

Organosilicon Compounds XVI. Preparation of Various
2-(5-Trimethylsilyl)thienyl Aryl Ketimines and Ketones

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Recently, Hardtmann and Ott (2) have synthesized several 2-thienyl aryl ketones and have described their physiological activity, particularly as antiinflammatory agents. In our continuing efforts to exploit the physiological effects engendered by the silicon atom, we have synthesized a series of 2-(5-trimethylsilyl)thienyl aryl ketimines and ketones for broad spectrum physiological evaluation. Recent investigations at this laboratory involving lithiation of substituted furans (3) and thiophenes (4,5) provided the foundation for this study. For instance, organolithium compounds derived from various substituted heterocycles have been allowed to react with nitrile-containing compounds, which after controlled acid hydrolysis provide either the ketimine or corresponding ketone (6,7).

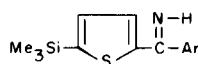
5-Trimethylsilyl-2-lithiothiophene (I) (8) is very reactive with various aromatic nitriles and affords, after hydrolysis with an aqueous ammonium chloride solution, the corresponding ketimines (Scheme A), which can subsequently be hydrolyzed with aqueous acid to the 2-(5-trimethylsilyl)thienyl aryl ketones. Structure verification was aided by the production of the urea derivative from the ketimine.

Five aromatic nitriles, *p*-chlorobenzonitrile, *o*-chlorobenzonitrile, *p*-methoxybenzonitrile, nicotinonitrile and isonicotinonitrile, were reacted with I to produce the corresponding silylthienyl ketimines (Table I) and silylthienyl ketones (Table II).

During this investigation a number of interesting events arose which merit further consideration. Upon attempted conversion to the ketone, 2-(5-trimethylsilyl)thienyl *o*-chlorophenyl ketimine (III), afforded a mixture of the anticipated ketone (carbonyl stretch 6.0-6.1 μ) and unconverted ketimine (N-H stretch 3.05 μ). Thus, as compared to the ready hydrolysis of 2-(5-trimethylsilyl)thienyl *p*-chlorophenyl ketimine (II), the bulk of the *ortho* chlorine of III significantly retards hydrolysis to the ketone. Such results conform to similar findings of Pickard, *et al.* (9,10) who have described the stabilizing influence which bulky groups attached to the ketimine carbon atom engender during acid hydrolysis.

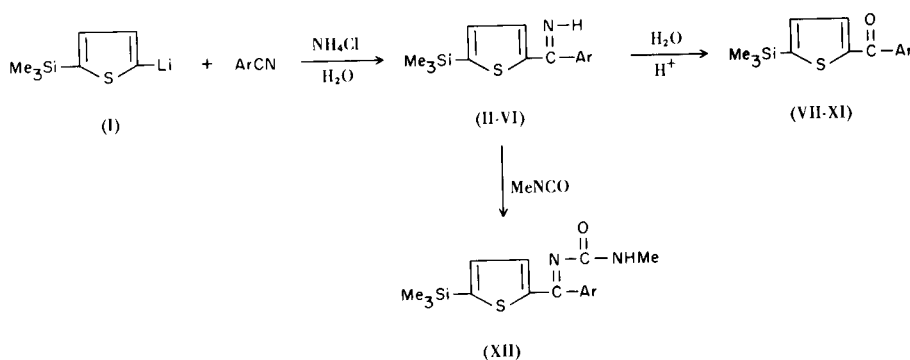
The reaction of I with trichloroacetonitrile at both 0° and -70° did not produce the anticipated ketimine but rather afforded a 40-50% yield of 5-trimethylsilyl-2-chloro-

TABLE I
2-(5-Trimethylsilyl)thienyl Aryl Ketimines

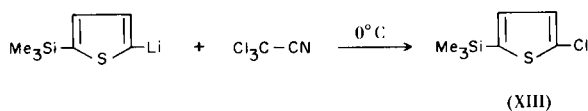


	Ar	M.p. (b.p.) °C	% Yield	Cryst'n Solvent	Formula	Analysis		
						C	H	N
II	<i>p</i> -chlorophenyl	97.5-99.5	75.5	hexane	C ₁₄ H ₁₆ ClN ₂ SSi	Found: 57.10 Calcd.: 57.20	5.50 5.50	4.99 4.77
III	<i>o</i> -chlorophenyl	(137.5/0.15 mm)	51	----	C ₁₄ H ₁₆ ClN ₂ SSi	Found: 57.45 Calcd.: 57.20	5.59 5.50	4.81 4.77
IV	<i>p</i> -methoxyphenyl	52.5-54.5	54	pet. ether	C ₁₅ H ₁₉ NOSSi	Found: 62.41 Calcd.: 62.23	6.50 6.63	4.89 4.84
V	3-pyridyl	75-78	30	hexane	C ₁₃ H ₁₆ N ₂ SSi	Found: 59.84 Calcd.: 59.94	6.27 6.20	10.60 10.76
VI	4-pyridyl	98-100	57.8	hexane	C ₁₃ H ₁₆ N ₂ SSi	Found: 60.06 Calcd.: 59.94	6.38 6.20	10.87 10.76

SCHEME A



SCHEME B



thiophene (XIII), arising by halogen-metal interconversion (Scheme B). To further confirm this finding, 2-lithiothiophene was likewise reacted with trichloroacetonitrile to produce 2-chlorothiophene (XIV) in 40% yield. Similar halogen-metal interconversions involving the Cl_3C -moiety have been documented by Reeve and Fine (11) in the reaction of chloral with phenyllithium to produce a 51% yield of chlorobenzene.

In contrast to the normal addition of organolithium reagents to aromatic nitriles, the reaction of I with 1,3-dicyanotetrachlorobenzene (Daconil 2787) (12) proceeded via a competitive nucleophilic attack on the electron-deficient benzene ring to eliminate lithium chloride and produce XV (Scheme C). Elemental analysis and ir spec-

SCHEME C

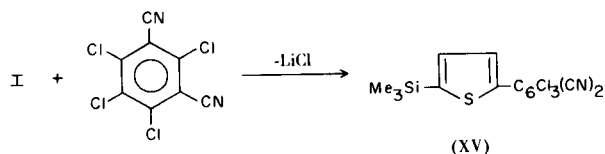


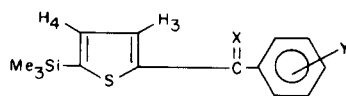
TABLE II

2-(5-Trimethylsilyl)thienyl Aryl Ketones

	Ar	M.p. (b.p.) °C	Formula	Analysis		2,4-DNP Derivative	
				C	H	M.p. °C	Analysis N
VII	<i>p</i> -chlorophenyl	94.5-97	$\text{C}_{14}\text{H}_{15}\text{ClOSSI}$	Found: 57.19 Calcd: 57.01	5.23 5.14	140-142	Found: 11.61 Calcd: 11.80
VIII	<i>o</i> -chlorophenyl	(122°/0.04 mm)	$\text{C}_{14}\text{H}_{15}\text{ClOSSI}$	Found: 57.31 Calcd: 57.01	4.97 5.14	---	-----
IX	<i>p</i> -methoxyphenyl	35-37	$\text{C}_{15}\text{H}_{18}\text{O}_2\text{SSi}$	Found: 62.21 Calcd: 62.02	6.30 6.26	179-181	Found: 11.81 Calcd: 11.91
X	3-pyridyl	54-57	$\text{C}_{13}\text{H}_{15}\text{NOSSI}$	Found: 59.76 Calcd: 59.72	5.88 5.79	181-183	Found: 15.63 Calcd: 15.86
XI	4-pyridyl	85-86.5	$\text{C}_{13}\text{H}_{15}\text{NOSSI}$	Found: 59.51 Calcd: 59.72	5.82 5.79	---	-----

TABLE III

Nmr Evidence for Steric Inhibition to Resonance



Compound	X	Y	NMR Chemical Shift (δ) (a)			
			H ₄	H ₃	H ₃ -H ₄	N-H
VII	O	<i>p</i> -Cl	7.20	7.60	0.40	---
VIII	O	<i>o</i> -Cl	7.18	7.38(b)	0.20	---
II	N-H	<i>p</i> -Cl	7.11	7.11	0.00	9.46
III	N-H	<i>o</i> -Cl	7.09	6.92	-0.17	9.35

(a) Spectra recorded at 50% concentration in carbon tetrachloride utilizing TMS as internal reference. (b) Estimated value since H₃ doublet partially obscured by phenyl protons.

trosopy served to establish both the molecular formula and the presence of the silyl substituent. However, at this time, the position of substitution has not been unequivocally established, although we favor the 2- or 4-positions as they are flanked by cyano groups and are necessarily very labile toward nucleophilic attack. Although nucleophilic displacement of chlorine atoms from aromatic rings laden with electron-withdrawing substituents is well known (13), the competition between chlorine displacement and addition to the nitrile is interesting in light of the reactivity of *p*-chlorobenzonitrile (Table I).

Furthermore, the nmr spectra of these silylthienyl ketones and ketimines (Table III) provide additional confirmation of steric inhibition to resonance. Variation in the *para* substituent in the phenyl ring of 2-thienyl phenyl ketones has little effect (14) on the chemical shift of the thienyl protons, yet corresponding *ortho* substituents do indeed show such an effect. For instance, the *ortho* chloro substituent in VIII provides for a large upfield shift of H₃. A similar effect is also noted in H₃ and in the imino hydrogen of III. Similarly, Martin, *et al.* (15,16) have shown that corresponding *ortho* substituents do indeed effect the chemical shift of the thienyl protons, particularly causing an upfield shift in the 3-thienyl protons. This disruptive effect by a relatively bulky *ortho* substituent has been viewed as a type of steric inhibition to resonance (16).

EXPERIMENTAL

The nmr spectra reported herein were obtained from a Varian A-60D spectrometer and the ir spectra were obtained from a Perkin-Elmer 257 infrared spectrophotometer.

Preparation of 2-(5-Trimethylsilyl)thienyl Aryl Ketimines.

The reaction of 2-trimethylsilylthiophene (15.6 g., 0.1 mole) and *n*-butyllithium (62 ml.; 1.6*N*) according to the procedure of Benkeser and Currie (8) afforded 5-trimethylsilyl-2-lithiothiophene (I). The ethereal solution of I was added dropwise with stirring

under anhydrous nitrogen to an equal molar quantity of aromatic nitrile dissolved in anhydrous ether at 0°. After stirring for 6-9 hours at room temperature, 150 ml. of cold ammonium chloride in aqueous solution was added rapidly and the reaction mixture was stirred for an additional hour at room temperature. The ethereal layer was removed and the water layer was extracted with several portions of ether. The ethereal portions were combined, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford, after fractional distillation or recrystallization, the corresponding ketimine listed in Table I.

Preparation of 2-(5-Trimethylsilyl)thienyl Aryl Ketones.

A solution of ketimine dissolved in 150 ml. of ether was refluxed mildly for 2-5 hours with 100 ml. of water containing 3-6 g. of 4-toluenesulfonic acid. The ether layer was separated and the water layer was extracted with several portions of ether. In the case of the ketimines containing the pyridine system, it was necessary to make the water solution slightly basic before extracting with ether. The ethereal portions were combined, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford, after fractional distillation or recrystallization, near quantitative yields of the appropriate ketones in Table II.

In the case of 2-(5-trimethylsilyl)thienyl *o*-chlorophenyl ketimine, it was necessary to reflux the ethereal solution of the ketimine with 6*N* hydrochloric acid over an extended period of 12-16 hours to afford a ketimine-free sample of the desired ketone.

2-(5-Trimethylsilyl)thienyl 4-Chlorophenyl Ketimine *N*-Methylcarbamide (XII).

2-(5-Trimethylsilyl)thienyl 4-chlorophenyl ketimine (5 g., 0.017 mole) was allowed to react with excess methyl isocyanate in 100 ml. of dry ethyl acetate at 75° for 4 hours to afford, after concentration *in vacuo* and recrystallization of the resultant solid from heptane, 4.2 g. (70%) of XII, m.p. 131-133°.

Anal. Calcd. for C₁₆H₁₉ClN₂OSSi: C, 54.74; H, 5.47; N, 7.98. Found: C, 54.66; H, 5.43; N, 8.17.

5-Trimethylsilyl-2-chlorothiophene (XIII).

The reaction of 2-trimethylsilylthiophene (10.5 g., 0.0674 mole), *n*-butyllithium (42 ml., 1.6*N*) and trichloroacetonitrile (9.7 g., 0.0674 mole), according to the procedure outlined above for the preparation of the ketimines, afforded after fractional distillation 5.8 g. (45%) of XIII, b.p. 94°C/23mm, n_D^{25} = 1.5070; nmr (17) (cyclohexane), δ 6.91 (d, 1H, thiophene), 6.82 (d, 1H, thio-

phene), and 0.24 (s, 9H, SiMe₃). Classical flame tests confirmed the presence of both Cl and Si.

5-Trimethylsilyl-2-(dicyanotrichlorophenyl)thiophene (XV).

The reaction of 2-trimethylsilylthiophene (7.8 g., 0.05 mole), *n*-butyllithium (31 ml., 1.6*N*) and 1,3-dicyanotetrachlorobenzene (13.3 g., 0.05 mole), according to the procedure outlined above for the preparation of the ketimines, afforded, after recrystallization of the reaction product from heptane, 5.6 g. (29%) of XV, m.p. 255-260°; ir 2220 cm⁻¹, 1250 cm⁻¹ and 840-870 cm⁻¹ (SiMe₃).

Anal. Calcd. for C₁₅H₁₁Cl₃N₂SSi: C, 46.69; H, 2.88; N, 7.26. Found: C, 46.53; H, 2.87; N, 7.41.

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