Preparation of 1,3-Disubstituted Isoquinoline Derivatives from *N*-Boc-3-Substituted-1,2-dihydroisoquinolines

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3-Substituted *N*-Boc-1,2-dihydroisoquinolines **2** can be functionalized at the 1-position *via* lithiation and subsequent electrophilic trapping. The resulting products **3** can be deprotected and oxidized to afford the corresponding 1,3-disubstituted isoquinolines **5**. Deprotection of dihydroisoquinoline **3k** followed by sodium borohydride reduction affords the *cis*-1,3-disubstituted tetrahydroisoquinoline **11**. The 1,3-disubstituted *N*-Boc-1,2-dihydroisoquinoline **3g** is efficiently alkylated at the 1-position to give 1,1,3-trisubstituted analogs **12**.

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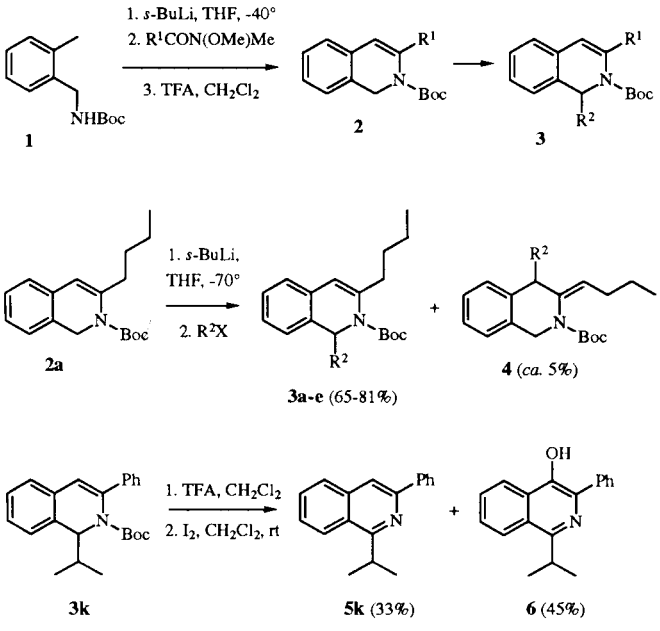
We have previously reported that 3-substituted 1,2-dihydroisoquinolines **2** are readily available *via* benzylic lithiation of *N*-Boc-2-methylbenzylamine (**1**) followed by acylation and acid-catalyzed cyclization [1,2]. These dihydroisoquinolines can be converted into a variety of 3-substituted 1,2,3,4-tetrahydroisoquinolines and 3-substituted isoquinolines [1,2]. As a continuation of that work, we investigated the preparation of 1-substituted derivatives **3** from lithiation of **2** followed by electrophilic trapping. Reported herein is the realization of that process which provides access to more highly substituted isoquinoline derivatives.



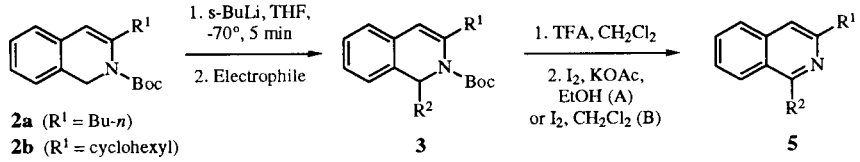
Initial lithation studies were performed on the 3-*n*-butyl-*n*-Boc-1,2-dihydroisoquinoline **2a** [2]. Treatment of **2a** with *sec*-butyllithium at -70° resulted in immediate formation of the lithio species as evidenced by the dark brown color of the resultant solution. Addition of various electrophiles gave the 1-substituted derivatives **3a-e** in good yield (Table I). Lithiation of **2a** was, however, not completely regiospecific for the 1-position as evidenced by the formation of 4-substituted products **4** in approximately 5% yield. These interesting minor products apparently arise from lithiation of **2a** at the allylic position of the side-chain butyl group. The resulting allyl lithio species then undergoes reaction with electrophiles in the middle of the extended (conjugated) system. The *z* configuration of the butylidene group in **4** (R^2 = allyl) was established by nuclear Overhauser effect (nOe) experiments (Experimental).

The 3-cyclohexyl and 3-phenyl analogs **2b** and **2c**, respectively, also underwent electrophilic trapping at the 1-position in high yield (Table I). In the case of **2b**, products analogous to **4** were not observed, indicating that the tertiary position of the cyclohexyl moiety does not undergo lithiation. The lithio species derived from **2a-c** undergo condensation in high yield with a wide variety of electrophiles including primary and secondary alkyl halides, allyl and benzyl bromides, benzaldehydes, and *N*-methoxy-*N*-methylbenzamide.

A number of the 1,3-disubstituted *N*-Boc-1,2-dihydroisoquinolines **3** prepared as described above were converted to the corresponding 1,3-disubstituted isoquinolines **5** *via* deprotection with trifluoroacetic acid followed by oxidation of the resultant iminium species with iodine (Table I). Two oxidation procedures from the literature, or modifications thereof, were used: 1) iodine/potassium acetate in ethanol at reflux [3] (Method A), and 2) iodine in dichloromethane and chloroform at room temperature [4] (Method B). No major differences in yield between the two procedures were noted; however, given the toxicological problems inherent in the use of chloroform, the iodine/potassium acetate in ethanol procedure may be more generally acceptable.

Oxidation of the iminium species derived from trifluoroacetic acid treatment of the 1-isopropyl-substituted *N*-Boc dihydroisoquinoline **3k** led to an anomalous result. In addition to the expected isoquinoline **5k**, a more polar product identified as the corresponding 4-hydroxyiso-

Table I



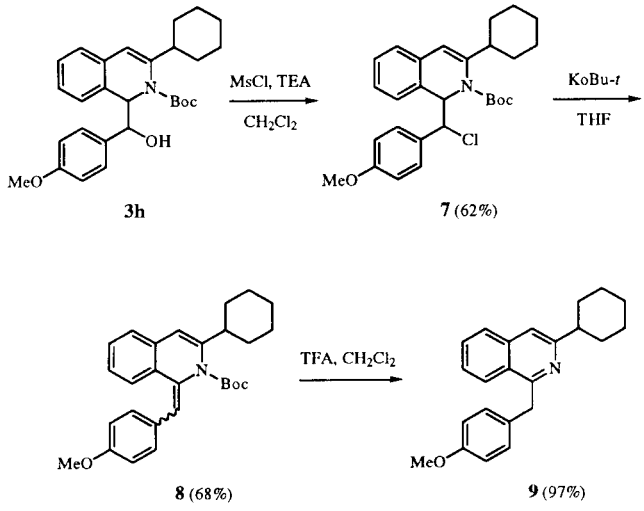
2a (R^1 = Bu-*n*)
2b (R^1 = cyclohexyl)
2c (R^1 = Ph)

3 **5**

R^1	Electrophile	Product (% Yield)	R^2	Method	Product (% Yield)
n-Bu	MeI	**3a** (80)	Me	B	**5a** (50)
n-Bu	CH_2=$CHCH_2Br$	**3b** (71)	CH_2CH=CH_2	-	-
n-Bu	*n*-BuI	**3c** (81)	Bu-*n*	A	**5c** (75)
				B	**5c** (62)
n-Bu	Me_2CHCH_2I	**3d** (65)	CH_2CHMe_2	B	**5d** (30)
n-Bu	$PhCH_2Br$	**3e** (66)	CH_2Ph	A	**5e** (75)
cyclohexyl	MeI	**3f** (93)	Me	B	**5f** (65)
cyclohexyl	*p*-$MeOC_6H_4CHO$	**3g** (90)	$CHOHC_6H_4OMe$-*p*	-	-
Ph	MeI	**3h** (82)	Me	B	**5h** (85)
Ph	*n*-BuI	**3i** (75)	Bu-*n*	B	**5i** (62)
Ph	Me_2CHI	**3j** (73)	$CHMe_2$	B	**5j** (33)
Ph	Me_2CHCH_2I	**3k** (95)	CH_2CHMe_2	B	**5k** (73)
Ph	CH_2=$CHCH_2Br$	**3l** (97)	CH_2CH=CH_2	-	-
Ph	$PhCH_2Br$	**3m** (73)	CH_2Ph	A	**5m** (34)
				B	**5m** (56)
Ph	PhCON(OMe)Me	**3n** (78)	COPh	B	**5n** (68)

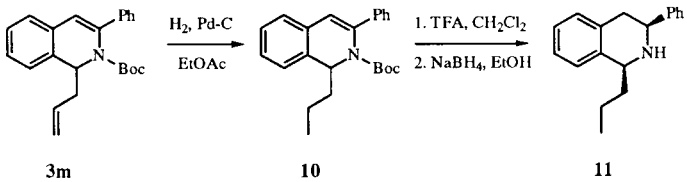
quinoline **6** was obtained. Compound **6** was in fact the major product from either oxidation procedure. A reasonable mechanistic rationale to explain the formation of **6** is lacking at this time; however, steric hindrance at the benzylic position adjacent to the isopropyl group is implicated as a contributing factor (the 4-hydroxy product was not observed upon conversion of the isobutyl analog **3l** to the isoquinoline **5l**.

An alternative, non-oxidative, route to 1-benzylisoquinolines was investigated. It was envisioned that acid treatment of benzaldehyde adducts such as **3h** would lead directly to the 1-benzylisoquinoline *via* a sequence involving dehydration/deprotection and subsequent aromatization. However, treatment of **3h** with trifluoroacetic acid in dichloromethane at room temperature resulted in an apparent reverse aldol process; the only identifiable products were anisaldehyde and 3-cyclohexylisoquinoline. The desired product **9** was obtained by the more circuitous route of conversion to the benzylic chloride **7** [5], base catalyzed elimination to the mixture of isomeric olefins **8**, and treatment with trifluoroacetic acid. In general, this multi-step approach would not appear to be competitive with the more direct sequence of benzylation, deprotection, and oxidation illustrated in Table I.



3h **7** (62%)

8 (68%) **9** (97%)



3m **10** **11**

1,3-Disubstituted tetrahydroisoquinolines are obviously readily available from dihydroisoquinolines **3** [2]; the preparation of **11** is illustrative of this utility. Reduction of the allyl derivative **3m** to the *n*-propyl analog **10** demonstrated that the *N*-Boc-dihydroisoquinoline 3,4-double bond in this system is relatively resistant to catalytic hydrogenation [6]. The tetrahydroisoquinoline **11** was obtained by the reverse sequence of deprotection with trifluoroacetic acid followed by sodium borohydride reduction. A single diastereomer **11** was obtained by this process; the *cis*-1,3 stereochemical assignment was made

Table II

Properties of 1,3-Disubstituted *N*-Boc-1,2-Dihydroisoquinolines **3**

Entry **3**	Mp (°C)	IR ν (cm^{-1}) C=O [a]	EIMS m/z	^1H NMR ($CDCl_3$) δ, J (Hz)	Molecular Formula	Calcd./Found C	H	N
a	oil	1707	301 (molecular ion), 245, 230, 186	0.94 (t, 3H, J = 7.0), 1.21 (d, 3H, J = 6.8), 1.35-1.48 (m, 4H), 1.49 (s, 9H), 2.26 (m, 1H), 3.00 (m, 1H), 5.46 (q, 1H, J = 6.8), 6.00 (s, 1H), 7.00-7.20 (m, 4H)	$C_{19}H_{27}NO_2$	75.71 75.96	9.03 9.17	4.65 4.75
b	oil	1700	327 (molecular ion), 286, 230, 186	0.95 (t, 3H, J = 7.0), 1.35-1.50 (m, 4H), 1.48 (s, 9H), 2.24 (m, 1H), 2.36 (m, 2H), 2.90 (m, 1H), 5.02 (m, 1H), 5.34 (br t, 1H), 5.78 (m, 1H), 6.00 (s, 1H), 7.00-7.20 (m, 4H)	$C_{21}H_{29}NO_2$	77.03 77.30	8.93 8.99	4.28 4.47
c	oil	1701	343 (molecular ion), 287, 230, 186	0.87 (t, 3H, J = 7.1), 0.95 (t, 3H, J = 7.0), 1.25-1.60 (m, 10H), 1.48 (s, 9H), 2.34 (m, 1H), 3.00 (m, 1H), 5.25 (dd, 1H, J = 5.8, 9.0), 6.00 (s, 1H), 7.00-7.20 (m, 4H)	$C_{22}H_{33}NO_2$	76.92 77.17	9.68 9.53	4.08 3.98
d	oil	1700	343 (molecular ion), 287, 230, 186	0.92 (d, 3H, J = 6.5), 0.94 (t, 3H, J = 7.0, 1.01 (d, 3H, J = 6.5), 1.15 (m, 1H), 1.30-1.65 (m, 6H), 1.48 (s, 9H), 2.34 (m, 1H), 2.95 (m, 1H), 5.35 (m, 1H), 6.02 (s, 1H), 7.00-7.20 (m, 4H)	$C_{22}H_{33}NO_2$	76.92 77.28	9.68 9.48	4.08 3.89
e	oil	1697	377 (molecular ion), 286, 230, 186	0.95 (t, 3H, J = 7.0), 1.40-1.55 (m, 4H), 1.43 (s, 9H), 2.45 (m, 1H), 2.75-2.92 (m, 3H), 5.48 (br t, 1H, J = 7.5), 6.07 (s, 1H), 6.50 (d, 1H, J = 7.4), 6.90-7.20 (m, 8H)	$C_{25}H_{31}NO_2$	79.54 79.54	8.28 8.38	3.71 3.93
f	73-74	1697	-	1.18 (d, 3H, J = 7.0), 1.20-1.40 (m, 6H), 1.48 (s, 9H), 1.70-2.10 (m, 4H), 2.74 (m, 1H), 5.44 (q, 1H, J = 7.0), 6.07 (s, 1H), 7.04-7.20 (m, 4H)	$C_{21}H_{29}NO_2$	77.03 77.20	8.93 9.25	4.28 4.23
h	117-118	1692	-	1.03 (s, 9H), 1.36 (d, 3H, J = 6.9), 5.64 (q, 1H, J = 6.9), 6.40 (s, 1H), 7.15-7.50 (m, 9H)	$C_{21}H_{23}NO_2$	78.47 78.72	7.21 7.22	4.36 4.58
i	83-84	1698	363 (molecular ion), 307, 250, 206	0.92 (t, 3H, J = 7.0), 1.04 (s, 9H), 1.30-1.60 (m, 5H), 1.80 (m, 1H), 5.42 (br dd, 1H), 6.40 (s, 1H), 7.12-7.50 (m, 9H)	$C_{24}H_{29}NO_2$	79.30 79.18	8.04 8.06	3.85 4.00
j	138-139	1698	349 (molecular ion), 306, 250, 206	0.82 (d, 3H, J = 6.8), 1.05 (br s, 9H), 1.16 (d, 3H, J = 6.8), 1.95 (m, 1H), 5.10 (d, 1H, J = 8.7), 6.40 (s, 1H), 7.10-7.40 (m, 7H), 7.54 (m, 2H)	$C_{23}H_{27}NO_2$	79.04 78.74	7.79 7.62	4.01 4.03
k	143-145	1698	-	1.00 (d, 3H, J = 6.4), 1.05 (br s, 9H), 1.09 (d, 1H, J = 6.4), 1.30 (m, 1H), 1.80 (m, 2H), 5.55 (br dd, 1H), 6.41 (s, 1H), 7.12-7.50 (m, 9H)	$C_{24}H_{29}NO_2$	79.30 79.53	8.04 7.87	3.85 3.97
l	98-100	1694	347 (molecular ion), 306, 250, 206	1.03 (br s, 9H), 2.34 (m, 1H), 2.55 (m, 1H), 5.10 (m, 1H), 5.14 (m, 1H), 5.56 (m, 1H), 5.95 (m, 1H), 6.41 (s, 1H), 7.10-7.40 (m, 7H), 7.54 (m, 2H)	$C_{23}H_{25}NO_2$	79.50 79.76	7.26 7.37	4.03 4.24
m	175-176	1696	397 (molecular ion), 306, 250, 206	1.00 (br s, 9H), 2.95 (dd, 1H, J = 8, 13.6), 3.04 (dd, 1H, J = 8, 13.6), 5.81 (t, 1H, J = 8), 6.49 (s, 1H), 6.70 (br d, 1H, J = 7.3), 7.05 (m, 1H), 7.10-7.35 (m, 12H)	$C_{27}H_{27}NO_2$	81.58 81.31	6.85 6.85	3.52 3.74
n	202-204	1694	306, 250, 206	1.03 (br s, 9H), 6.41 (s, 1H), 6.90 (s, 1H), 7.00 (m, 2H), 7.10-7.38 (m, 7H), 7.50 (m, 1H), 7.62 (m, 1H), 8.10 (m, 2H)	$C_{27}H_{25}NO_3$	78.81 78.58	6.13 5.93	3.40 3.65

[a] Determined as a film (oils) or as a potassium bromide pellet.

on the basis of nuclear Overhauser effects observed between the protons at the two tertiary benzylic positions (H-1 and H-3).

Given the facility with which dihydroisoquinolines **2** could be lithiated and functionalized at the 1-position, it was of interest to determine if the process could be repeated on the resulting products **3**. Thus the lithiation and alkylation of **3g** was studied as a representative example. Lithiation at the tertiary benzylic position of this substrate was more difficult than lithiation at the secondary benzylic position of **2**, but was effectively achieved with excess (2 equivalents) *sec*-butyllithium-tetramethylethylenediamine (TMEDA) complex at -40°. Respectable yields of the 1,1-dialkylated products **12a-d** were obtained from the resulting lithio species.

Successsful lithiation and electrophilic trapping of

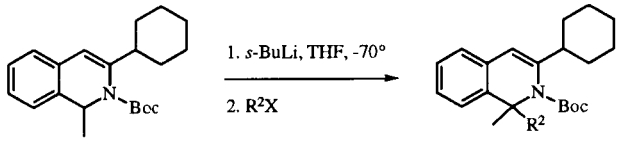
Table III

Properties of 1,3-Disubstituted Isoquinolines **5**

Entry 5	HCl salt Mp (°C) [a]	EIMS m/z [b]	^{1}H NMR ($CDCl_3$) δ, J (Hz) [b]	Molecular Formula	Calcd./Found C	H	N
a	oil [b]	199 (molecular ion), 184, 171, 170, 157	0.96 (t, 3H, J = 7.3), 1.42 (m, 2H), 1.80 (m, 2H), 2.90 (t, 2H, J = 7.3), 2.95 (s, 3H), 7.32 (s, 1H), 7.52 (ddd, 1H, J = 1.3, 8.0, 8.4), 7.62 (ddd, 1H, J = 1.3, 8.0, 8.0), 7.72 (br d, 1H, J = 8.0), 8.06 (br d, 1H, J = 8.4)	$C_{14}H_{17}N$	84.37 84.07	8.60 8.78	7.03 6.99
c	139-140	-	0.96 (t, 3H, J = 7.2), 0.97 (t, 3H, J = 7.2), 1.35-1.56 (m, 4H), 1.72-1.90 (m, 4H), 2.90 (m, 2H), 3.26 (m, 2H), 7.30 (s, 1H), 7.48 (ddd, 1H, J = 1.3, 8.0, 8.4), 7.60 (ddd, 1H, J = 1.3, 8.0, 8.0), 7.72 (br d, 1H, J = 8.0), 8.10 (br d, 1H, J = 8.4)	$C_{17}H_{23}N$•HCl	73.49 73.17	8.71 8.68	5.04 5.10
d	oil [b]	-	0.95 (t, 3H, J = 7.2), 0.98 (d, 6H, J = 6.6), 1.40 (m, 2H), 1.80 (m, 2H), 2.28 (m, 1H), 2.90 (t, 2H, J = 7.7), 3.15 (d, 2H, J = 7.2), 7.31 (s, 1H), 7.48 (ddd, 1H, J = 1.2, 8.0, 8.4), 7.60 (ddd, 1H, J = 1.2, 8.0, 8.0), 7.72 (br d, 1H, J = 8.0), 8.08 (br d, 1H, J = 8.4)	$C_{17}H_{23}N$	84.59 84.23	9.60 9.50	5.80 5.68
e	180-181	-	0.97 (t, 3H, J = 7.3), 1.45 (m, 2H), 1.70 (m, 2H), 2.94 (t, 2H, J = 7.5), 4.65 (s, 2H), 7.10-7.28 (m, 5H), 7.38 (s, 1H), 7.42 (ddd, 1H, J = 1.3, 8.0, 9.3), 7.60 (ddd, 1H, J = 1.2, 8.0, 8.2), 7.72 (br d, 1H, J = 8.2), 8.08 (br d, 1H, J = 9.3)	$C_{20}H_{21}N$•HCl	77.03 76.87	7.11 7.01	4.49 4.29
f	205-206	-	1.25-1.60 (m, 5H), 1.70-1.94 (m, 3H), 2.08 (m, 2H, 2.90 (m, 1H), 2.94 (s, 3H), 7.31 (s, 1H), 7.50 (ddd, 1H, J = 1.3, 8.0, 8.0), 7.60 (ddd, 1H, J = 1.2, 8.0, 8.0), 7.74 (br d, 1H, J = 8.0), 8.08 (br d, 1H, J = 8.0)	$C_{16}H_{19}N$•HCl	73.41 73.10	7.70 7.59	5.35 5.51
h	207-208	-	3.02 (s, 3H), 7.38 (m, 1H), 7.45-7.60 (m, 3H), 7.65 (ddd, 1H, J = 1.3, 8.0, 8.0), 7.74 (br d, 1H, J = 8.0), 7.90 (s, 1H), 8.12 (m, 3H)	$C_{16}H_{13}N$•HCl	75.14 75.18	5.52 5.52	5.48 5.64
i	162-165	261 (molecular ion), 246, 232, 219	1.02 (t, 3H, J = 7.3), 1.52 (m, 2H), 1.95 (m, 2H), 3.37 (t, 2H, J = 7.8), 7.38 (m, 1H), 7.45-7.60 (m, 3H), 7.65 (ddd, 1H, J = 1.3, 8.0, 8.0), 7.85 (br d, 1H, J = 8.0), 7.91 (s, 1H), 8.16 (m, 3H)	$C_{19}H_{19}N$•HCl	76.62 76.70	6.77 6.74	4.70 4.60
j	157-161	247 (molecular ion), 232, 219, 204	1.51 (d, 3H, J = 6.7), 3.98 (heptet, 1H, J = 6.7), 7.40 (m, 1H), 7.46-7.58 (m, 3H), 7.64 (ddd, 1H, J = 1.3, 8.0, 8.0), 7.84 (br d, 1H, J = 8.0), 7.93 (s, 1H), 8.24 (m, 3H)	$C_{18}H_{17}N$•HCl	76.18 76.02	6.39 6.70	4.94 5.30
k	192-194	-	1.05 (d, 3H, J = 6.6), 2.44 (m, 1H), 3.23 (d, 2H, J = 7.2), 7.40 (m, 1H), 7.46-7.54 (m, 3H), 7.64 (ddd, 1H, J = 1.3, 8.0, 8.0), 7.84 (br d, 1H, J = 8.0), 7.91 (s, 1H), 8.16 (m, 3H)	$C_{19}H_{19}N$•HCl	76.62 76.59	6.77 6.82	4.70 4.87
m	67-68 [b]	295 (molecular ion), 294, 293, 217	4.75 (s, 2H), 7.12-7.54 (m, 9H), 7.62 (ddd, 1H, J = 1.0, 8.0, 8.0), 7.86 (br d, 1H, J = 8.0), 7.98 (s, 1H), 8.12 (br d, 1H, J = 8.0), 8.20 (m, 2H)	$C_{22}H_{17}N$	89.46 89.03	5.80 5.83	4.74 4.96
n	134-136 [b]	311 (molecular ion), 234, 205, 204	7.20-7.32 (m, 3H), 7.35-7.48 (m, 4H), 7.52-7.65 (m, 3H), 7.84 (d, 1H, J = 8.0), 7.94 (d, 1H, J = 8.0), 8.07 (s, 1H), 8.20 (m, 2H)	$C_{22}H_{15}NO$ [c]	83.21 83.22	5.19 5.23	4.20 4.38

[a] Hydrochloride salts were crystallized from ethanol/ether. [b] Free base. [c] Contains 0.27 equivalents of ethyl acetate (^{1}H nmr).

N-Boc-1,2-dihydroisoquinolines appears to be limited to examples in which a substituent is present at the 3-position. Treatment of the parent *N*-Boc-1,2-dihydroisoquinoline (**2**, R^1 = H) with *sec*-butyllithium (or lithium diisopropylamide) at -70° gave a deeply colored solution, the color of which did not dissipate upon addition of methyl iodide and subsequent warming to room temperature. No recognizable products were obtained from the reaction mixture upon workup. Similar observations were made when this sequence was applied to *N*-Boc-1,2-dihydro-4-phenylisoquinoline. Further investigation is required to explain these results; however, from a synthetic point of view it should be noted that 1-substituted isoquinolines and tetrahydroisoquinolines are available by more direct methods. Thus certain 1-substituted isoquinolines can be prepared by the Reissert reaction [7], and 1-substituted 1,2,3,4-tetrahydroisoquinolines are available *via* lithiation of tetrahydroisoquinoline *N*-pivaloyl [8], *N-bis*-(dimethylamino)phosphinoyl [9], *N*-formamidinyl [10], *N*-oxazolinyl [11], and *N*-Boc [12] derivatives. The methodology presented in this paper based on the lithiation of dihydroisoquinolines **2** would appear to complement these well-



3g **12a-d**

R^2X	Product (% Yield)	R^2
MeI	**12a** (70)	Me
n-BuI	**12b** (75)	Bu-*n*
CH_2=$CHCH_2Br$	**12c** (53)	CH_2CH=CH_2
$PhCH_2Br$	**12d** (50)	CH_2Ph

established procedures in terms of the facility with which 1,3-disubstituted isoquinoline derivatives can be prepared.

EXPERIMENTAL

Silica gel chromatography was performed under medium pressure using 230-400 mesh Merck Kieselgel. Melting points are uncorrected. Microanalyses were performed by the Syntex Analytical Department. The pmr and cmr spectra were measured on a Bruker WM 300 and AM 500 spectrometers in deuteriochloroform solution referenced to internal tetramethylsilane. Dihydroisoquinolines **2a** and **2c** have been described previously [2].

2-(*tert*-Butoxycarbonyl)-3-cyclohexyl-1,2-dihydroisoquinoline (**2b**).

This was prepared in 60% overall yield from *N*-Boc-2-methylbenzylamine (**1**) as previously described, mp 65-66°; ir (potassium bromide): ν 1707 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.20-1.35 (m, 6H), 1.47 (s, 9H), 1.57-2.10 (m, 4H), 2.80 (br t, 1H), 4.63 (s, 2H), 6.10 (s, 1H), 7.06-7.24 (m, 4H).

Anal. Calcd. for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68; N, 4.47. Found: C, 77.04; H, 8.85; N, 4.63.

General Procedure for the Preparation of 1,3-Disubstituted-*N*-Boc-1,2-dihydroisoquinolines **3**.

A solution of dihydroisoquinoline **2** (5 mmoles) in 25 ml of tetrahydrofuran was cooled to -70° and *sec*-butyllithium (1.3 *M* solution in cyclohexane, 6 mmoles) was added *via* syringe over a period of *ca.* 1 minute. The resulting deeply colored solution (dark brown for **2a,b**; deep blue for **2c**) was stirred at -70° for 15 minutes, and the electrophile (6 mmoles) was then added. The solution became essentially colorless at once. The mixture was poured into 100 ml of water and extracted with ethyl acetate. The extract was washed with brine, dried (sodium sulfate), filtered and concentrated under reduced pressure to afford the crude product **3**. Purification was effected by silica gel chromatography (**3a-g**: elution with 2-5% ethyl acetate/hexane) or crystallization (**3i** from hexane, **3l** from ethyl acetate/hexane). In the chromatographic purification of **3b**, **3c**, and **3e**, minor amounts (*ca.* 5% yield) of the more polar products **4b**, **4c**, and, **4e** were also isolated. Yields for the products **3** are given in Table I and spectral and analytical data are given in Table II.

2-(*tert*-Butoxycarbonyl)-3-*z*-(*n*-butylidene)-4-(2-propen-1-yl)-1,2,3,4-tetrahydroisoquinoline (**4b**).

This compound was obtained as an oil; ir (film): ν 1698 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.87 (t, 3H, J = 7.3 Hz), 1.26-1.50 (m, 2H), 1.48 (s, 9H), 1.96 (m, 2H), 2.25 (m, 1H), 2.40 (m, 1H), 3.26 (dd, 1H, J = 4.7, 9.8 Hz, H-4), 4.28 (br d, 1H, J = 16 Hz, H-1a), 5.00 (m, 1H), 5.04 (m, 1H), 5.16 (br d, 1H, J = 16 Hz, H-1b), 5.32 (t, 1H, J = 7 Hz, butylidene H-1'), 5.94 (m, 1H), 7.00-7.20 (m, 4H); ms: (electron impact) m/z 327 (molecular ion), 271, 230.

Nuclear Overhauser experiments were used to establish the configuration of the butylidine side chain: irradiation at δ 5.32 (butylidine H-1') gave an enhancement of the signal at δ 3.26 (H-4); irradiation at δ 3.26 gave enhancements of the signals at δ 5.32 and δ 7.10 (H-5).

Anal. Calcd. for $C_{21}H_{29}NO_2$: C, 77.03; H, 8.93; N, 4.28. Found: C, 77.22; H, 8.97; N, 4.37.

2-(*tert*-Butoxycarbonyl)-3-*z*-(*n*-butylidene)-4-(*n*-butyl)-1,2,3,4-tetrahydroisoquinoline (**4c**).

This compound was obtained as an oil; ir (film): ν 1698 cm^{-1}; ^1H (deuteriochloroform): δ 0.87 (t, 3H, J = 7.3 Hz), 0.90 (t, 3H, J = 7.0 Hz), 1.24-1.55 (m, 8H), 1.46 (s, 9H), 2.00 (m, 2H), 3.16 (m, 1H, H-4), 4.26 (br d, 1H, J = 16 Hz, H-1a), 5.18 (br d, 1H, J = 16 Hz, H-1b), 5.30 (t, 1H, J = 7.2 Hz, butylidine H-1'), 7.00-7.20 (m, 4H); ms: (electron impact) m/z 343 (molecular ion), 286, 231.

Anal. Calcd. for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68; N, 4.08. Found: C, 77.29; H, 9.60; N, 4.18.

General Procedures for the Conversion of *N*-Boc-1,2-dihydroisoquinolines **3** to Isoquinolines **5**.

Method A.

Trifluoroacetic acid (2 ml) was added to a solution of *N*-Boc-1,2-dihydroisoquinoline **3** (3.2 mmoles) in 2 ml of dichloromethane at room temperature. After 15 minutes the mixture was concentrated under reduced pressure and the residue was dissolved in 15 ml of ethanol. Potassium acetate (980 mg, 10 mmoles) and iodine (810 mg, 3.2 mmoles) were added and the mixture was heated under reflux for 30 minutes after which time the iodine color had dissipated. The cooled reaction mixture was added to aqueous 5% ammonium hydroxide and extracted twice with ethyl acetate. The combined extract was washed with brine, dried over sodium sulfate, and concentrated to afford the crude isoquinoline **5**. Purification by silica gel chromatography (5% ethyl acetate/hexane) afforded the pure free base which could be converted to the hydrochloride salt with ethanolic-hydrogen chloride and ether.

Method B.

Trifluoroacetic acid (2 ml) was added to a solution of *N*-Boc-1,2-dihydroisoquinoline **3** (1.9 mmoles) in 7 ml of dichloromethane at room temperature. The resulting solution was stirred for 1 hour. The reaction mixture was diluted with 25 ml of dichloromethane and was then carefully washed with cold 10% aqueous ammonium hydroxide. The dichloromethane layer was washed with brine and filtered through a pad of anhydrous sodium sulfate. The dried dichloromethane solution was stirred at room temperature, and a solution of iodine (506 mg, 2 mmoles) in *ca.* 15 ml of chloroform was added. The resulting solution was stirred for 30 minutes and was then washed with aqueous sodium bisulfite solution, dried (sodium sulfate), and concentrated *in vacuo* to afford the crude isoquinoline **5**. Yields for the products **5** are given in Table I and spectral and analyti-

cal data are given in Table III.

4-Hydroxy-3-phenyl-1-(prop-2-yl)isoquinoline (**6**).

Deprotection and oxidation of *N*-Boc-1,2-dihydroisoquinoline **3k** according to Method B afforded a mixture of products that were separated by silica gel chromatography (5% ethyl acetate/hexane). The first component eluted was isoquinoline **5k** (33%) (Table III). The second component eluted was the 4-hydroxy derivative **6** (45%) which was crystallized from hexane, mp 123-124°; ir (potassium bromide): ν 3200 (br), 3063, 1394, 1383, 1273 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.45 (d, 6H, J = 6.8 Hz), 3.86 (heptuplet, 1H, J = 6.8 Hz), 4.80 (br s, 1H, exchanges with deuterium oxide -OH), 7.42 (br t, 1H), 7.55 (m, 3H), 7.68 (br t, 1H), 7.86 (br d, 2H), 8.18 (d, 1H, J = 8.3 Hz), 8.28 (d, 1H, J = 8.6 Hz); cmr (deuteriochloroform): δ 22.3 (q), 30.9 (d), 122.3 (d), 124.5 (d), 126.6 (s), 127.0 (d), 128.2 (s), 128.9 (d), 129.4 (d), 133.9 (s), 137.9 (s), 157.9 (s); ms: (electron impact) m/z 263 (molecular ion), 262, 248, 235.

Anal. Calcd. for $C_{18}H_{17}NO$: C, 82.09; H, 6.51; N, 5.32. Found: C, 82.38; H, 6.48; N, 5.55.

3-Cyclohexyl-1-[(4-methoxyphenyl)methyl]isoquinoline (**9**).

Condensation of the lithio species of **2b** with 4-methoxybenzaldehyde as described above afforded **3h** as a diastereomeric mixture (oil, 90% yield). Methanesulfonyl chloride (185 mg, 1.53 mmoles) was added to a solution of **3h** (624 mg, 1.4 mmoles) and triethylamine (0.3 ml) in 10 ml of dichloromethane at room temperature. The mixture was stirred for 12 hours, and was then quenched by addition of ice-water and extracted with dichloromethane. The extract was washed with aqueous sodium bicarbonate and brine, dried over sodium sulfate, and concentrated under reduced pressure. Purification by silica gel chromatography (5% ethyl acetate/hexane) afforded 400 mg (62%) of chloride **7** as a mixture of diasteriomers: ms: (electron impact) m/z 332 (molecular ion -Cl). This material was dissolved in 10 ml of tetrahydrofuran, potassium *tert*-butoxide (300 mg) was added, and the mixture was heated under reflux for 4 hours. The cooled reaction mixture was diluted with ethyl acetate, washed with water and brine, and dried over sodium sulfate. Evaporation under reduced pressure afforded a residue that was purified by silica gel chromatography (5% ethyl acetate/hexane) to give 250 mg (68%) of the mixture of olefins **8**. This material was dissolved in 6 ml of dichloromethane and 0.5 ml of trifluoroacetic acid was added. The mixture was stirred at room temperature for 10 minutes, and was then concentrated under reduced pressure. The residue was partitioned between ethyl acetate and 1*N* sodium hydroxide solution. The ethyl acetate layer was washed with water and brine, dried over sodium sulfate, and evaporated. Silica gel chromatography (5% ethyl acetate/hexane) afforded 187 mg (97%) of isoquinoline **9**, mp 68-69°; ^1H nmr (deuteriochloroform): δ 1.25-1.55 (m, 5H), 1.78 (m, 1H), 1.90 (m, 2H), 2.12 (m, 2H), 2.85 (m, 1H), 3.73 (s, 3H), 4.56 (s, 2H), 6.76 (d, 2H, J = 8.7 Hz), 7.18 (d, 2H, J = 8.7 Hz), 7.35 (s, 1H), 7.40 (ddd, 1H, J = 1.0, 8.0, 8.0 Hz), 7.54 (ddd, 1H, J = 1.0, 8.0, 8.0 Hz), 7.72 (dd, J = 1.0, 8.0 Hz), 8.04 (dd, J = 1.0, 8.0 Hz); ms: (electron impact) m/z 331 (molecular ion), 302, 290, 277, 276, 263.

Anal. Calcd. for $C_{23}H_{25}NO$: C, 83.39; H, 7.55; N, 4.23. Found: C, 83.08; H, 7.74; N, 4.34.

cis-3-Phenyl-1-(*n*-propyl)-1,2,3,4-tetrahydroisoquinoline (**11**).

A solution of **3m** (400 mg, 1.15 mmoles) in 20 ml of ethyl acetate containing 100 mg of 10% palladium on carbon was hydrogenated at 50 psi for 18 hours. The mixture was filtered and evaporated to afford dihydroisoquinoline **10** (singlet for H-4 at δ 6.40 in the ^1H nmr spectrum) in quantitative yield. This material was dissolved in 3 ml of dichloromethane and 2 ml of trifluoroacetic acid was added. The solution was stirred at room temperature for 15 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in 15 ml of ethanol. The solution was cooled in an ice-bath and sodium borohydride was added in small portions until the mixture was basic (litmus paper). Excess sodium borohydride was decomposed with acetic acid, and the reaction mixture was partitioned between ethyl acetate and dilute aqueous ammonium hydroxide solution. The organic layer was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (5% ethyl acetate/hexane) to give 205 mg (71% overall) of tetrahydroisoquinoline **11** as an oil; ^1H nmr (deuteriochloroform): δ 0.98 (t, 3H, J = 7.3 Hz), 1.48 (sextet, 2H, J = 7.3 Hz), 1.70 (br s, exchanges with deuterium oxide, NH), 1.68 (m, 1H), 2.00 (m, 1H), 2.90 (dd, 1H, J = 3.8, 15.8 Hz, $H\text{-}4_{eq}$), 2.98 (dd, 1H, J = 10.8, 15.8 Hz, $H\text{-}4_{ax}$), 4.00 (dd, 1H, J = 3.8, 10.8 Hz, H-3), 4.25 (br d, 1H, H-1), 7.05-7.40 (m, 7H), 7.45 (m, 2H); ms: (electron impact) m/z 250 (molecular ion), 209, 208.

Nuclear Overhauser experiments were used to establish the *cis*-1,3 stereochemistry: irradiation at δ 4.25 (H-1) gave an enhancement of the signal at δ 4.00 (H-3) and vice versa. The base was converted to the hydrochloride salt from ethanolic hydrogen chloride and ether, mp 259-261°.

Anal. Calcd. for $C_{18}H_{21}N\bullet HCl$: C, 75.11; H, 7.70; N, 4.87. Found: C, 75.48; H, 7.70; N, 5.06.

Typical Procedure for Preparation of 1,1,3-Trisubstituted-*N*-Boc-1,2-dihydroisoquinolines **12**.

2-(*tert*-Butoxycarbonyl)-1-(*n*-butyl)-3-cyclohexyl-1,2-dihydro-1-methylisoquinoline (**12b**).

To a -70° solution of dihydroisoquinoline **3g** (327 mg, 1 mmole) and TMEDA (0.3 ml, 2 mmoles) in 15 ml of tetrahydrofuran was added *sec*-butyllithium (1.5 ml of 1.3*M* solution in cyclohexane, 2 mmoles). The resulting purple solution was stirred at -70° for 1 hour and was then allowed to warm to *ca.* -40° over a period of 30 minutes. Addition of *n*-butyl iodide (0.23 ml, 2 mmoles) caused the solution to decolorize. The reaction mixture was quenched with aqueous ammonium chloride and extracted with ether. The ether extract was washed with 5% hydrochloric acid and brine, dried over sodium sulfate, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography (2% ethyl acetate/hexane) afforded 285 mg (74%) of **12b** as a thick oil; ir (film): ν 1713, 1643 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.82 (t, 3H, J = 7.0 Hz), 1.1-1.4 (m, 10 H), 1.44 (s, 9H), 1.70-1.85 (m, 4H), 1.84 (s, 3H), 2.04 (m, 2H), 2.70 (m, 1H), 5.96 (s, 1H), 6.98 (m, 1H), 7.15 (m, 3H); ms: (electron impact) m/z 383 (molecular ion), 326, 270, 226.

Anal. Calcd. for $C_{25}H_{37}NO_2$: C, 78.28; H, 9.72; N, 3.65. Found: C, 78.56; H, 9.98; N, 3.77.

The following compounds were similarly prepared:

2-(*tert*-Butoxycarbonyl)-3-cyclohexyl-1,2-dihydro-1,1-dimethylisoquinoline (**12a**).

This compound was crystallized from hexane at -70° (yield 70%), mp 91-92°; ir (potassium bromide): ν 1714, 1645 cm^{-1};

^{1}H nmr (deuteriochloroform): δ 1.20-1.35 (m, 6 H), 1.42 (s, 9H), 1.70 (s, 6H), 1.84 (m, 2H), 2.06 (m, 2H), 2.32 (m, 1H), 6.10 (s, 1H), 7.05 (m, 1H), 7.15 (m, 2H), 7.22 (m, 1H); ms (electron impact) m/z 341 (molecular ion), 285, 270, 226.

Anal. Calcd. for $C_{22}H_{31}NO_2$: C, 77.38; H, 9.15; N, 4.10. Found: C, 77.10; H, 9.12; N, 3.89.

2-(*tert*-Butoxycarbonyl)-3-cyclohexyl-1,2-dihydro-1-methyl-1-(2-propen-1-yl)isoquinoline (**12c**).

This compound was obtained as a low melting waxy solid (yield 53%); ir (potassium bromide): ν 1716, 1641 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.15-1.40 (m, 6 H), 1.43 (s, 9H), 1.70 (m, 2H), 1.86 (s, 6H), 2.08 (m, 2H), 2.32 (m, 1H), 2.60 (br d, 2H), 4.95 (m, 1H), 4.98 (m, 1H), 5.60 (m, 1H), 6.04 (s, 1H), 7.05 (m, 1H), 7.15 (m, 3H); ms: (chemical ionization, NH_3) m/z 368 (molecular ion +1), 326, 268, 226.

Anal. Calcd. for $C_{24}H_{33}NO_2$: C, 78.43; H, 9.05; N, 3.81. Found: C, 78.55; H, 9.26; N, 3.70.

1-Benzyl-2-(*tert*-butoxycarbonyl)-3-cyclohexyl-1,2-dihydro-1-methylisoquinoline (**12d**).

This compound was obtained as an oil (yield 50%); ir (film): ν 1714, 1641 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.15-1.40 (m, 6 H), 1.44 (s, 9H), 1.75 (m, 2H), 1.87 (s, 6H), 2.15 (m, 2H), 2.38 (m, 1H), 2.70 (d, 1H, J = 12.7 Hz), 3.44 (d, 1H, J = 12.7 Hz), 6.16 (s, 1H), 6.50 (m, 1H), 6.58 (br d, 1H), 6.92 (m, 1H), 7.00-7.30 (m, 6H); ms: (chemical ionization, NH_3) m/z 418 (molecular ion +1), 326, 318, 316, 226.

Anal. Calcd. for $C_{28}H_{35}NO_2$: C, 80.36; H, 8.45; N, 3.35. Found: C, 80.56; H, 8.64; N, 3.15.

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[5] A 20% yield of the oxazolidone resulting from cyclization of the Boc group onto the benzylic position of **3h** was also obtained.

[6] Compound **10** is obviously available by direct alkylation of **2c**. Preparation *via* **3m** was carried out to investigate the susceptibility of the 3,4-double bond to hydrogenation. The reluctance of the 3,4-double bond in **3m** and **10** to undergo hydrogenation appears to be due to the presence of the 3-phenyl group. Related 3-alkyl-*N*-Boc-1,2-dihydroisoquinolines have been reduced under similar conditions (reference 2).

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