nu_{C=O}$ 1653 cm^{-1}; MS m/z 295 (M^+). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 3.60 (3H, s), 3.95 (3H, s), 4.04 (3H, s), 6.91(1H, s), 7.25 (2H, m), 7.38–7.49 (5H, m). Anal. calcd. for $C_{19}H_{19}NO_4$ (295.34): C, 70.14; H, 5.89; N, 4.31. Found: C, 70.15; H, 6.00; N, 4.28.

6-Benzoyl-2,3-dimethoxy-N-methyl-benzamide. Colorless oil; FTIR (KBr) $\nu_{C=O}$ 1680 cm^{-1}; MS m/z 299 (M^+). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.93 (3H, s), 3.88 (3H, s), 4.18 (3H, s), 5.24 (1H, s), 6.81 (1H, d, $J = 8.2$), 7.00 (1H, d, $J = 8.2$), 7.16 (2H, d, $J = 6.7$), 7.38 (3H, m). Anal. calcd. for $C_{17}H_{17}NO_4$ (299.32): C, 68.21; H, 5.72; N, 4.68. Found: C, 68.28; H, 5.70; N, 4.70.

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REFERENCES

1. (a) Dandridge, P. A.; Kaiser, C.; Brenner, M.; Gaitanopoulos, D.; Davis, L. D.; Webb, R. L.; Foley, J. J.; Sarau, H. M. *J. Med. Chem.* **1984**, *27*, 28–35; (b) Toome, V.; Blount, J. F.; Grethe, G.; Uskokovic, M. *Tetrahedron Lett.* **1970**, *11*, 49–52; (c) Kihara, M.; Ikeuchi, M.; Adachi, S.; Nagao, Y.; Moritoki, H.; Yamaguchi, M.; Taira, Z. *Chem. Pharm. Bull.* **1995**, *43*, 1543–1546; (d) Couture, A.; Deniau, E.; Grandclaudon, P.; Lebrun, S. *Tetrahedron: Asymmetry* **2003**, *14*, 1309–1316; (e) Honda, T.; Namiki, H.; Satoh, F. *Org. Lett.* **2001**, *3*, 631–633; (f) Ulin, J.; Gee, A. D.; Malmborg, P.; Tedroff, J.; Laangstroem, B. *Appl. Radiat. Isot.* **1989**, *40*, 171–176; (g) Omer, L. M. *Int. J. Clin. Pharmacol. Ther. Toxicol.* **1982**, *20*, 320–326.
2. Wildman, W. C. *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1968; Vol. XI, Chapter 10.
3. (a) Narasimhan, N. S.; Patil, P. A. *J. Chem. Soc. Chem. Comm.* **1987**, *3*, 191–192; (b) Couture, A.; Deniau, E.; Woisel, P.; Grandclaudon, P.; Carpentier, J. F. *Tetrahedron Lett.* **1996**, *37*, 3697–3700; (c) Couture, A.; Deniau, E.; Grandclaudon, P.; Woisel, P. *Tetrahedron* **1996**, *52*, 4433–4448.
4. Pelletier, S. W. *Chemistry of the Alkaloids*; Van Nostrand Reinhold Co.: New York, 1970.
5. Cava, M. P.; Buck, K. T. *Tetrahedron* **1969**, *23*, 2795–2805.
6. (a) Ukita, T.; Nakamura, Y.; Kubo, A.; Yamamoto, Y.; Moritani, Y.; Saruta, K.; Higashijima, T.; Kotera, J.; Takagi, M.; Kikkawa, K.; Omori, K. *J. Med. Chem.* **2001**, *44*, 2204–2218; (b) Ukita, T.; Nakamura, Y.; Kubo, A.; Yamamoto, Y.; Moritani, Y.; Saruta, K.; Higashijima, T.; Kotera, J.; Fujishige, K.; Takagi, M.; Kikkawa, K.; Omori, K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2341–2345.
7. (a) Venkov, A. P.; Vodenicharov, D. M. (now N. Coşkun); Ivanov, I. I. *Synthesis* **1991**, 476–478; (b) Coşkun, N.; Sümengen, D. *Synth. Commun.* **1993**, *23*, 1393–1402.
8. (a) Venkov, A. P.; Vodenicharov, D. M. (now N. Coşkun), *Synthesis* **1990**, 253–255; (b) Coşkun, N.; Sümengen, D. *Chim. Acta Turc.* **1996**, *24*, 151; (c) Coşkun, N.; Tirli, F. *Synth. Commun.* **1997**, *27*, 1–9.
9. Coşkun, N.; Büyükuysal, L. *Heterocycles* **1998**, *48*, 53–59.
10. Bunting, J. W.; Stefanidis, D. *J. Org. Chem.* **1986**, *51*, 2060–2067.