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CARBON DIOXIDE: A REAGENT FOR THE PROTECTION OF NUCLEOPHILIC CENTRES AND THE SIMULTANEOUS ACTIVATION OF ELECTROPHILIC ATTACK. PART II. A NEW SYNTHETIC METHOD FOR THE 1-SUBSTITUTION OF 1,2,3,4-TETRAHYDROISOQUINOLINES.

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Abstract: Tetrahydroisoquinoline was converted into several 1-substituted derivatives by using carbon dioxide both for N-protection and to give an intermediate carbanion stabilizing group. t-Butyllithium was used as a lithating agent at the alpha-carbon atom of the secondary amino group. The resulting 1-substituted 1,2,3,4-tetrahydroisoquinoline-2-carboxylic acids underwent smooth acid-catalysed decarboxylation under mild conditions.

The formation of a new carbon-carbon bond at the alpha-position of secondary amines utilizing the dipole stabilized carbanion concept[1], has enabled Seebach,[2] Meyers,[3] and Beak,[4] to design efficient approaches to natural products synthesis.[3a] We recently successfully transformed[5] N-unsubstituted indoles into N-unsubstituted 2-substituted indoles, using carbon dioxide as an easily removed protecting group and simultaneously activating group, with t-butyllithium as a lithiating agent. This prompted us to investigate similar conditions for carbon-carbon bond formation at the alpha-position of secondary amines.

We now describe novel conversions of 1,2,3,4-tetrahydro-isoquinoline,[2a,2b,3b] into 1-substituted derivatives by the following one-pot sequence:-

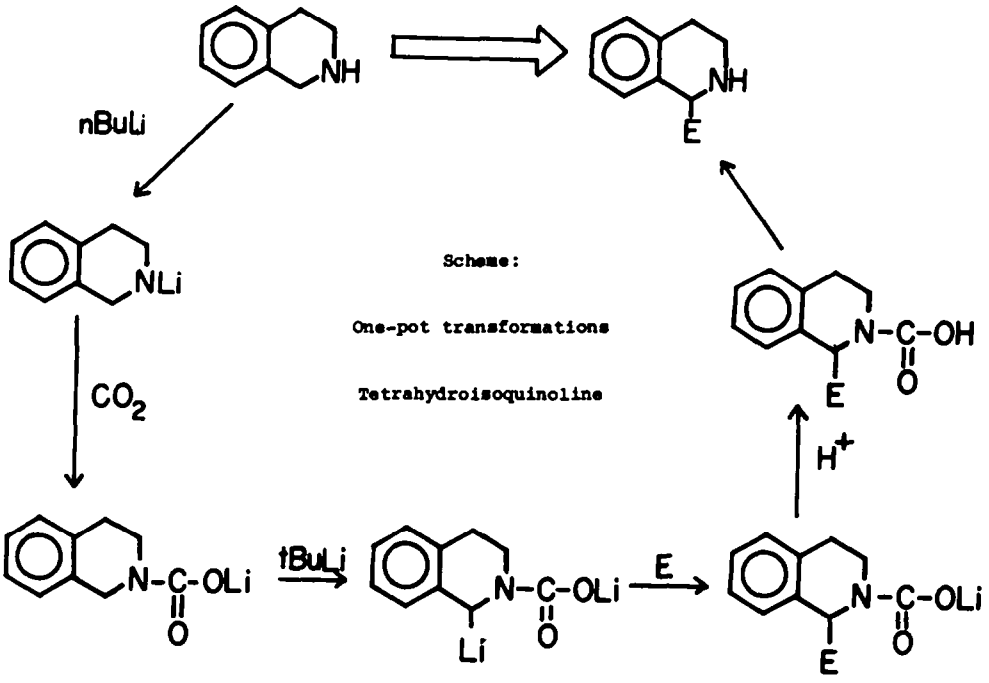
(i) Protection. Tetrahydroisoquinoline was converted quantitatively into the corresponding N-lithium carboxylate by reaction with n-butyllithium in tetrahydrofuran, followed by quenching with carbon dioxide in tetrahydrofuran.

(ii) Lithiation. Lithiation of this N-lithium carboxylate was accomplished by the addition of 1.2 equivalents of t-butyllithium in tetrahydrofuran at ca -20 °C.

(iii) C-C bond formation. This was performed by adding 1.0 equivalent of the electrophile at -70 °C and then allowing the mixture to rise to 25 °C over a few hours.

(iv) Deprotection. The reaction mixture was poured into aqueous 2N hydrochloric acid at 0 °C, and kept for a few minutes.

(v) Work-up. The solution was made alkaline with sodium hydroxide at 0 °C, extracted with ethyl ether, dried ($MgSO_4$), the solvent removed, and the whole purified by distillation or column chromatography (silica gel). This gave the corresponding 1-substituted isoquinoline in high yield.



Scheme:

One-pot transformations

Tetrahydroisoquinoline

The results are shown in the Table. Alkyl iodides, both primary and secondary, react readily to give 1-alkyl-1,2,3,4-tetrahydroisoquinolines in good yield. Aldehydes and ketones afford the expected 1-(alpha-hydroxyalkyl) derivatives, and an example of an epoxide reacting to yield the corresponding 1-(beta-hydroxyalkyl) compound is provided. Finally it has been possible to introduce the ethoxycarbonyl group using ethyl chloroformate as the electrophile.

The value of a synthetic method should be judged by its convenience, and by its versatility. The presently reporting method is convenient in that it is a one-part procedure using readily available reagents. It is versatile in that each of the three vital stages, i.e. protection, main reaction, and deprotection, is accomplished readily. The particular ease of introduction and of removal characterize our use of carbon dioxide as a protecting group. In previously reported methods, the protection step was generally rather readily performed, however the deprotection step was not so mildly accomplished. Deprotection by alkaline or acid hydrolysis[2,3,4] does not allow the survival of, for example, an ester group,[3b] while in our method an ethoxycarbonyl group could be introduced unchanged (entry 9 in Table). Although our method requires the use of t-butyllithium, it has been shown that this reagent can be handled under conditions similar to those used for n-butyllithium.

Table. Preparation of 1-Substituted 1,2,3,4-Tetrahydroisoquinolines

Entry	1-Substituent	Electrophile	Yield (%)	Bp(°C/mmHg[a]) or Mp(°C)	Spectral Charact.
1	D	D_2O	85	58°/4.0	b
2	CH_3	CH_3I	62	60°/2.5	c
3	Et	EtI	60	70°/1.5	d
4	n-Bu	n-BuI	69	85°/1.5	e
5	i-Pr	i-PrI	66	75°/2.0	f
6	$(CH_2)_4C(OH)$	$(CH_2)_4C=O$	86	102.0-103.0	g
7	$Ph_2C(OH)$	$Ph_2C=O$	74	259.0-260.0[h]	i
8	3,4-$(MeO)_2C_6H_3CH(OH)$	3,4-$(MeO)_2C_6H_3CHO$	71	198.5-200.5[h]	j
9	EtOCO	$ClCO_2Et$	54	Oil	k
10	HOCH-$(CH_2)_4$-CH	Cyclohexene oxide	71	158.0-160.0	l

Footnotes to Table:

[a] Bulb to bulb distillation bath temperature.

[b] ^{1}H NMR ($CDCl_3$) 1.92 (s, 1H, =NH), 2.70-3.28 (m, 4H, -$(CH_2)_2$-), 4.07 (s, 1H, =CH-N=), and 7.27 ppm (s, 4H, aromatic protons).

[c] IR (NaCl) 3275, (N-H) cm^{-1}. ^{1}H NMR ($CDCl_3$) 1.44 (d, J = 7 Hz, 3H, CH_3), 1.80 (s, 1H, =NH), 2.63-3.37, (m,4H, -$(CH_2)_2$-), 4.13 (q, J = 7 Hz, 1H, =CH-N=), and 7.23 ppm (s, 4H, aromatic protons), bp (lit.[2a]) 125 °C/14 mmHg.

[d] IR (NaCl) 3300 (N-H) cm^{-1}. ^{1}H NMR ($CDCl_3$) 0.98 (t, J = 7 Hz, 3H, -CH_2CH_3) 1.76 (s, 1H, =NH), 1.83 (q, 2H, -CH_2CH_3), 2.57-3.28 (m, 4H, -$(CH_2)_2$-), 3.93 (brt, 1H, =CHN=), and 7.20 ppm (s, 4H, aromatic protons), bp (lit.[7]) 75-78 °C/0.5 mmHg.

[e] IR (NaCl) 3290, (N-H) cm^{-1}. ^{1}H NMR ($CDCl_3$) 0.83-1.02 (m, 3H, CH_3), 1.23-1.83 (m, 7H, -$(CH_2)_3$- and =NH), 2.63-3.30 (m, 4H, Ar-(CH_2)-N=), 4.02 (brt, J = 7 Hz, 1H, =CH-N=), and 7.22 ppm (s, 4H, aromatic protons), bp (lit.[2a])
110°C/0.4 mmHg.

[f] IR (NaCl) 3300 (N-H) cm^{-1}. ^{1}H NMR ($CDCl_3$) 0.74 (d, J = 7 Hz, 3H, CH_3), 1.11 (d, J = 7 Hz, 3H, CH_3), 1.68 (s, 1H, =NH), 2.00-2.53 (m, 1H, -$CH(CH_3)_2$), 2.62-3.47 (m, 4H, -$(CH_2)_2$-), 3.98 (d, J = 6 Hz, 1H, =CH-N=), and 7.22 ppm (s, 4H, aromatic protons), bp (lit.[2a]) 155 °C/14 mmHg.

[g] IR (KBr) 3290 (N-H), 3225, (O-H) cm^{-1}. ^{1}H NMR ($CDCl_3$) 1.60-1.80 (m, 8H, -$(CH_2)_4$-), 2.58-3.50 (m, 6H, -$(CH_2)_2$-, =NH, and -OH), 4.12 (s, 1H, =CH-N=), 7.25 ppm (s, 4H, aromatic protons), mp (lit.[2b]) 106 °C.

[h] mp of hydrochloride salt.

[i] Hydrochloride salt: IR (KBr) 3320, (OH), 2740 (NH_2^+) cm^{-1}, ^{1}H NMR (D_2O) 2.50-3.17 (m, 4H, -$(CH_2)_2$-), 5.40 (s, 1H, =CH-N=), 5.93 (d, J = 8 Hz, 1H, C(8)-H), and 6.4-7.75 ppm (m, 13H, aromatic protons), mp. (lit.[8]) 259-260 °C (of hydrochloride salt).

[j] Hydrochloride salt IR (KBr) 3360 (OH), 2775 (NH_2^+) cm^{-1}. Free base ^{1}H NMR ($CDCl_3$) 2.22-3.12 (m, 4H, -$(CH_2)_2$-), 3.45-4.28 (m, 9H, =N-H, =CHOH, -OH, -OCH_3), 4.68 (d, J = 6 Hz, 0.42H, =CH-NH-), 4.92 (d, J = 5 H, 0.58H, =CH,
-NH-), and 6.40-7.25 (m, 7H, aromatic protons). Mixture of diastereomers (4:3), mp (lit.[3b]) 198-200 °C (hydrochloride salt).

[k] IR (NaCl) 3340, (NH), 1735 (=C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$) 1.17 (t, J = 8 Hz, 3H, -OCH_2CH_3), 2.22 (s, 1H, =N-H), 2.57-3.45 (m, 4H, -$(CH_2)_2$-), 4.13 (q, J = 8 Hz, 2H, -OCH_2CH_3), 4.63 (s, 1H, =CH-N=), and 7.00-7.42 ppm (m, 4H, aromatic protons).

[l] IR (KBr) 3290 (N-H), 3070 (O-H) cm^{-1}. ^{1}H NMR ($CDCl_3$) 0.77-2.17 (m, 8H, -$(CH_2)_3$-), 2.50-4.03 (m, 8H, -(CH_2)-, -OH, =N-H, =CH-CH(OH)-), 4.67 (d, J = 4 Hz, 1H, =CH-N=), and 7.23-7.43 ppm (m, 4H, aromatic protons). Elemental analysis requires C:77.88; H:9.15, N:6.05 %, Found C:77.90, H:9.47, N:5.85 %.

Experimental

General Melting points of the products were measured by a Thomas HOOVER Capillary Melting Point Apparatus and are uncorrected. Ir spectra are of NaCl or KBr discs using a PERKIN-ELMER 283 B. ^1H NMR spectra were obtained with a Varian EM 360 L using tetramethylsilane as an internal standard. Elemental analyses were carried out under the supervision of Dr. R. King of this Department. n-Butyllithium and t-butyllithium (Aldrich) were used without further purification. Tetrahydrofuran, reagent grade from Fisher Chemical Co., was dried with calcium hydride and used directly after distillation under dry argon. Carbon dioxide (Matheson) was used after passing over anhydrous calcium sulfate. Electrophiles were distilled before use.

Processes (i) and (ii) were carried out under dry argon.

General Procedure Tetrahydrofuran (30.0 ml) was added to 1,2,3,4-tetrahydroisoquinoline (500 mg, 3.8 mmole) in a Shlenk type reactor in an Ar atmosphere at 25 °C. The resulting solution was cooled to -70 °C and n-butyllithium (1.5 ml of 2.5M n-hexane solution) was added dropwise. The solution was held at -70 °C for 5 min., allowed to rise to 0 °C, and kept at 0 °C for 5 min. The lithium derivative of the tetrahydroisoquinoline in solution in tetrahydrofuran was added to tetrahydrofuran (50.0 ml) which had previously been saturated with carbon dioxide; during the addition more carbon dioxide was passed through the solution. The solution was allowed to rise to 25 °C. The solvent was evaporated under reduced pressure and the pale yellow residue of N-lithium isoquinoline carboxylate was thoroughly washed with 50 ml of ethyl ether - n-hexane (1:9). The solid was placed into a Shlenk type reactor, and the atmosphere was replaced by argon. Tetrahydrofuran (30.0 ml) was added: after stirring for several minutes the whole formed a homogeneous solution which was cooled to -70 °C. t-Butyllithium (2.8 ml, 1.6M n-pentane solution) was added in one portion, the color became dark red. The cooling bath was replaced by an ice-salt bath, and the solution was kept ca -20 °C for 30 minutes when a pale yellow precipitate formed. The whole was cooled to -70 °C and the electrophile (3.8 mmole) in tetrahydrofuran (1.0 ml) was added. The reaction mixture was allowed to regain room temperature, and then was added to aqueous hydrochloric acid (2N) and ice at 0 °C. Gas was evolved. The solution was kept for a few minutes at 0 °C and then brought to pH ca 11 by aqueous sodium hydroxide at 0 °C. The solution was extracted with ethyl ether, the extracts dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The pale yellow oily product was purified by bulb to bulb distillation or column chromatography (silica gel).

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