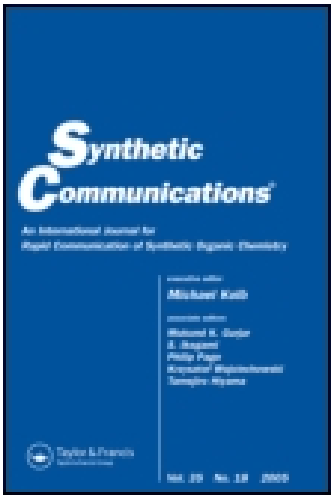

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A Convenient Synthesis of 3-Aryl-2-Methyl-3,4-Dihydro-1(2H)-Isoquinolones and -1,2,3,4-Tetrahydroisoquinolines

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A CONVENIENT SYNTHESIS OF 3-ARYL-2-METHYL-3,4-DIHYDRO-1(2*H*)-ISOQUINOLONES AND -1,2,3,4-TETRAHYDROISOQUINOLINES

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Abstract: A new methodology for the synthesis of 3-aryl-2-methyl-3,4-dihydro-2*H*-isoquinolin-1-ones and 3-aryl-2-methyl-1,2,3,4-tetrahydroisoquinolines is reported.

The 1,2,3,4-tetrahydroisoquinoline ring system is a structural component of many biologically active natural products[1] and is a useful template for the construction of bioactive synthetic substances and pharmacophores endowed with potential therapeutic applications.[2] The long list of articles and patents dealing with the synthesis of such heterocycles is a testimony to their importance.[3] The

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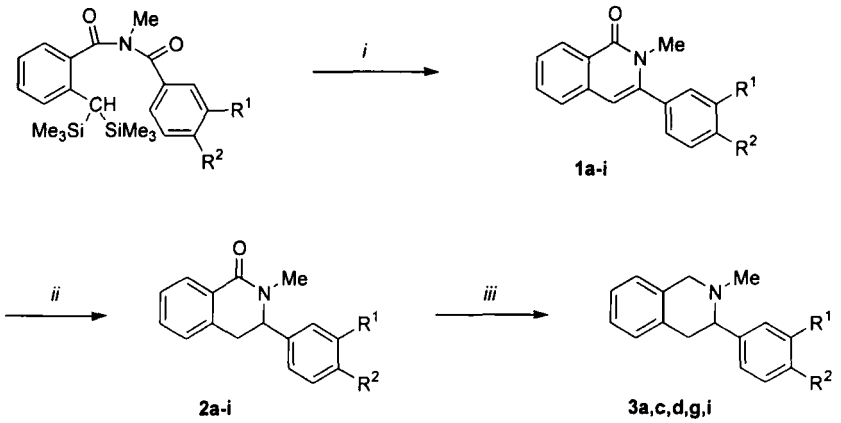
most classical methods available for the construction of 1,2,3,4-tetrahydroisoquinoline derivatives include the well-known Bischler-Napieralski[4] and Pictet-Spengler[5] cyclization reactions but other strategies have emerged in more recent times and numerous modifications and improvements of these older processes have been devised.[3,6] However many of these routes are sensitive to the aromatic substituents. Indeed an electron-donating hydroxy or an alkoxy group on the aromatic nucleus is generally the minimum requisite for a facile reaction and substrates lacking electron donating groups often failed to cyclize or gave low yields.[5,6] Consequently there continues to be a lack of general methods for the synthesis of a wide range of 1,2,3,4-tetrahydroisoquinolines devoid of substituents on the aromatic moiety of the structure.

We wish to report in this paper an alternative synthesis of 1,2,3,4-tetrahydroisoquinoline derivatives unaffected by substituents on the benzene ring and particularly of the 3-aryl substituted derivatives **3** which are generally less easily accessible than other members of the 1,2,3,4-tetrahydroisoquinoline family. Our newly established procedure relies upon the sequential reduction of the C=C double bond of the 1(2*H*)-isoquinolones **1** followed by reduction of the carbonyl function of the resulting 3,4-dihydro-1(2*H*)-isoquinolones **2** (Scheme). Initially the diversely substituted isoquinolones **1** were easily obtained by fluoride ion-induced cyclization of *o*-[bis-(trimethylsilyl)methyl]-*N*-aroylbenzamide derivatives, a procedure recently developed in our laboratory.[7]

This new approach offers a double advantage which is worth underlining. It gives rise not only to the target compounds **3** but equally to the 3-aryl-3,4-

Scheme.



Reagents and conditions. *i*, Bu_4NF, THF, ref. 7; *ii*, Pd/C, $HCOONH_4$, MeOH, reflux, 5 h; *iii*, $LiAlH_4$, THF, 0°C, 2 h, then 0°C to rt, 1 h.

Table. 3-Aryl-2-methyl-3,4-dihydro-2*H*-isoquinolin-1-ones **2a-i** and 3-Aryl-2-methyl-1,2,3,4-tetrahydroisoquinolines **3a,c,d,g,i** Prepared

			3,4-dihydro-2*H*-isoquinolin-1-one **2**		1,2,3,4-tetrahydro isoquinoline **3**	
	R^1	R^2	Yield (%)	mp (°C) [lit.][ref.]	Yield (%)	mp (°C) [lit.][ref.]
a	H	H	70	118-119 [118-119][19]	84	70-71 [70-71][20]
b	H	OMe	65	97-98 [98-99][16a]	-	-
c	OMe	H	72	81-82	85	oil
d	OMe	OMe	68	98-99 [98-99][16b]	90	89-90
e	OCH_2O		75	81-82 [80-81][16b]	-	-
f	H	Cl	65	102-103	-	-
g	Cl	H	70	110-111	80	oil
h	H	CF_3	62	70-71	-	-
i	H	$N(Me)_2$	69	121-122	80	oil

dihydro-1(2*H*)-isoquinolones **2**. Previous reports on the synthesis of 3,4-dihydroisoquinolones involve the ring closure of isocyanates with $POCl_3$,[8] $SnCl_4$,[9] BF_3/etherate,[10] $SnCl_4/POCl_3$[11] and of carbamates with PPA,[12] $POCl_3$,[13] Tf_2O[14] and $POCl_3/P_2O_5$.[15] However none of these methods permits the introduction of a great diversity of aromatic units onto the six-membered heterocyclic moiety. Such compounds are only accessible by condensation of lithiated *N,N*-diethyl-*o*-toluamide with imines[16] or by photoinduced ring closure of appropriately substituted aromatic enamides under anaerobic conditions.[17]

For the reduction of the styryl moiety of the annulated compounds **1** we opted to employ a rarely utilised method,[18] making use of Pd on C and ammonium formate. The results of a representative series of compounds which we have prepared following this protocol are presented in the Table where it may be seen that this simple procedure affords fairly good yields of the 3-aryl-2-methyl-3,4-dihydro-2*H*-isoquinolin-1-ones **2a-i**. Subsequent reduction of the carbonyl function of **2** with $LiAlH_4$ in THF proceeded uneventfully to deliver excellent yields of the target 3-aryl-2-methyl-1,2,3,4-tetrahydroisoquinolines **3a,c,d,g,i**.

Experimental

Melting points are uncorrected. ^{13}C and ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AC 300 spectrometer. Elemental analyses were run by the CNRS.

1(2*H*)-Isoquinolones **1a-i** were prepared according to the literature.[7]

Preparation of the 3-Aryl-2-methyl-3,4-dihydro-2H-isoquinolin-1-ones 2a-i. General Procedure. A suspension of the 3-aryl-2-methyl-2*H*-isoquinolin-1-one **1a-i** (4 mmol) and Pd/C (10%, 60 mg) in methanol (50 mL) was vigorously stirred and a solution of $HCOONH_4$ (1,28g, 20 mmol) in distilled water (10 mL) was slowly added. The reaction mixture was refluxed for 5 h with stirring and then filtered on Celite®. Water (50 mL) was added and the mixture extracted with CH_2Cl_2 (2 × 30 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum to left an oily product which was purified by flash column chromatography on silica gel using ethyl acetate/hexanes (2:3) as eluent and further recrystallization from EtOH.

3-(3-Methoxyphenyl)-2-methyl-3,4-dihydro-2H-isoquinolin-1-one **(2c)**. ^{1}H NMR δ (ppm) 3.01 (1H, dd, *J* = 3.0, 15.9), 3.09 (3H, s), 3.64 (1H, dd, *J* = 6.8, 15.9), 3.67 (3H, s), 4.72 (1H, dd, *J* = 3.0, 6.8), 6.60 (1H, s), 6.64 (1H, d, *J* = 7.5), 6.73 (1H, dd, *J* = 2.3, 8.1), 7.00 (1H, dd, *J* = 5.5, 8.1), 7.12-7.34 (3H, m), 8.10-8.14 (1H, m); ^{13}C NMR δ (ppm) C 164.9, 159.8, 141.6, 135.2, 129.1, CH 131.8, 129.8, 127.7, 127.4, 127.1, 118.6, 112.8, 112.2, 61.9, CH_2 35.7, CH_3 55.1, 34.3. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N 5.24. Found: C, 76.24; H, 6.56; N 5.22.

3-(4-Chlorophenyl)-2-methyl-3,4-dihydro-2H-isoquinolin-1-one **(2f)**. ^{1}H NMR δ (ppm) 3.01 (1H, dd, *J* = 2.9, 15.9), 3.08 (3H, s), 3.64 (1H, dd, *J* = 6.8, 15.9), 4.74 (1H, dd, *J* = 2.9, 6.8), 6.92-7.38 (7H, m), 8.11-8.18 (1H, m); ^{13}C NMR δ (ppm) C 164.9, 139.9, 135.1, 131.8, 129.2, CH 128.7, 127.8, 127.7, 127.5, 127.1, 126.2, 61.9, CH_2 35.7, CH_3 34.3. Anal. Calcd for $C_{16}H_{14}ClNO$: C, 70.72; H, 5.19; N

5.15. Found: C, 70.84; H, 5.06; N 4.98.

*3-(3-Chlorophenyl)-2-methyl-3,4-dihydro-2*H*-isoquinolin-1-one* **(2g)**. ^{1}H NMR δ (ppm) 3.02 (1H, dd, *J* = 3.0, 15.8), 3.09 (3H, s), 3.66 (1H, dd, *J* = 6.8, 15.8), 4.76 (1H, dd, *J* = 3.0, 6.8), 6.97-7.08 (3H, m), 7.20-7.34 (4H, m), 8.12-8.15 (1H, m); ^{13}C NMR δ (ppm) C 165.0, 139.9, 135.1, 131.8, 129.2, CH 128.7, 127.8, 127.7, 127.5, 127.1, 126.2, 61.9, CH_2 35.8, CH_3 34.3. Anal. Calcd for $C_{16}H_{14}ClNO$: C, 70.72; H, 5.19; N 5.15. Found: C, 70.61; H, 5.30; N 5.02.

3-(4-Trifluoromethylphenyl)-2-methyl-3,4-dihydro-2H-isoquinolin-1-one **(2h)**. ^{1}H NMR δ (ppm) 3.02 (1H, dd, *J* = 3.0, 15.9), 3.09 (3H, s), 3.64 (1H, dd, *J* = 7.0, 15.9), 4.72 (1H, dd, *J* = 3.0, 7.0), 6.60 (1H, s), 6.65 (1H, d, *J* = 7.6), 6.74 (1H, dd, *J* = 2.2, 8.0), 7.00 (1H, dd, *J* = 2.2, 8.0), 7.12-7.36 (3H, m), 8.10-8.14 (1H, m); ^{13}C NMR δ (ppm) C 164.7, 141.7, 135.2, 132.1 (d, *J* = 35), 129.1, 125.8 (d, *J* = 269), CH 131.8, 129.7, 127.7, 127.4, 127.1, 118.6, 112.8, 112.1, 61.9, CH_2 35.7, CH_3 34.3. Anal. Calcd for $C_{17}H_{14}F_3NO$: C, 66.88; H, 4.62; N 4.59. Found: C, 67.03; H, 4.44; N 4.47.

3-(4-Dimethylaminophenyl)-2-methyl-3,4-dihydro-2H-isoquinolin-1-one **(2i)**. ^{1}H NMR δ (ppm) 2.87 (6H, s), 3.02 (1H, dd, *J* = 3.5, 15.8), 3.06 (3H, s), 3.57 (1H, dd, *J* = 6.5, 15.8), 4.65 (1H, dd, *J* = 3.5, 6.5), 6.57 (2H, d, *J* = 8.8), 6.89 (2H, d, *J* = 8.8), 7.12-7.34 (3H, m), 8.07-8.12 (1H, m); ^{13}C NMR δ (ppm) C 165.1, 150.0, 131.7, 130.9, 129.8, CH 127.7, 127.5, 127.2, 126.9, 126.6, 112.4, 61.5, CH_2 35.9, CH_3 40.4, 34.1. Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N 9.99. Found: C, 77.01; H, 7.00; N 10.12.

Preparation of the 3-Aryl-2-methyl-1,2,3,4-tetrahydroisoquinolines* 3a,c,d,g,i.** ***General Procedure. $LiAlH_4$ (160 mg, 4 mmol) was added to a stirred solution of **2** (0.8 mmol) in anhydrous THF (40 mL) at 0°C. After stirring at 0°C for 2 h, the reaction mixture was allowed to come to room temperature over 1 h. Ethyl acetate (40 mL) was added and the resulting mixture was filtered on Celite®. After drying over $MgSO_4$, the organic layer was concentrated under vacuum and the residue purified by flash column chromatography on silica gel using ethyl acetate/hexanes (3:2) as eluent.

3-(3-Methoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline **(3c)**. ^1H NMR δ (ppm) 2.19 (3H, s), 2.97 (1H, dd, J = 4.0, 16.6), 3.10-3.19 (1H, m), 3.36 (1H, dd, J = 4.0, 10.3), 3.59 (1H, d, J = 15.5), 3.80 (3H, s), 4.01 (1H, d, J = 15.5), 6.81-7.29 (8H, m); ^{13}C NMR δ (ppm) C 144.5, 134.4, 132.7, 130.7, CH 129.5, 128.0, 127.8, 126.3, 126.0, 125.8, 120.3, 113.0, 66.7, CH_2 58.8, 43.4, CH_3 55.2, 38.4. Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N 5.53. Found: C, 80.71; H, 7.39; N 5.40.

3-(3,4-Dimethoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline **(3d)**. ^1H NMR δ (ppm) 2.17 (3H, s), 2.95 (1H, dd, J = 4.0, 16.4), 3.14 (1H, dd, J = 10.1, 16.4), 3.33 (1H, dd, J = 4.0, 10.1), 3.58 (1H, d, J = 15.4), 3.86 (3H, s), 3.87 (1H, d, J = 15.4), 6.83 (1H, s), 6.85 (1H, d, J = 1.9), 6.93 (1H, d, J = 1.9), 7.03-7.15 (4H, m); ^{13}C NMR δ (ppm) C 149.3, 148.3, 135.4, 134.3, 134.2, CH 128.0, 126.3, 125.8, 120.2, 110.8, 110.2, 66.4, CH_2 58.9, 43.4, CH_3 55.9, 55.8, 38.5. Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.30; H, 7.47; N 4.94. Found: C, 76.51; H, 7.35; N 5.09.

3-(3-Chlorophenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline **(3g)**. ^1H NMR δ

(ppm) 2.17 (3H, s), 2.96 (1H, dd, J = 3.9, 16.5), 3.08-3.19 (1H, m), 3.40 (1H, dd, J = 3.9, 10.1), 3.60 (1H, d, J = 15.4), 4.01 (1H, d, J = 15.4), 7.03-7.15 (8H, m); ^{13}C NMR δ (ppm) C 140.1, 135.7, 132.3, 129.8, CH 129.1, 128.0, 127.6, 127.4, 126.5, 125.6, 123.3, 120.1, 66.5, CH_2 58.7, 43.3, CH_3 38.5. Anal. Calcd for $C_{16}H_{16}ClN$: C, 74.56; H, 6.26; N 5.43. Found: C, 74.52; H, 6.36; N 5.34.

3-(4-Dimethylaminophenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline **(3i)**. ^{1}H NMR δ (ppm) 2.39 (3H, s), 2.92 (3H, s), 2.94 (1H, dd, J = 4.1, 16.5), 2.98 (3H, s), 3.09 (1H, m), 3.31 (1H, dd, J = 4.1, 10.1), 3.55 (1H, d, J = 15.3), 3.96 (1H, d, J = 15.3), 6.71 (1H, s), 6.95-7.29 (6H, m); ^{13}C NMR δ (ppm) C 150.0, 136.6, 135.9, 134.6, CH 130.9, 129.7, 128.6, 126.2, 125.6, 112.6, 65.8, CH_2 58.8, 43.3, CH_3 40.7, 38.1. Anal. Calcd for $C_{18}H_{22}N_2$: C, 81.16; H, 8.32; N 10.52. Found: C, 81.02; H, 8.35; N 10.69.

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