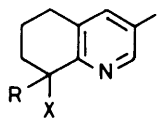
5,6,7,8-Tetrahydroquinolines. Part 6. Silylation *vs.* Thioamidation in the Reaction of Silyl Isothiocyanates with Organometallics: Influence of the Solvent and of the Substituents on Silicon.[1]

Roger Crossley* and Robin G. Shepherd
Institute of Medical Research, Wyeth Research (UK), Huntercombe Lane South, Taplow, Maidenhead, Berks. SL6 OPH.

The influence of a number of variables on carbophilic *vs.* silicophilic attack by 8-lithio-3-methyl-5,6,7,8-tetrahydroquinoline on silyl isothiocyanates is reported. In general carbophilic attack (*i.e.* thiomidation) is favoured in solvents of low polarity and by bulky and/or electron-donating substituents on silicon. Preliminary blockage of the 8-position with a trimethylsilyl group leads to improved yields as a consequence of the suppression of a yield-limiting proton transfer. A mechanism is proposed for the formation of nitriles in the presence of an excess of reagent.

We have previously reported the reaction of 8-lithio-5,6,7,8-tetrahydroquinolines with trimethylsilyl isothiocyanate to give modest yields of the corresponding 8-thiocarboxamides.[2] However, the reaction exhibited a number of peculiarities. (1) No thioamides were obtained using THF or ether as solvent, unfunctionalised 5,6,7,8-tetrahydroquinolines (THQs) being recovered after aqueous acidic work up. (2) With some related substrates (*e.g.* α-picoline), thioamides could not be obtained under any conditions. (3) Even with tetrahydroquinolines, the yields depended markedly on what appeared to be quite minor and remote changes in structure. (4) With an excess of silyl isothiocyanate, nitriles were obtained in place of thioamides. (5) Irrespective of conditions, a maximum yield of 50% was achieved. (6) Yields were greatly influenced by the presence of secondary amines and by the structure of such amines.

A continuing interest in tetrahydroquinoline-8-thiocarboxamides as anti-secretory agents[3] prompted us to reinvestigate the thioamidation of 8-lithiotetrahydroquinolines in order to improve the efficiency of the process. We now report on the influence of the substituents on the silyl group and of the molar ratios of the reactants and the effect of solvents on the reactions of 8-lithio-3-methyl-5,6,7,8-tetrahydroquinoline (**1**), generated using butyl-lithium. The nature of the THQ anion and the effects of the presence of amines will be the subject of a subsequent paper.[4]



(**1**) R = H X = Li
(**2**) R = H X = $CSNH_2$
(**3**) R = H X = $CSNHSiMe_3$
(**4**) R = H X = CN
(**5**) R = H X = $SiMe_3$
(**6**) R = H X = H
(**7**) R = X = $CSNH_2$
(**8**) R = Me X = H
(**9**) $R^1R^2R^3SiNCS$

Results and Discussion

Isothiocyanate has long been known as a pseudohalide in inorganic chemistry, and in our work the possibility emerged that attack at silicon was occurring with expulsion of the isothiocyanate anion. This was reinforced by a report[5] that the reaction of Grignard reagents with trimethylsilyl isocyanate affords products of silylation in addition to products of amidation.

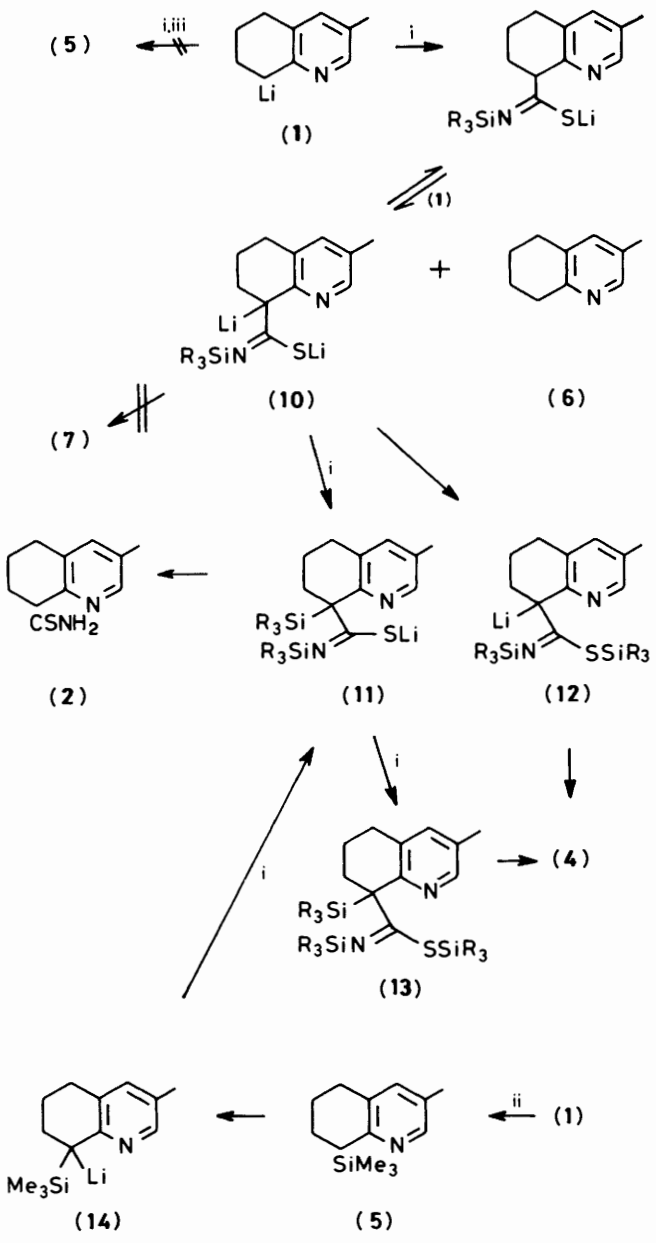
In order to test the hypothesis that silylation of 8-lithio-THQ's was a competing reaction, 8-lithio-3-methyl-5,6,7,8-tetrahydroquinoline (**1**) was added to trimethylsilyl isothiocyanate (**9a**) in THF–hexane followed by work-up at pH 8. No thioamide (**2**), silylthioamide (**3**), or nitrile (**4**) was observed but only the 8-trimethylsilyl derivative (**5**), identical with that produced using trimethylsilyl chloride. Treatment of this silyl derivative (**5**) with 2M-aqueous acid resulted in rapid desilylation and regeneration of the parent tetrahydroquinoline (**6**).

The ratio of silylation [to give (**5**)] to thioamidation [to give (**2**)] is solvent dependent. In non-polar mixtures (toluene–hexane) reaction of (**1**) and (**9**) results mainly in thioamidation [35—40% isolated yield of (**2**)] although some silyl product (**5**) is produced. In solvents more polar than toluene–hexane (*i.e.* ether–hexane or THF–hexane) only traces of the thioamide (**2**) are obtained, the almost exclusive product being the silyl derivative (**5**). This influence of the solvent on the outcome of the reaction (attack at silicon *vs.* attack at carbon) is similar to the solvent effect observed in the addition of organometallics to ketones (enolisation *vs.* carbonyl addition) and is explicable by a similar application of the HSAB principle,[6] with the silyl group corresponding to the α-proton and the isothiocyanate carbon corresponding to the carbonyl group of the ketone.

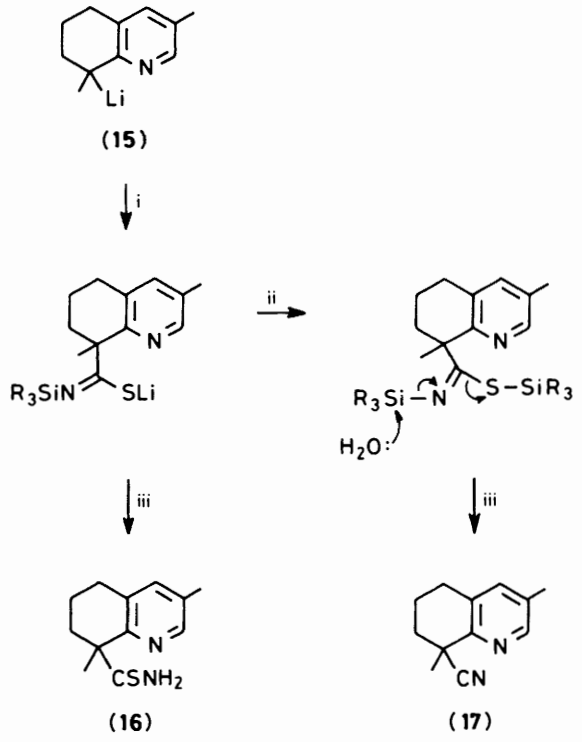
Since attack at silicon is a major factor in reducing the yield of thioamides, we investigated the effect of changing the substituents on silicon in three ways: (i) by increasing the steric bulk of these substituents (**9b—e**); (ii) by adding substituents to modify the electron density at silicon (**9f—j**); and (iii) by a combination of these two approaches (**9k**) (Table).

As can be seen, these strategies were successful—indeed quite a modest degree of steric hindrance (one t-butyl group) is sufficient to suppress reaction at silicon completely. Such silyl isothiocyanates with a greater degree of steric hindrance are useful for those organometallics (*e.g.* 2-lithiomethylpyridine) which are more prone than (**1**) to silylation.[4]

Even under conditions where silylation was not observed (*e.g.* using dimethyl-t-butylsilyl isothiocyanate) the yield of thioamide is only 50%, 50% of parent tetrahydroquinoline (**6**) being recovered; this suggests the occurrence of a proton transfer step (Scheme 1). Formation of the bis-thioamide (**7**) was not observed, in spite of the propensity of (**1**) with methyl isothiocyanate to give a mixture of mono- and bis-thioamides as



Scheme 1. *Reagents:* i, R_3SiNCS; ii, Me_3SiCl; iii, Hydrocarbon solvents.



Scheme 2. *Reagents:* i, R_3SiNCS; ii, R_3SiCl; iii, H_2O/H^+

well as recovered tetrahydroquinoline.[2] Accordingly the corresponding reaction with the 3,8-dimethyltetrahydroquinoline (**8**), in which such a proton transfer is precluded, was investigated. Reaction of the lithio-derivative (**15**) with the hindered silyl isothiocyanate (**9b**) gave an almost quantitative yield of crude thioamide (**16**) (75% after recrystallisation) with no recovered (**8**), thus confirming the proton transfer of Scheme 1.

The lack of bis-thioamide (**7**) was surprising in view of the experience with methyl isothiocyanate. Since silylation of anions with silyl isothiocyanates had now been established, it is likely that the dianion (**10**) undergoes silylation instead of further thioamidation. Furthermore when the lithio-derivative (**15**) of the 3,8-dimethyltetrahydroquinoline (**8**) was treated with reagent (**9b**) (1 equiv.) followed by dimethyl-t-butylsilyl chloride (1 equiv.), the sole product (t.l.c. analysis) of this sequence was the nitrile (**17**), isolated in 75% yield. This is interpreted as occurring *via* this secondary *S*-silylation. (Scheme 2.)

Since we had the 8-trimethylsilyl derivative (**5**) available, we generated the corresponding lithium anion (**14**) with butyllithium and allowed it to react with silyl isothiocyanate (**9b**). The sole product (t.l.c. analysis) after aqueous acidic work-up was the thioamide (**2**), isolated in quantitative crude yield. Interception of the adduct (**11**) with a further equiv. of (**9b**) led, after aqueous acidic work-up, to the nitrile (**4**) presumably *via* the intermediate (**13**). (Scheme 1).

We had previously observed that reaction in hydrocarbon solvents of (**1**) with 0.2 and 0.5 mol equiv. of Me_3SiNCS gave *ca.* 20 and 50% yields of thioamides, respectively. This rules out a process involving an initial *C*-silylation followed by subsequent thioamidation to give (**5**) and hence (**11**) by anion exchange and then thioamidation.

Conclusions.—It is thus likely that reaction of the anion (**1**) with 1 equiv. of a silyl isothiocyanate leads, *via* proton transfer, to the bis-lithio derivative (**10**) which undergoes *C*-silylation to give intermediate (**11**), rather than thioamidation leading to the bis-thioamide (**7**); hydrolysis of (**11**) then leads to the thioamide (**2**). In the presence of an excess of silyl isothiocyanate, the intermediate (**11**) undergoes *S*-silylation to give (**13**) and thus the nitrile (**4**) after hydrolysis.

The use of very hindered silyl isothiocyanates (**9c**) and (**9d**) now illustrates how it is possible by steric bulk alone to affect the reactivity of the isothiocyanates with the various anions in Scheme 1. In the reaction of Ph_3SiNCS with (**1**) some 10% of the corresponding nitrile is formed. This is interpreted as proceeding *via* silylation of (**10**) on sulphur rather than on carbon to give (**12**). It is, however, with the Pr^i_3Si group that the most fundamental change occurs. In this case both *C*- and *S*-silylation of (**10**) are slowed down and, because the proton transfer step leading to its formation is reversible, (**1**) is regenerated and may react further with (**9d**). This means that by increasing bulk alone, yields in excess of 50% of thioamide may be formed, the

Table

	$R_1R_2R_3SiNCS$									Yield of thioamide (3)[b]
	R_1	R_2	R_3	Solvent	Time (h)	Yield[a] (%)	B.p. (°C)/mmHg	M.p. (°C)	Rx. Solvent	Lit.	(%)
(**9a**)	Me	Me	Me	CH	24	90	71—73/68			2	0
(**9b**)	Bu^t	Me	Me	B	24	93	62/16			[c]	50[f]
(**9c**)	Ph	Ph	Ph	*d*	*d*	*d*	—	98—100	Hexane	7	25[g]
(**9d**)	Pr^i	Pr^i	Pr^i	T	168	71	126/15			[c]	85[h]
(**9e**)	Ph	Me	Me	T	72	80	144/15			[c]	0[i]
(**9f**)	MeO	Me	Me	CH	4	65	148			[c]	5
(**9g**)	Pr^{i}O	Me	Me	CH	4	76	68/15			[c]	30
(**9h**)	MeO	MeO	Me	CH	30	12	90/15			[c]	10
(**9i**)	Me_2N	Me_2N	Me_2N	CH	30	16	140/15			[c]	35
(**9j**)	EtO	EtO	EtO	CH	40	90	98—100/15			[c]	10
(**9k**)	ArO[e]	Me	Me	T	48	48	—	83—84	MeCN	[c]	50[f]

CH = Cyclohexane, B = benzene, T = Toluene. [a] Yields of silyl isothiocyanates are of pure, isolated material but are not optimised. [b] By n.m.r. assay of the products of reaction in THF–hexane: see Experimental section. [c] New: all new compounds had satisfactory CHN analysis (±0.4%). [d] Prepared from the corresponding halide and thiourea following the procedure of ref. 7. [e] 2,6-Di-4-methyl-t-butylphenoxy; the corresponding silyl chloride was prepared from dichlorodimethylsilane, 4-methyl-2,6-di-t-butylphenol and triethylamine in acetonitrile using the procedure of ref. 8. Yield 57%, m.p. 119—121 °C (acetonitrile). [f] No 8-silyl THQ observed prior to acid hydrolysis (t.l.c. comparison with authentic material). [g] 10% Of the corresponding nitrile also formed. [h] Only 50% of material recovered due to the prolonged hydrolysis needed to remove the Pr^i_3Si group (16 h). Work-up with NH_4Cl solution instead of HCl gave a quantitative recovery of the silylated thioamide (80%) and unchanged starting material (20%). [i] Trace (≤1%) detectable by t.l.c.

yield limiting effect of the anion exchange having effectively been overcome.

Experimental

General procedures are as described previously.[1] Structural assignments are supported by n.m.r. and i.r. spectra. 3-Methyl-5,6,7,8-tetrahydroquinoline (**6**) and trimethylsilyl isothiocyanate (**9a**) were prepared as previously described.[2]

3-*Methyl*-8-*trimethylsilyl*-5,6,7,8-*tetrahydroquinoline* (**5**).—A mixture of 3-methyl-5,6,7,8-tetrahydroquinoline (29.4 g, 0.2 mol) and THF (50 ml) was added to a mixture of a 1.55M solution of butyl-lithium in hexane (129 ml, 0.2 mol) and THF (50 ml), maintained below 10 °C. After 0.5 h the mixture was blown over by inert gas onto a mixture of trimethylsilyl chloride (50 ml, 0.4 mol) in THF (100 ml), maintained below 10 °C. After a further 0.5 h, the mixture was evaporated and the residue extracted with hexane. The hexane extracts were evaporated and the residue distilled to give the *silyl derivative* (**5**) (40 g, 91%), b.p. 118—124 °C/5 mbar (Found: C, 70.9; H, 9.65; N, 6.4. $C_{13}H_{21}NSi$ requires C, 71.2; H, 9.6; N, 6.4%).

3,8-*Dimethyl*-5,6,7,8-*tetrahydroquinoline* (**8**).—A mixture of 3-methyl-5,6,7,8-tetrahydroquinoline (100 ml), paraformaldehyde (30 g), and acetic anhydride (100 ml) was heated at reflux for 30 h. The residue was distilled to give a mixture of starting tetrahydroquinoline and 3,8-dimethyl-5,6-dihydroquinoline (40 g), b.p. 126—180 °C/15 mmHg. Chromatography on silica gel (500 g, Woëlm active, 100—200) using di-isopropyl ether gave 3,8-dimethyl-5,6-dihydroquinoline (22 g). A solution of the dihydroquinoline (22 g) in ethanol (200 ml) was hydrogenated over 10% palladium on carbon (1 g) at 25 °C and 1 atm. After the theoretical uptake had occurred (1.5 h) the catalyst was filtered off, the filtrate evaporated, and the residue distilled to give the *tetrahydroquinoline* (**8**) (22 g), b.p. 124 °C/mmHg (Found: C, 81.85; H, 9.1; N, 8.3. $C_{11}H_{15}N$ requires C, 81.9; H, 9.4; N, 8.7%).

3,8-*Dimethyl*-5,6,7,8-*tetrahydroquinoline*-8-*thiocarboxamide* (**16**).—A 1.55M solution of butyl-lithium in hexane (12.9 ml, 20 mmol) maintained below 10 °C was treated with a solution of tetrahydroquinoline (**8**) (3.22 g, 20 mmol) in THF (10 ml). After 0.5 h a 22% solution of dimethyl-t-butylsilyl isothiocyanate (**2b**) in benzene (13.7 g, 20 mmol) was added dropwise. After a further 0.5 h the reaction was quenched with water (100 ml) and then acidified (to pH 1). After 1 h the layers were separated and the aqueous layer basified (to pH 9) and extracted with dichloromethane (2 × 50 ml). The organic extracts were dried and evaporated. Recrystallisation of the residue from toluene gave the title thioamide (**16**) (3.3 g, 75%), m.p. 160—162 °C, identical to material prepared according to ref. 3 (Found: C, 65.45; H, 7.2; N, 12.9. Calc. for $C_{12}H_{16}N_2S$: C, 65.4; H, 7.3; N, 12.7%).

8-*Cyano*-5,6,7,8-*tetrahydroquinoline* (**17**).—A solution of 3,8-dimethyl-8-lithio-5,6,7,8-tetrahydroquinoline (**15**) (20 mmol) was generated and allowed to react with dimethyl-t-butylsilyl isothiocyanate (20 mmol) as described under the preparation of (**16**). After 0.5 h a solution of dimethyl-t-butylsilyl chloride (3.1 g, 20 mmol) in THF (10 ml) was added and the mixture allowed to stand for 16 h at ambient temperature. The reaction was quenched with 2M-hydrochloric acid (50 ml). After 1 h the aqueous layer was separated, basified (to pH 9), and extracted with dichloromethane (2 × 50 ml); the organic extracts were dried and evaporated. Kugelrohr distillation of the residue gave the *nitrile* (**17**) (2.8 g, 75%), b.p. 90 °C/0.01 mmHg (bath temp.) (Found: C, 77.1; H, 8.1; N, 14.5. $C_{12}H_{14}N_2$ requires C, 77.4; H, 7.6; N, 15.0%).

3-*Methyl*-5,6,7,8-*tetrahydroquinoline*-8-*thiocarboxamide* (**2**).—A mixture of a 1.55M-solution of butyl-lithium in hexane (6.45 ml, 10 mmol) and THF (10 ml) maintained below 10 °C was treated with a solution of the silyltetrahydroquinoline (**5**) (2.2 g, 10 mmol) in THF (10 mmol). After 0.5 h a 22% solution of silyl isothiocyanate (**9b**) in benzene (6.9 g, 10 mmol) was added dropwise. After 0.5 h the reaction mixture was quenched with 2M-hydrochloric acid (25 ml) and after 1 h the aqueous layer was separated, basified (to pH 9), and extracted with dichloromethane (2 × 50 ml). The organic extracts were dried and evaporated to give the title thioamide (2.1 g, *ca.* 100%). Recrystallisation from benzene gave analytically pure material (1.9 g, 88%), m.p. 153 °C, identical to material prepared according to ref. 2 (Found: C, 63.7; H, 6.9; N, 13.4. Calc. for $C_{11}H_{14}N_2S$: C, 64.0; H, 6.8; N, 13.6%).

8-*Cyano-3-methyl-5,6,7,8-tetrahydroquinoline* (**4**).—A mixture of a 1.55M solution of butyl-lithium in hexane (12.9 ml, 20 mmol), and THF (10 ml) maintained at 5 °C was treated with a solution of silyltetrahydroquinoline (**5**) (4.34 g, 20 mmol) in THF (10 ml). After 0.5 h a solution of dimethyl-t-butylsilyl isothiocyanate (**9b**) (7.0 g, 40 mmol) was added and the mixture allowed to warm to 20 °C over 12 h. The reaction was quenched with M-hydrochloric acid (50 ml) and stirred for 1 h; ether (50 ml) was added and the aqueous layer was separated and adjusted to pH 10. The mixture was extracted with ether (2 × 50 ml) and the organic extracts were dried and evaporated to give the nitrile (**4**) (3.0 g, 85%). The hydrochloride (from propan-2-ol) had m.p. 189 °C (lit.,[9] 189—190 °C).

Dimethyl-t-butylsilyl Isothiocyanate (**9b**).—A mixture of ammonium thiocyanate (58 g, 0.76 mol) and benzene (400 ml) was azeotroped in a Dean-Stark apparatus until no more water was evolved. Dimethyl-t-butylsilyl chloride (100 g, 0.66 mol) was then added and the mixture maintained at reflux for 24 h. The mixture was cooled to ambient temperature, filtered, and evaporated. Distillation gave the *silyl isothiocyanate* (**9b**) (106 g, 93%), b.p. 62 °C/16 mmHg (Found: C, 48.2; H, 8.8; N, 8.3. $C_7H_{15}NSSi$ requires C, 48.5; H, 8.7; N, 8.1%). Other silyl isothiocyanates (**9d**—**k**) were prepared in an analogous manner in a variety of solvents (Table).

General Procedure for the Reaction of Tetrahydroquinolines with Silyl Isothiocyanates.—3-Methyl-5,6,7,8-tetrahydroquinoline (1.46 g, 10 mmol) in THF (10 ml) maintained below 10 °C was treated with a 1.55M solution of butyl-lithium in hexane (6.45 ml, 10 mmol). After 0.5 h, the silyl isothiocyanate (10 mmol) in THF (5 ml) was added and after a further 0.5 h the reaction mixture was quenched with 2M-HCl. After t.l.c. had indicated complete desilylation of the intermediate (5 min to 1 h, depending on the nature of the silyl group), the THF was removed under reduced pressure and the residue extracted with ethyl acetate (50 ml). The aqueous phase was basified (to pH 9) and extracted with dichloromethane (2 × 50 ml). The organic extracts were dried and evaporated to give a quantitative recovery of a mixture of starting material and thioamide except as indicated in the Table. The thioamide content of the residue was estimated by ^1H n.m.r.

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