REACTIONS OF 2-(2-LITHIOPHENYL)ETHYL CHLORIDE WITH IMINES AND ISOCYANATES. SYNTHESIS OF 1,2,3,4-TETRAHYDROISOQUINOLINES AND 3,4-DIHYDRO-1(2H)-ISOQUINOLINONES

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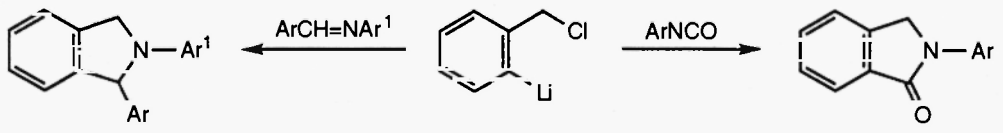
Abstract

2-(2-Lithiophenyl)ethyl chloride **4** condenses with appropriately substituted imines **5a-c** (R_1 = H, R_2 = aryl, R_3 = aryl, benzenesulfonyl) to give the corresponding 1,2-disubstituted 1,2,3,4-tetrahydroisoquinolines **6**. Hindered imines **5f-g** (R_1, R_2 = aryl) or N-alkyl substituted imines **5e-f** fail to react, while those bearing α-hydrogens react as acids with **4**, thus precluding formation of **6**. Treatment of **4** with phenanthridine affords 10,11-dihydrotribenzo[a,c,h]15bH-quinolizine **6e** in a convenient one-step synthesis. 2-Substituted-3,4-dihydro-1(2H)-isoquinolinones **8** are obtained in good yields from the reaction of **4** with alkyl and aryl isocyanates **7**.

Introduction

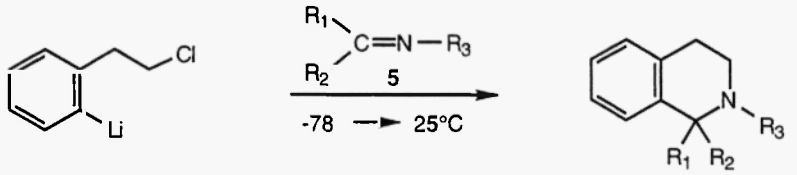
In connection with a search for convenient, new methods for the synthesis of isoquinolines and isoquinolinones, we were drawn to earlier reports of the preparation of indolines **1** (1) and phthalimidines **3** (2) via reactions of 2-lithiobenzyl chloride **2** with imines and isocyanates, respectively. The success of these reactions prompted us to investigate the feasibility of developing possible general syntheses of isoquinolines **6** and isoquinolinones **8** by similar reactions utilizing 2-(2-lithiophenyl)ethyl chloride **4**. We now report on the scope and limitations of this synthetic method.



1 **2** **3**

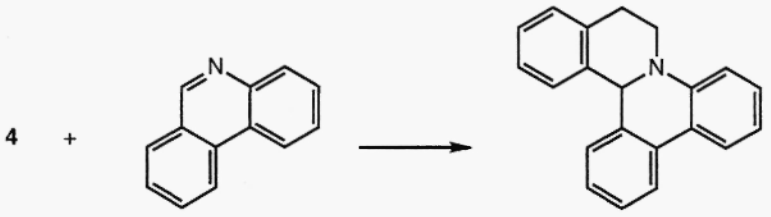
Results and Discussion

Reaction of **4**, generated by halogen-metal exchange from 2-(2-bromophenyl)ethyl chloride using 1.1 equiv of n-BuLi in THF at -78°C, with C, N-diaryl imines **5a-c** afforded good yields (Table 1) of 1,2-diaryl-1,2,3,4-tetrahydroisoquinolines **6a-c** (3,4). Similar treatment of phenanthridine **5d**



4 **6**

with **4** gave 10,11-dihydrotribenzo[a,c,h]15bH-quinolizine **6e** in 81% yield. This facile synthesis of **6e** represents a significant improvement over that reported previously (5).



5d **6e**

The success of the reaction of lithio derivative **4** with imines **5** is dependent on the nature of both the C- and N-substituents of the imine. For example, the failure of imine **5e** ($R_3 = CH_3$) to react with **4** demonstrates the necessity for an electron withdrawing N-substituent to stablize the incipient negative charge on nitrogen resulting from attack of the phenyl carbanion at the imine carbon. The lack of reactivity of **5f** and **5g** ($R_1 = R_2 = Ph$) towards **4** may be attributed to steric hindrance at the imine carbon. Imine **5h**, which contains α-hydrogens, underwent deprotonation in the presence of **4**, leading ultimately to the formation of 1-phenyl-1-hexanone via alkylation of its α-carbanion by n-butyl bromide formed in the initial metal-halogen exchange, followed by hydrolysis of the resulting C-alkylated imine. Although imines unsubstituted on nitrogen, i.e., with $R_3 = H$, cannot be used in this methodology, tetrahydroisoquinolines **6** with $R_3 = H$ can be obtained as illustrated by the condensation of **4** with N-benzenesulfonyl imine **5c**, followed by reductive cleavage of the $PhSO_2$ group of the resulting 2-benzenesulfonyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline **6c** with sodium naphthalenide in DME (**6**) to afford 1-phenyl-1,2,3,4-tetrahydroisoquinoline **6d** (1,7) in 85% yield.

Treatment of a variety of alkyl and aryl isocyanates **7** with organolithium reagent **4** afforded 2-substituted-3,4-dihydro-1(2H)-isoquinolinones **8** in yields of 71-85% (Table 2). This general reaction appears to be limited only by the availability of the isocyanate. The parent 3,4-dihydro-1(2H)-isoquinolinone **8b** was prepared by reductive cleavage of 2-(4-toluenesulfonyl)-3,4-dihydro-

1(2H)-isoquinolinone **8e** in 51% yield using a refluxing mixture of zinc and acetic and hydrochloric acids (8).

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Table 1. Reactions of 2-(2-Lithiophenyl)ethyl Chloride **4** with Imines **5**

Imine	R_1	R_2	R_3	Product	Yield (%)	MP °C
5a	H	Ph	4-MePh	**6a**	78	78-79[a]
5b	H	Ph	4-ClPh	**6b**	64	110-111.5
5c	H	Ph	$PhSO_2$	**6c**	67	102.5-103.5
5c	H	Ph	$PhSO_2$	**6d**[b]	85	99.5-100.5[c]
5d		phenanthridine		**6e**	81	154-157[d]
5e	H	Ph	Me	—[e]	—	—
5f	Ph	Ph	Me	—[f]	—	—
5g	Ph	Ph	4-MePh	**5g**	100	—
5h	Me	Ph	4-MePh	—[g]	—	—

[a] Lit. (12) mp 74-75°C. [b] From reductive cleavage of **6c**. [c] Lit. (7a) mp 98-100°C. [d] Lit. (5) mp 155°C. [e] Benzaldehyde (79%) was obtained following aqueous workup. [f] Benzophenone was quantitatively recovered upon workup. [g] 1-Phenyl-1-hexanone (62%) was isolated by column chromatography.

Table 2. Reactions of 2-(2-Lithiophenyl)ethyl Chloride **4** with Isocyanates **7**

Isocyanate	R	Product	Yield (%)	MP °C
7a	Me	**8a**	85	—[a, b]
7b	n-Pr	**8b**	72	—[a]
7c	i-Pr	**8c**	75	—[a]
7d	Ph	**8d**	74	104-105[c]
7e	4-Tosyl	**8e**	71	137-138.5
7f	4-Tosyl	**8f**[d,e]	51	—[a]

[a] Colorless liquid. [b] Ref. 13. [c] Lit. (13a) mp 101-103°C. [d] From reductive cleavage of **8e**. [e] ^1H NMR data for **8f** was consistent with that reported earlier (14).

Experimental

Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia. ^1H and ^{13}C NMR spectra were recorded on a Bruker WP-270 spectrometer using $CDCl_3$ as solvent and TMS as the internal reference. Analytical TLC was performed on Eastman chromatogram sheets, type 13181 (silica gel) with fluorescent indicator. Flash chromatography refers to standard MPLC as described by Still (9) on silica gel 60 (230-400 mesh). All reagents were the best grade commercially available and were used without further purification. 2-(2-Bromophenyl)ethyl chloride was prepared as reported previously (10). n-BuLi was titrated prior to use with diphenylacetic acid as indicator (11).

General Procedure for the Reaction of 2-(2-Lithiophenyl)ethyl Chloride 4 with Isocyanates and Imines

To a magnetically stirred solution of 2-(2-bromophenyl)ethyl chloride (1.10 g, 5.0 mmol) in 50 mL of anhydrous THF at -78°C was added via syringe a solution of n-BuLi in hexane (5.5 mmol). The resulting solution was stirred at -78°C under N_2 for 30 min, then a solution of the appropriate isocyanate or imine (5.5 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred at -78°C for an additional 30 min and allowed to gradually warm to room temperature. After being stirred at ambient temperature overnight, the reaction mixture was quenched with 20 mL of a saturated NH_4Cl solution and the THF was removed under reduced pressure at the rotary evaporator. Additional water (50 mL) was added, and the mixture was extracted with ether (3 X 75 mL). The combined ethereal layers were washed with water, dried ($MgSO_4$), filtered, and concentrated to give the crude product which was purified by flash column chromatography.

2-(4-Chlorophenyl)-1-phenyl-1,2,3,4-tetrahydroisoquinoline 6b

^1H NMR: δ 7.11-7.24 (m, 11H), 6.71 (br d, 2H, J = 9.0 Hz), 5.73 (s, 1H), 3.61-3.70 (m, 1H), 3.36-3.46 (m, 1H), 2.86-2.90 (m, 2H). ^{13}C NMR: δ 148.2, 142.7, 137.5, 135.4, 128.9, 128.3, 128.1, 127.8, 127.2, 126.9, 126.2, 122.4, 115.2, 63.0, 44.0, 28.0. Anal. Calcd for $C_{21}H_{18}NCl$: C, 78.86; H, 5.67; N, 4.38. Found: C, 78.92; H, 5.69; N, 4.37.

2-(Benzenesulfonyl)-1-phenyl-1,2,3,4-tetrahydroisoquinoline 6c

^1H NMR: δ 7.65-7.68 (br d, 2H, J = 7.1 Hz) 7.37-7.43 (m, 1H), 7.11-7.31 (m, 9H), 6.95-7.00 (m, 2H), 6.25 (S, 1H), 3.81 (dddd, 1H, J = 14.2, 6.2, 3.0, 1.2 Hz), 3.33 (ddd, 1H, J = 14.2, 10.6, 5.7 Hz), 2.67 (ddd, 1H, J = 16.7, 10.6, 6.2 Hz), 2.56 (ddd, 1H, J = 16.7, 5.7, 3.0 Hz). ^{13}C NMR: δ 134.2, 133.9, 132.2, 130.0, 128.7, 128.4, 128.3, 127.3, 127.1, 59.5, 39.3, 26.9. Anal. Calcd for $C_{21}H_{19}NO_2S$: C, 72.18; H, 5.48; N, 4.01. Found: C, 72.18; H, 5.52; N, 4.01.

2-(n-Propyl)-3,4-dihydro-1(2H)-isoquinolinone 8b

^1H NMR: δ 8.07 (d, 1H, J = 7.5 Hz), 7.28-7.41 (m, 2H), 7.15 (d, 1H, J = 7.2 Hz), 3.52 (2

overlapping t, 4H, J = 7.4, 6.5 Hz), 2.95 (t, 2H, J = 6.5 Hz), 1.65 (sextet, 2H, J = 7.4 Hz), 0.96 (t, 3H, J = 7.4 Hz). ^{13}C NMR: δ 164.1, 137.9, 131.2, 129.6, 128.0, 126.8, 126.6, 48.9, 46.0, 28.0, 20.8, 11.2. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.53; H, 8.11; N, 7.40.

2-(i-Propyl)-3,4-dihydro-1(2H)-isoquinolinone 8c

^{1}H NMR: δ 8.07 (br d, 1H, J = 7.5 Hz), 7.28-7.41 (m, 2H), 7.15 (br d, 1H, J = 7.5 Hz), 5.09 (heptet, 1H, J = 6.8 Hz), 3.41 (t, 2H, J = 6.5 Hz), 2.92 (t, 2H, J = 6.5 Hz), 1.10 (d, 6H, J = 6.8 Hz). ^{13}C NMR: δ 163.6, 137.7, 131.2, 130.0, 128.2, 126.8, 126.5, 43.7, 38.8, 28.4, 19.6. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.14; H, 8.18; N, 7.14.

2-(4-Toluenesulfonyl)-3,4-dihydro-1(2H)-isoquinolinone 8e

^{1}H NMR: δ 7.97 (br d, 3H, J = 8.3 Hz), 7.46 (dd, 1H, J = 7.4, 6.3 Hz), 7.31 (br d, 3H, J = 8.3 Hz), 7.21 (br d, 1H, J = 7.4 Hz), 4.22 (t, 2H, J = 6.2 Hz), 3.11 (t, 2H, J = 6.2 Hz), 2.40 (s, 3H). ^{13}C NMR: δ 163.3, 144.6, 139.2, 136.3, 133.3, 129.3, 129.0, 128.4, 128.2, 127.3, 44.7, 28.8, 21.5. Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.84; H, 5.01; N, 4.69.

1-Phenyl-1,2,3,4-tetrahydroisoquinoline 6d

Sodium (0.46 g, 20 mmol) was added to a solution of naphthalene (2.56g, 20 mmol) in 40 mL of anhydrous DME in a 100 mL flask which was then capped with a rubber septrum. The mixture was stirred at room temperature until the green color persisted (ca. 2 h). A solution of **6c** (1.75 g, 5.0 mmol) in 10 mL of DME was injected via syringe and the mixture was stirred for 1 h then quenched by the addition of 1 mL of water. The organic solvent was distilled on the rotary evaporator and 50 mL of water was added to the residue. The mixture was extracted with 3 X 50 mL portions of $CHCl_3$ and the combined extracts were washed with water, dried ($MgSO_4$) and concentrated. The residue was chromatographed (gradient elution, 0-100% EtOAc in $CHCl_3$) to yield 0.78 g (85%) of **6d** as a white solid, mp 98-100°C. Recrystallization form hexane afforded 6**d** as delicate white needles, mp 99.5-100.5°C.

3,4-Dihydro-1(2H)-isoquinolinone 8f

2-(4-Toluenesulfonyl)-3,4-dihydro-1(2H)-isoquinolinone **8e** (1.51 g, 5.0 mmol) was dissolved in a mixture of 20 mL of glacial AcOH and 2 mL of concentrated HCl by warming. After heating to near reflux, zinc dust (6.54 g, 100 mmol) was added cautiously. The reaction mixture was then heated under reflux for 4 h during which time two additional 2.0 mL aliquots of concentrated HCl were added. After cooling the reaction mixture to room temperature, the unreacted zinc was filtered. The filtrate was concentrated to a pale yellow viscous oil to which was added 100 mL of water. The aqueous mixture was extracted with 3 X 75 mL portions of ether and the combined ethereal extracts were washed with water and dried ($MgSO_4$). Concentration then afforded a pale yellow oil which was chromatographed. Elution with CH_2Cl_2 afforded first 0.31 g (50%) of p-thiocresol as a white solid, mp 43-45°C followed by 0.19 (13%) of unreacted **8e**. The eluent was changed to EtOAc and 0.38 g (51%) of **8f** was collected as a pale yellow oil.

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