Synthesis of 3-Substituted and 3,4-Disubstituted 3,4-Dihydro-1(2*H*)-isoquinolones by Condensation of Lithiated *N*,*N*-Diethyl-*o*-toluamide with Imines[1]

Robin D. Clark* and Jahangir[2]

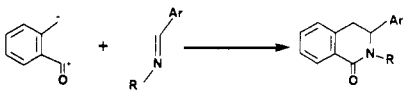
Institute of Organic Chemistry, Syntex Research, Palo Alto, California 94304

Received May 27, 1987

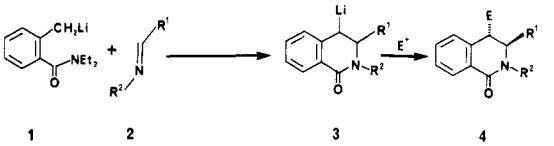
Lithiated *N*,*N*-diethyl-*o*-toluamide was condensed with imines to afford 3,4-dihydro-1(2*H*)-isoquinolones. The products were deprotonated under the reaction conditions, and electrophilic trapping afforded *trans*-2,3,4-trisubstituted-2,3-dihydro-1(2*H*)-isoquinolones. This methodology was also applied to the synthesis of 7-substituted 7,8-dihydro-1,6-naphthyridin-5(6*H*)-ones.

Our interest in the preparaton of certain 3-aryl-3,4-dihydro-1(2*H*)-isoquinolones prompted us to investigate the annelation approach outlined in Scheme I.[3] We felt that this synthetic approach would offer significant advantages over classical methodology, such as cyclization of phenylethyl isocyanates, which would be expected to involve multistep and often low-yielding reaction sequences.[4] Since 3,4-dihydro-1(2*H*)-isoquinolones can be reduced to 1,2,3,4-tetrahydroisoquinolines, this methodology would also afford tetrahydroisoquinolines with substitution patterns not readily accessible by other means.[5] Related methodology is the condensaton of lithiated phthalides with 3,4-dihydroisoquinolines, which affords fused 3,4-dihydro-1(2*H*)-isoquinolones substituted with hydroxyl groups.[6] Also directly related are the condensations of homophthalic anhydrides[7a,b] and esters[7c] with benzaldimines, which afford 4-carboxy-3,4-dihydro-1(2*H*)-isoquinolones. The reaction of trimethylsilyl triflate activated imines with lithiated 3-cyano-4-methylpyridine to give isoquino[2,1-*b*][2,7]naphthyridines in a two-step sequence formally analogous to that depicted in Scheme I has also recently been reported.[8] In this paper, we describe the realization of the annelation in Scheme I by condensation of lithiated *N*,*N*-diethyl-*o*-toluamide (**1**) with imines (**2**). Trapping of the intermediate 4-lithio-3,4-dihydro-1-(2*H*)-isoquinoline **3** permits introduction of a 4-substituent (Scheme II).

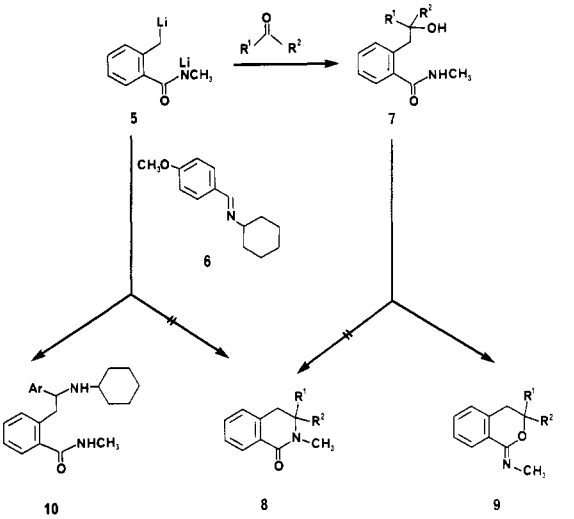
Scheme I



Scheme II



Scheme III



Results

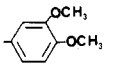
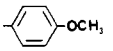
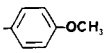
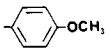
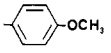
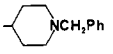
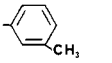
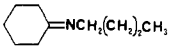
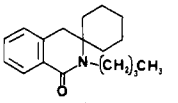
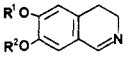
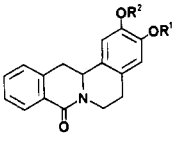
Condensation of Lithiated *N*,*N*-Diethyl-*o*-toluamide with Imines. As a starting point we investigated the reaction of dilithiated *N*-methyl-*o*-toluamide[9] **5** with benzaldimine **6** (Scheme III). The related condensation of **5** with carbonyl compounds, followed by acid treatment of adducts **7**, was initially formulated as giving 3,4-dihydro-1(2*H*)-isoquinolones **8**.[10] However, the products obtained by this sequence were subsequently shown to be the cyclic imino ethers **9**.[11] We found that addition of **5** to imine **6** gave adduct **10**, which did not close to the desired 3,4-dihydro-1(2*H*)-isoquinolone (**8**; R^1 = H, R^2 = cyclohexyl) either under the reaction conditions or upon workup. This is in contrast to the reported reaction of **5** with certain nitriles which led, after acidic workup, to 3-substituted 1(2*H*)-isoquinolones.[12] While in principle adduct **10** could be cyclized to the 3,4-dihydro-1(2*H*)-isoquinolone **8** (e.g. by thermolysis under acid catalysis; vide infra), we were interested in a more direct route, and this transformation was not investigated further. Other unsuccessful attempts to prepare **8** (R^1 = H, R^2 = cyclohexyl) directly included addition of imine **6** to dilithiated *o*-toluic

(1) Contribution No. 741 from the Syntex Institute of Organic Chemistry.
(2) Syntex Postdoctoral Fellow, 1987–1988.
(3) A preliminary account of some of this work has been published: Clark, R. D. *Heterocycles* **1985**, *23*, 825.
(4) Irie, H.; Shiina, A.; Fushimi, T.; Katakawa, J.; Fujii, N.; Yajima, H. *Chem. Lett.* **1980**, 875.
(5) The syntheses of isoquinoline and derivatives have been divided systematically into 15 different types: Kametani, T.; Fukumoto, K. In *The Chemistry of Heterocyclic Compounds: Isoquinolines, Part 1*; Grethe, G., Ed.; Wiley: New York, 1981; Vol. 38, p 139. There are relatively few syntheses of tetrahydroisoquinolines that employ the type 7 connectivity exemplified in Scheme I. These include cycloadditions of *o*-quinodimethanes with nitriles or imines and condensations described in ref 6–8.
(6) Marsden, R.; MacLean, D. B. *Tetrahedron Lett.* **1983**, *24*, 2063.
(7) (a) Haimova, M. A.; Mollov, N. M.; Ivanova, S. C.; Dimitrova, A. I.; Ognyanov, V. I. *Tetrahedron* **1977**, *33*, 331. (b) Cushman, M.; Cheng, L. *J. Org. Chem.* **1978**, *43*, 286. (c) Shamma, M.; Tomlinson, H. H. *J. Org. Chem.* **1978**, *43*, 2852.
(8) Jahangir; MacLean, D. B.; Brook, M. A.; Holland, H. L. *J. Chem. Soc., Chem. Commun.* **1986**, 1608.
(9) Vaulx, R. L.; Puterbaugh, W. H.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 3514.
(10) Mao, C. L.; Barnish, I. T.; Hauser, C. R. *J. Heterocyclic Chem.* **1969**, *6*, 83.
(11) Bailey, D. M.; DeGrazia, C. G. *Tetrahedron Lett.* **1970**, 633.
(12) Poindexter, G. S. *J. Org. Chem.* **1982**, *47*, 3787.

0022-3263/87/1952-5378$01.50/0

Table I. 3-Substituted 3,4-Dihydro-1(2*H*)-isoquinolines from Condensation of Lithiated *N*,*N*-Diethyl-*o*-toluamide with Imines

11 12 13

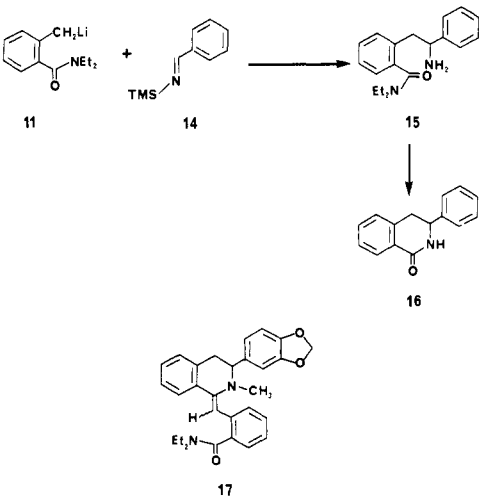
entry	imine	R^1	R^2	product (% yield)	mp, °C
1	**12a**		CH_3	**13a** (37)	98–99
2	**12b**		$(CH_2)_3CH_3$	**13b** (42)	oil
3	**12c**			**13c** (48)	oil
4	**12d**		$CH_2CH_2N(CH_3)_2$	**13d** (37)	oil
5	**12e**			**13e** (24)	oil
6	**12f**		CH_2Ph	**13f** (55)	oil
7	**12g**		CH_3	**13g** (47)	80–81
8	**12h**			**13h** (42)	oil
9	**12i**		CH_3	**13i** (56)	80–81
10	**12j**		CH_3	**13j** (30)	150–151
11	**12k**		CH_3	**13k** (44)	oil
12	**12l**			 **13l** (44)	oil
13	**12m**, $R^1 = R^2 = CH_3$			 **13m** (43), $R^1 = R^2 = CH_3$	138–139[a]
14	**12n**, $R^1 + R^2 = CH_2$			**13n** (59), $R^1 + R^2 = CH_2$	171–173

[a] Literature mp 142 °C.[19]

acid[13] and lithiated methyl *o*-toluate both of which gave complex product mixtures containing no **8**.

The transformation depicted in Scheme I was successfully realized when it was found that addition of benzaldimines to lithiated *N*,*N*-diethyl-*o*-toluamide (**11**)[14] directly afforded 3,4-dihydro-1(2*H*)-isoquinolones **13**. A number of examples of this reaction are listed in Table I. These reactions were carried out at −70 °C by addition of the imine to a preformed solution of **11** (LDA) in THF.[15] The mixture was then stirred at low temperature for 5–30 min followed by quenching with dilute aqueous HCl. It was found that quenching the reaction at low temperature was desirable since the product (**13**) underwent a number of side reactions, e.g. stilbene formation, under the basic conditions if the reaction mixture was allowed to warm to room temperature. The yields were generally in the

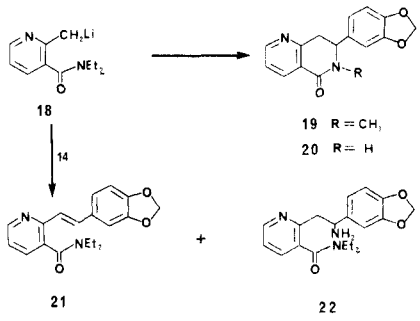
Scheme IV



11 14 15 16 17

(13) Creger, P. L. *J. Am. Chem. Soc.* **1970**, *92*, 1396.
(14) The addition of lithiated *N*,*N*-dimethyl-6-methoxy-*o*-toluamide to aldehydes has been reported: Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306.
(15) It was subsequently determined during the trapping studies (vide infra) that the reaction may also be carried out by addition of a mixture of the toluamide and imine to a −70 °C solution of 1 equiv of LDA. Yields in certain cases may be better with this protocol.

Scheme V



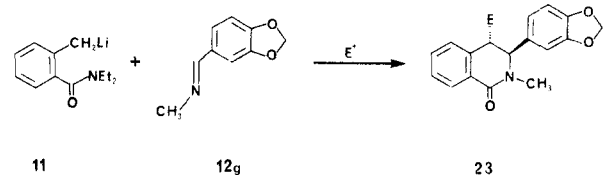
40–60% range and should be considered unoptimized. The reaction was applicable not only to benzaldimines (entries 1–10) but to certain enolizable aldimines (entry 11) and ketimines (entry 12) as well. Addition to 3,4-dihydroisoquinolones (entries 13–14) afforded 8-oxoberbines (**13m,n**).

In an attempt to prepare N-unsubstituted 3,4-dihydro-1(2*H*)-isoquinolones, the reaction of **11** with *N*-(trimethylsilyl)benzaldimine (**14**)[16a,b] was investigated (Scheme IV). In this case, the product isolated after aqueous workup was the adduct **15** (75% yield). This material was cyclized to **16** by heating in xylene in the presence of a catalytic amount of *p*-toluenesulfonic acid. The isolation of **15** led us to postulate that the mechanism of formation of the 3,4-dihydro-1(2*H*)-isoquinolones in Table I involves sequential addition of the lithio species (**11**) to the imine followed by ring closure with expulsion of lithium diethylamide. The reactions do not appear to involve the direct cycloaddition of an *o*-quinodimethane (vinyl ketene equivalent), which would be derived by elimination of lithium diethylamide from **11**. We have also isolated basic side products, such as **17** from the synthesis of **13g**, which are probably derived from attack of **11** on the product 3,4-dihydro-1(2*H*)-isoquinolone. This implies not only the intermediacy of **11** in the original condensation (as opposed to a vinyl ketene) but that the rate of the addition–ring closure sequence is close to being competitive with the initial addition itself.

Application of this methodology to lithiated *N,N*-diethyl-2-methylnicotinamide (**18**) led to the 7-substituted 7,8-dihydro-1,6-naphthyridin-5(6*H*)-one **19** in 55% yield. Reaction of **18** with *N*-(trimethylsilyl)benzaldimine (**14**) gave the uncyclized adduct **22** as before along with the elimination product **21**. Compound **22** was cyclized thermally to afford **20** (Scheme V). In principle, this annelation route should be applicable to a number of other heteroaromatic systems depending upon the availability of the requisite *o*-methyl carboxylic acid or carboxamide.

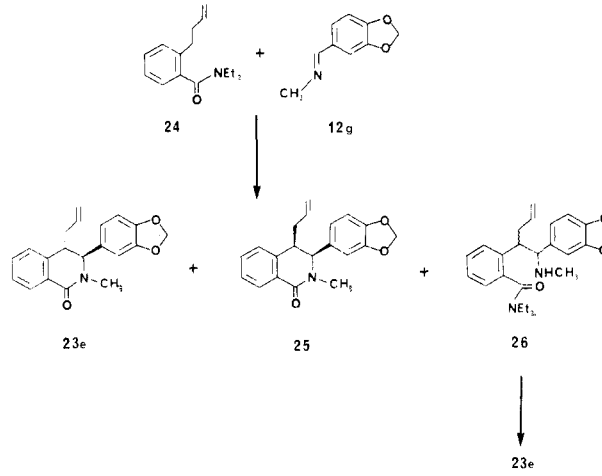
Electrophilic Trapping of Lithiated 3,4-Dihydro-1(2*H*)-isoquinolones. An additional feature of the cycloaddition process is that 1 equiv of strong base (lithium diethylamide)[17] is generated upon ring closure. This serves to deprotonate the product 3,4-dihydro-1(2*H*)-isoquinolone at the 4-position, giving a species that can be trapped with a suitable electrophile (Scheme II). The results of this cycloaddition–electrophilic trapping sequence with **11** and imine **12g** and a number of electrophiles are presented in Table II. These reactions were carried out by addition of a mixture of 1 equiv of *N,N*-diethyl-*o*-toluamide and imine to 1 equiv of LDA at −70 °C followed by addition of the electrophile after a suitable time period. One interesting, and initially confusing, aspect of the alkylations was that less active alkylating agents ($TMSCH_2Cl$, *n*-BuCl) could be added to the −70 °C reaction mixture almost immediately after the amide and imine. When the mixture was warmed to room temperature, respectable yields of alkylated products were obtained. However, immediate addition of more reactive agents (CH_3I, allyl bromide) led to recovered unalkylated 3,4-dihydro-1(2*H*)-isoquinolone. In these cases, the reaction mixture required stirring at low temperature for 1 h before addition of the alkylating agent for trapping to be observed. Apparently the subsequent deprotonation of the 3,4-dihydro-1(2*H*)-isoquinolone is relatively slow (compared to the initial immediate deprotonation of **11**). The unreactive alkylating agents do not react with the amide base(s), and deprotonation followed by alkylation occurs upon warming. Reactive agents, on the other hand, appear to quench the amide base before deprotonation of the product 3,4-dihydro-1(2*H*)-isoquinolone. Thus, additional time is required to allow the subsequent deprotonation before reactive electrophiles can be added.

Table II. 3,4-Disubstituted 3,4-Dihydro-1(2*H*)-isoquinolones from Electrophilic Trapping



entry	electrophile (E)	product (% yield)	mp, °C
1	TMSCl	**23a** (32)	170–171
2	$TMSCH_2Cl$	**23b** (58)	138–139
3	CH_3I	**23c** (62)	98–99
4	$CH_3(CH_2)_2CH_2Cl$	**23d** (59)	118–119
5	$CH_3(CH_2)_2CH_2Br$	**23d** (53)	
6	$CH_3(CH_2)_2CH_2I$	**23d** (68)	
7	$CH_2{=}CHCH_2Br$	**23e** (51)	119–120
8	$PhCH_2Cl$	**23f** (59)	oil

Scheme VI



The stereochemistry of the products (**23**) was assigned as trans on the basis of the small coupling constant (J_{AB} = 0–2 Hz) between H-3 and H-4 on the isoquinolone ring. This low J_{AB} is consistent with previous observations on related compounds and has been ascribed to pseudoaxial orientation of the C-3 and C-4 substituents.[18] For com-

(16) (a) Krüger, C.; Rochow, E. G.; Wannagat, U. *Chem. Ber.* **1963**, *96*, 2132. (b) Hart, D. J.; Kanai, K.; Thomas, D. G.; Yang, T.-K. *J. Org. Chem.* **1983**, *48*, 289.

(17) The base that leads to the subsequent deprotonation could also be LDA, since 1 equiv of diisopropylamine is present.

(18) Cushman, M.; Choong, T.-C.; Valko, S. T.; Koleck, M. P. *J. Org. Chem.* **1980**, *45*, 5067.

parative purposes, the trans allylated compound **23e** and its cis isomer **25** were prepared by a different route (Scheme VI). Condensation of lithiated *N,N*-diethyl-2-but-3-enylbenzamide (**24**) with imine **12g** afforded low yields of the separable diastereomers **23e** and **25** along with the main product adduct **26**. The latter compound gave **23e** upon thermolysis in xylene in the presence of *p*-toluenesulfonic acid. The coupling constants J_{AB} for H-3 and H-4 for **23e** (J_{AB} = 0.5 Hz) and **25** (J_{AB} = 5.9 Hz) were in accord with the assigned stereochemistry.[18]

Conclusion

The methodology described in this paper affords a route to 3,4-dihydro-1(2*H*)-isoquinolones with variable substituents at the 2-, 3-, and 4-positions. The groups in the 3- and 4-positions are introduced stereospecifically trans. These relatively complex structures, which would be difficult to prepare by classical synthetic routes, are assembled in a simple, one-pot procedure. Application of this annelation approach to a number of other 3,4-dihydro-1-(2*H*)-isoquinolones and 1,2,3,4-tetrahydroisoquinolines can be anticipated.

Experimental Section

Proton magnetic resonance spectra were measured on Varian HA-100 and Bruker WM 300 instruments and are reported in ppm (δ) downfield from an internal standard of tetramethylsilane. Mass spectra were obtained on an Atlaswerke CH-4 or CH-7 instrument. Medium-pressure (flash) chromatography was performed with 230–400 mesh Merck Kieselgel. Melting points are uncorrected. Elemental analyses were obtained from the Syntex analytical department. The *N*-methyl imines used in the condensation reactions were prepared by reaction of the requisite aldehyde and aqueous methylamine in CH_2Cl_2 in the presence of 4A molecular sieves. Other imines were prepared by azeotropically distilling water from a benzene solution of the aldehyde or ketone and the amine.

Typical Procedure for the Preparation of Compounds in Table I: 3-(1,3-Benzodioxol-5-yl)-2-methyl-3,4-dihydro-1-(2*H*)-isoquinolone (13g). A solution of LDA was prepared at −70 °C by addition of 6.3 mL of 1.6 M *n*-butyllithium in hexane to 1.7 mL (10 mmol) of diisopropylamine in 20 mL of THF. A solution of *N,N*-diethyl-*o*-toluamide (1.91 g, 10 mmol) in 4 mL of THF was added dropwise at such a rate as to maintain the internal temperature below −65 °C. A solution of piperonal *N*-methylimine (**12g**) (1.79 g, 11 mmol) in 4 mL of THF was added dropwise over a period of 1 min. After an additional 5 min at −70 °C, dilute aqueous HCl was added, and the mixture was allowed to warm to room temperature. The mixture was extracted with ether, and the ether extract was dried (Na_2SO_4) and evaporated to an oil, which was approximately 95% pure **13g** (TLC, 75% EtOAc–hexane). Medium-pressure chromatography on silica gel (50% EtOAc–hexane) afforded 1.32 g (47%) of **13g**: mp 80–81 °C; IR (KBr) 1640 cm^{-1}; NMR ($CDCl_3$) δ 8.13 (m, 1 H), 7.34 (m, 2 H), 7.02 (d, 1 H, J = 7.6 Hz), 6.66 (d, 1 H, J = 8.5 Hz), 6.54 (d, 1 H, J = 8.5 Hz), 6.60 (s, 1 H), 5.88 (AB q, 2 H, J = 1.3 Hz), 4.68 (dd, 1 H, J = 3, 6.7 Hz), 3.60 (dd, 1 H, J = 6.7, 15.8 Hz), 3.08 (s, 3 H), 2.96 (dd, 1 H, J = 3, 15.8 Hz). Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.38; N, 4.98. Found: C, 72.64; H, 5.41; N, 4.96.

The aqueous acidic layer from above was basified with NH_4OH and extracted with ether. The ether extract was dried (Na_2SO_4) and evaporated to a residue that was purified by silica gel chromatography (5% CH_3OH–CH_2Cl_2) to afford 0.5 g (10% based on imine **12g**) of **17** as a pale yellow foam: NMR ($CDCl_3$) δ 7.92 (d, 1 H, J = 7.8 Hz), 7.50 (m, 1 H), 7.40–6.80 (m, 9 H), 5.96 (d, 2 H, J = 5 Hz), 5.82 (br s, 1 H), 3.95 (m, 1 H), 3.40 (m, 1 H), 3.16 (q, 2 H, J = 7 Hz), 2.95 (q, 2 H, J = 7 Hz), 2.86 (m, 1 H), 2.56 (s, 3 H), 1.36 (t, 3 H, J = 7 Hz), 1.05 (t, 3 H, J = 7 Hz); MS, *m/e* (relative intensity) 454 (68, M^+), 354 (94), 264 (100), 246 (34), 189 (28), 135 (46). Anal. Calcd for $C_{29}H_{30}N_2O_3$: C, 76.62; H, 6.65; N, 6.16. Found: C, 76.29; H, 6.74; N, 6.04.

3-Phenyl-3,4-dihydro-1(2*H*)-isoquinolone (16). A solution of LDA was prepared at −70 °C by addition of 12.5 mL of 1.6 M *n*-butyllithium (20 mmol) in hexane to 3.0 mL (22 mmol) of diisopropylamine in 40 mL of THF. A solution of *N,N*-diethyl-*o*-toluamide (3.82 g, 20 mmol) in 10 mL of THF was added dropwise followed by dropwise addition of *N*-(trimethylsilyl)-benzaldimine[16a,b] (**14**) (5.2 mL, 25 mmol). After 10 min, dilute aqueous HCl was added to the −70 °C mixture, which was then allowed to warm to room temperature. The acidic aqueous layer was separated, made basic with NH_4OH, and extracted with ether. The ether extract was dried (Na_2SO_4) and evaporated, and the residue was chromatographed on silica gel (5% CH_3OH–CH_2Cl_2, 0.1% NH_4OH) to afford 4.42 g (75%) of amine **15**: oil; NMR ($CDCl_3$) δ 7.55–7.16 (m, 9 H), 4.25 (m, 1 H), 3.58 (m, 1 H), 3.06 (q, 4 H, J = 5 Hz), 2.83 (m, 1 H), 1.83 (s, 2 H, exchanges with D_2O), 1.25 (t, 3 H, J = 5 Hz), 1.00 (t, 3 H, J = 5 Hz). Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 76.89; H, 8.07; N, 9.20.

A solution of **15** (4.2 g, 14.1 mmol) in 10 mL of xylene containing 0.09 g of *p*-toluenesulfonic acid was stirred at reflux for 48 h. The solution was concentrated in vacuo, diluted with ethyl acetate, washed with aqueous HCl and brine, dried (Na_2SO_4), and evaporated to a crystalline residue, which was triturated with hexane to afford 2.50 g (83%) of **16**: mp 130–131 °C; IR (KBr) 3200, 1650 cm^{-1}; NMR ($CDCl_3$) δ 8.10 (m, 1 H), 7.50–7.00 (m, 8 H), 6.23 (s, 1 H, exchanges with D_2O), 4.80 (t, 1 H, J = 5 Hz), 3.10 (d, 2 H, J = 5 Hz). Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.28. Found: C, 80.33; H, 6.02; N, 6.18.

7-(1,3-Benzodioxol-5-yl)-6-methyl-7,8-dihydro-5(6*H*)-1,6-naphthyridinone (19). This compound was prepared from *N,N*-diethyl-2-methylnicotinamide (**18**)[20] and imine **12g** according to the general procedure described for **13g**. Purification by silica gel chromatography (5% CH_3OH–CH_2Cl_2) afforded **19** in 55% yield: mp 147–148 °C; NMR ($CDCl_3$) δ 8.58 (dd, 1 H, J = 1.5, 3.5 Hz), 8.42 (dd, 1 H, J = 1.5, 5.5 Hz), 7.28 (dd, 1 H, J = 3.5, 5.5 Hz), 6.76–6.50 (m, 3 H), 5.90 (s, 2 H), 4.78 (dd, 1 H, J = 2, 5 Hz), 3.75 (dd, 1 H, J = 5, 11 Hz), 3.26 (dd, 1 H, J = 2, 11 Hz), 3.13 (s, 3 H). Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.93. Found: C, 68.35; H, 5.09; N, 9.84.

7-Phenyl-7,8-dihydro-5(6*H*)-1,6-naphthyridinone (20). A solution of amide **18**[20] (4.7 g, 24.5 mmol) in 5 mL of THF was added to a −70 °C solution of LDA (from 3.5 mL (25 mmol) of diisopropylamine and 15.6 mL (25 mmol) of 1.6 M *n*-BuLi in hexane) in 50 mL of THF. After 5 min, *N*-(trimethylsilyl)-benzaldimine[16a,b] (**14**) (6.2 mL, 30 mmol) was added, and the resulting mixture was allowed to warm to 0 °C. Water was added, and the mixture was partitioned between ether and aqueous 5% HCl. The ether layer was dried (Na_2SO_4) and evaporated to afford a residue, which was purified by silica gel chromatography (5% CH_3OH–CH_2Cl_2) to afford 1.37 g (20%) of styrene **21**: oil; IR (film) 1640, 1580 cm^{-1}; NMR ($CDCl_3$) δ 8.64 (m, 1 H), 7.86 (d, 1 H, J = 16 Hz), 7.55 (m, 2 H), 7.35 (m, 2 H), 7.20 (dd, 1 H), 7.15 (d, 1 H, J = 16 Hz), 3.14 (t, 4 H, J = 7 Hz), 1.35 (t, 3 H, J = 7 Hz), 1.02 (t, 3 H, J = 7 Hz). Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 76.96; H, 7.18; N, 9.59.

The acidic aqueous layer from above was basified with NH_4OH and extracted with CH_2Cl_2 to afford crude adduct **22**. This material was dissolved in 75 mL of xylene, 0.15 g of *p*-toluenesulfonic acid was added, and the solution was stirred at reflux for 48 h. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (5% CH_3OH–CH_2Cl_2) to afford 2.2 g (40%) of **20**: mp 130–133 °C; NMR ($CDCl_3$) δ 8.67 (dd, 1 H, J = 1, 4 Hz), 8.33 (dd, 1 H, J = 1, 6 Hz), 7.33 (m, 6 H), 6.70 (s, 1 H, exchanges with D_2O), 4.90 (t, 1 H, J = 5 Hz), 3.30 (d, 2 H, J = 5 Hz). Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.40; N, 12.49. Found: C, 74.82; H, 5.39; N, 12.45.

Typical Procedure for the Preparation of Electrophilic Trapping Products 23 in Table II: *trans*-3-(1,3-Benzodioxol-5-yl)-2,4-dimethyl-3,4-dihydro-1(2*H*)-isoquinolone (23c). A solution of *N,N*-diethyl-*o*-toluamide (0.95 g, 5 mmol) and imine **12g** (0.90 g, 5.5 mmol) in 6 mL of THF was added dropwise to

(19) Lenz, G. R. *J. Org. Chem.* **1974**, *39*, 2846.

(20) Baumgarten, P.; Dornow, A. *Ber. Dtsch. Chem. Ges. B* **1939**, *72*, 563.

a −70 °C solution of LDA (from 0.84 mL (6 mmol) of diisopropylamine and 3.75 mL (6 mmol) of 1.6 M *n*-BuLi in hexane) in 10 mL of THF. The reaction mixture was allowed to stir with gradual warming to −45 °C over 2 h and was then cooled back to −70 °C. Iodomethane (1.24 mL, 20 mmol) was added, and the mixture was stirred at −70 °C for 1 h and then allowed to warm to room temperature. After dilution with ether, the mixture was washed with dilute aqueous HCl. The ether was dried (Na_2SO_4) and evaporated, and the residue was chromatographed on silica gel (medium pressure, 50% ethyl acetate–hexane) to afford 0.92 g of **23c**: mp 98–99 °C; NMR ($CDCl_3$) δ 8.14 (m, 1 H), 7.35 (m, 2 H), 7.01 (m, 1 H), 6.65 (d, 1 H, *J* = 7.9 Hz), 6.50 (m, 2 H), 5.87 (AB q, 2 H, *J* = 1.4 Hz), 4.38 (d, 1 H, *J* = 1.5 Hz), 3.12 (s, 3 H), 3.10 (dq, 1 H, *J* = 1.5, 7.1 Hz), 1.45 (d, 3 H, *J* = 7.1 Hz). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.22; H, 5.76; N, 4.75. Found: C, 73.08; H, 5.83; N, 4.69.

***trans*-3-(1,3-Benzodioxol-5-yl)-2-methyl-4-(2-propenyl)-3,4-dihydro-1(2*H*)-isoquinolone (23e)**: mp 119–120 °C; NMR ($CDCl_3$) δ 8.15 (m, 1 H), 7.35 (m, 2 H), 6.98 (m, 1 H), 6.64 (d, 1 H, *J* = 8 Hz), 6.46 (m, 2 H), 5.88 (AB q, 2 H, *J* = 1.35 Hz), 5.86 (m, 1 H), 5.18 (dd, 1 H, *J* = 1, 9 Hz), 5.10 (dd, 1 H, *J* = 1, 16 Hz), 4.54 (s, 1 H), 3.10 (s, 3 H), 2.95 (t, 1 H, *J* = 6 Hz), 2.45 (m, 2 H); MS, *m/e* (relative intensity) 321 (82, M^+), 306 (13), 280 (100), 279 (68), 239 (61), 159 (78), 158 (95), 130 (95), 129 (88), 115 (63). Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.68; H, 6.92; N, 4.09.

***trans*- and *cis*-3-(1,3-Benzodioxol-5-yl)-2-methyl-4-(2-propenyl)-3,4-dihydro-1(2*H*)-isoquinolone (23e and 25).** *N,N*-Diethyl-2-(3-butenyl)benzamide (**24**) was prepared by reaction of *o*-toluic acid dianion[13] with allyl bromide followed by conversion to the acid chloride (oxalyl chloride) and treatment with diethylamine. A solution of **24** (2.3 g, 10 mmol) in 5 mL of THF was added to a −70 °C solution of LDA (from 1.7 mL (12 mmol) of diisopropylamine and 6.25 mL of 1.6 M *n*-BuLi in hexane) in 40 mL of THF. After 5 min, a solution of imine **12g** (1.96 g, 12 mmol) was added, and the resulting solution was stirred 10 min at −70 °C. Dilute aqueous HCl was added, and the mixture was allowed to warm to room temperature. The mixture was poured into aqueous HCl and extracted with ether. The ether extract was dried (Na_2SO_4) and evaporated to a mixture of crude isomers **23e** and **25**, which were separated by silica gel chromatography (30% ethyl acetate–hexane). The less polar isomer (**23e**, 0.28 g, 9%) was identical with that from Table II). The more polar isomer was the cis compound **25** (0.07 g, 2%): mp 116–118 °C; NMR ($CDCl_3$) δ 8.16 (dd, 1 H, *J* = 1.5, 7.3 Hz), 7.42 (m, 2 H), 7.22 (d, 1 H, *J* = 7.5 Hz), 6.60 (d, 1 H, *J* = 8 Hz), 6.45 (dd, 1 H, *J* = 1.8, 8 Hz), 6.35 (d, 1 H, *J* = 1.8 Hz), 5.94 (m, 1 H), 5.86 (AB q, 2 H, *J* = 1.35 Hz), 5.21 (dd, 1 H, *J* = 1, 9 Hz), 5.15 (dd, 1 H, *J* = 1, 15 Hz), 4.42 (d, 1 H, *J* = 5.9 Hz), 3.76 (m, 1 H), 3.06 (s, 3 H), 2.68 (m, 1 H), 2.08 (m, 1 H). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.74; H, 5.96; N, 4.36. Found: C, 74.72; H, 6.00; N, 4.32.

The acidic aqueous layer from above was basified with NH_4OH and extracted with ether to afford 3 g of crude adduct **26**: oil; NMR ($CDCl_3$) δ 7.40–7.15 (m, 4 H), 6.90 (s, 1 H), 6.75 (br s, 2 H), 5.95 (s, 2 H), 5.30 (m, 1 H), 4.80 (m, 1 H), 4.70 (m, 1 H), 3.85 (m, 1 H), 3.52 (d, 1 H, *J* = 9 Hz), 3.30 (m, 1 H), 3.15 (m, 1 H), 3.00 (m, 1 H), 2.90 (m, 1 H), 2.20 (m, 2 H), 2.05 (s, 3 H), 1.30 (t, 3 H, *J* = 6 Hz), 1.10 (t, 3 H, *J* = 6 Hz). This material was heated at reflux in 50 mL of xylene with 0.1 g of *p*-toluenesulfonic acid for 48 h. TLC analysis showed conversion to trans isomer **23c** with only a trace amount of cis isomer **25** present. Silica gel chromatography (30% ethyl acetate–hexane) afforded 1.34 g (total yield 51%) of additional **23e**.

Acknowledgment. We thank Dr. M. L. Maddox and J. Nelson for interpretation of NMR spectral data. We are indebted to Dr. J. M. Muchowski for his constant advice and encouragement during the course of this work. We also thank Bert Harris and Mary Kavanagh for the typing of the manuscript.

Supplementary Material Available: Spectral and analytical data on compounds listed in Tables I and II (6 pages). Ordering information is given on any current masthead page.

Photostimulated $S_{RN}1$ Reactions of Halothiophenes with Benzenethiolate Ion in Acetonitrile

Marino Novi,* Giacomo Garbarino,* Giovanni Petrillo, and Carlo Dell'Erba

Istituto di Chimica Organica, CNR Centro di Studio sui Diariloidi e loro Applicazioni, Corso Europa 26, 16132 Genova, Italy

Received April 21, 1987

The photostimulated reactions between benzenethiolate and 2-chloro-, 2-bromo-, 2-iodo-, and 3-bromothiophene in MeCN lead to rather complex product mixtures where the phenyl thienyl sulfide (ThSPh), the ipso-substitution product, represents the main component. The collected results agree well with the occurrence of an $S_{RN}1$ chain pathway. As to the obtainable yield of sulfide, the main drawback is represented by the fragmentation into ThS^- and Ph• of the $ThSPh^{\bullet-}$ radical anion, formed either along the propagation cycle or by single-electron reduction of the sulfide itself. Optimization of the yield of ThSPh, although at the expense of the overall reaction rate, can be achieved by the employment of suitable electron acceptors. The overall reactivity orders (2-I > 2-Br > 2-Cl and 2-Br > 3-Br) are also discussed.

The behavior of various nitrothiophene derivatives to nucleophilic substitutions on a side-chain carbon atom via the $S_{RN}1$ mechanism has been widely studied, and the scope and limitations of such reactions have been defined sufficiently.[1] Conversely, notwithstanding its obvious value in synthesis, the aromatic $S_{RN}1$ reaction[2,3] in the thiophene series has received relatively little attention.[4,5] The available results,[4-6] however, suggest some remarkable differences with respect to other more extensively explored arene series: for instance, in spite of the presence of a good nucleofugal group and the use of very reactive $S_{RN}1$ nucleophiles,[2,3] the photoinduced reactions of 2-iodothiophene with ammonium benzenethiolate or potassium diethyl

(1) Newcombe, P. J.; Norris, R. K. *Aust. J. Chem.* **1978**, *31*, 2463; **1979**, *32*, 2647. Norris, R. K.; Randles, D. *J. Org. Chem.* **1982**, *47*, 1047.

(2) For relevant reviews, see: (a) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413. (b) Beletskaya, I. P.; Drozd, V. N. *Russ. Chem. Rev. (Engl. Trans.)* **1979**, *48*, 431. (c) Saveant, J. M. *Acc. Chem. Res.* **1980**, *13*, 323. (d) Rossi, R. A. *Ibid.* **1982**, *15*, 164. (e) Norris, R. K. In *The Chemistry of Functional Groups*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1983; Supplement D, Chapter 16. (f) Julliard, M.; Chanon, M. *Chem. Rev.* **1983**, *83*, 425.

(3) Rossi, R. A.; de Rossi, R. H. *Aromatic Substitution by the $S_{RN}1$ Mechanism*, ACS Monographs 178; American Chemical Society: Washington, DC, 1983.

(4) Bunnett, J. F.; Gloor, B. F. *Heterocycles* **1976**, *5*, 377.

(5) Gol'dfarb, Ya. L.; Yakubov, A. P.; Belen'kii, L. I. *Khim. Geterotsikl. Soedin.* **1979**, 1044; *Chem. Abstr.* **1979**, *91*, 193081n.

(6) Creary, X., unpublished experiments cited in ref 4.

0022-3263/87/1952-5382$01.50/0