

Addition Reactions of Thiophenols with Dihydro- and Tetrahydropyridinecarbonitriles.

A Comparison with Reactions of Phenols

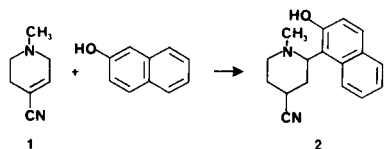
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p-Chlorothiophenol reacts with 1-methyl-1,2,5,6-tetrahydropyridine-*X*-carbonitriles (**1**, *X* = 4, **6**, *X* = 3) and with 1-methyl-1,*Y*-dihydropyridine-3-carbonitrile (**7**, *Y* = 6, **8**, *Y* = 4) to give the anticipated addition products. Geometric isomers were formed from **6**, but not from **1**, and the stereochemistry of the products has been determined. The chemistry of the reactions with *p*-cresol was quite different. No reaction occurred with **6** or **7**, while **8** gave a 6-(2-hydroxy-5-methylphenyl)- derivative, analogous to the unexpected product obtained previously from **1**.

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We recently showed [1] that the product of the reaction of 2-naphthol (and other phenols) with 1-methyl-1,2,5,6-tetrahydropyridine-4-carbonitrile **1** under basic conditions was **2**, rather than the result of Michael addition to the activated double bond.

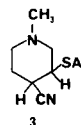


This unexpected finding prompted us to investigate similar reactions with a different nucleophile. We chose thiophenols, where there existed a report [2] of normal Michael addition to a carbocyclic analog of **1**, 4-*t*-butylcyclohexene-1-carbonitrile. This paper reports on this reaction of **1**, and reactions of related partially reduced pyridines with phenols and thiophenols. Interesting differences in behaviour between (a), phenols and thiophenols, and (b), heterocyclic and carbocyclic compounds, were observed.

The results discussed below are restricted to reactions of *p*-cresol and *p*-chlorothiophenol. A limited number of reactions with *p*-thiocresol have also been carried out. Results in all cases were as for the *p*-chloro compound. Reactions with *p*-cresol were carried out in an excess of the phenol, and with a little sodium, at 100°, as previously [1]. Reactions with *p*-chlorothiophenol were carried out under the same conditions as for the cresol reactions, and/or, in ethanol, as previously carried out on 4-*t*-butylcyclohexene-1-carbonitrile [2].

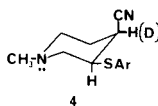
1-Methyl-1,2,5,6-tetrahydropyridine-4-carbonitrile (**1**).

Irrespective of the method used, only one product was detected and isolated from reaction with *p*-chlorothiophenol, in 40% yield. This had a significantly different spectrum from **2** and was evidently a product of the expected Michael addition, *i.e.* **3**.



The nmr spectral analysis allowed the stereochemistry to be determined. The preferred orientation of an *N*-methylpiperidine ring is with the methyl group equatorial. The ¹³C nmr spectrum is characteristic, and it has been established from fixed chair conformation model compounds that shifts of approximately δ 43 (equatorial) and 33 (axial) ppm occur for the methyl signal [3]. All compounds isolated from reactions of **1** with phenols [structures proved by x-ray crystallography [1]] have an *N*-Me peak close to 43 ppm. In **3**, and all other products of thiophenol addition obtained in this work, the *N*-Me resonance is assigned to a peak in the region 41-46 ppm and thus all compounds have an equatorial *N*-Me group.

Our prime analysis of the remaining stereochemistry was based on the ¹H nmr spectrum in deuteriochloroform. While complex, the three most downfield signals arising from the heterocyclic ring protons could be distinguished [δ 3.32, dt, *J* = 10, 4 Hz, 3.07, q, *J* = 4 Hz, 2.9, dd, *J* = 11, 4 Hz (these last two signals were partially overlapped)]. Since the H-4 proton comes from the solvent, the spectrum of the product obtained from reaction in ethanol-*d* was most informative. The signal at 3.07 disappeared, *i.e.*, this is from H-4, and the small coupling of this signal in the protio compound indicates that it is H-4e. The doublet of triplets at 3.32 (part of 4 spin system) simplifies to a doublet of doublets (3 spin) and is therefore H-3a (*J*_{2a,3a} = 10 Hz, *J*_{2e,3a} = 4 Hz). The doublet of doublets (3-spin) at 2.9 remains unchanged, but is now clearly distinguished (*J* = 11, 4 Hz) and is assigned to H-2e. Thus, the stereochemistry is determined as **4** in which the added proton



and thiophenoxy group are equatorial and *trans* to each other. In the analogous reaction with 4-*t*-butylcyclohexene-1-carbonitrile [2], two geometrical isomers were isolated from reaction in ethanol (*cf* one above). Both arose from axial thiophenoxide attack and differed in the configuration of the cyano function (equatorial in the kinetic product from *trans* addition, and axial in the thermodynamic product). An additional isomer, with configuration corresponding to **4**, was isolated from reaction in boiling dimethylformamide. It is apparent that the addition reaction in the heterocyclic compound has more stereochemical limitations. Unfortunately, because of nitrogen inversion and general conformational mobility in the heterocyclic system, it is not possible to specify the stereochemistry of the addition reaction itself, even though the configuration of **4** is established.

On the basis of this stereochemistry for **4**, the heterocyclic ring carbon signals in the ^{13}C nmr spectrum, in deuteriochloroform, could be assigned. The two peaks at lowest field arise from carbons α to the hetero atom. Since an equatorial S-Me group on a cyclohexane ring has been shown to result in a downfield shift of about 7 ppm for the C-2 with respect to the C-4 signal [4,5], the peaks in **4** are assigned at δ 57.3 (C-2) and 51.3 (C-6). The peak at 46.4 is assigned to C-3 (*cf.* 44.9 for C-1 in the methylthiocyclohexane [5]), that at 32.3 to C-4 (this is a triplet in the D-4 compound), and the remaining peak at 28.3 to C-5.

1-Methyl-1,2,5,6-tetrahydropyridine-3-carbonitrile (**6**).

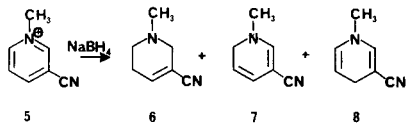


Table 1

^{13}C NMR Chemical Shifts [a]

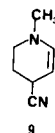
Compound No.	Carbon					N-Me
	2	3	4	5	6	
1	49.8	141.6	109.7	27.0	53.5	44.8
4	57.3	46.4	32.3	28.3	51.3	45.9
6	50.1	110.0	141.8	27.1	53.7	45.1
7	148.8	132.7	121.4	110.8	49.7	42.9
8	144.0	139.0	22.6	101.4	129.2	40.5
11	56.4	34.7	45.7	29.1	54.7	46.2
12	56.4	34.3	45.2	31.5	54.0	46.3
13 [b]	148.2	128.3	25.5	18.2	54.4	41.6
14	145.1	132.0	26.6	18.0	68.0	41.7
15	148.8	132.7	43.0	26.4	43.0	42.5

[a] δ ppm in deuteriochloroform. [b] $\text{ArMe} = 20.6$.

This compound is one of the products produced by borohydride reduction of **5** [6], and was obtained by distillation.

(a) *p*-Cresol.

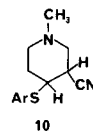
It seemed that the formation of **2** from **1** involved isomerization of **1** to **9** under the basic conditions of the reaction [1]. Thus, H-2 in **1** is made acidic by delocalization of any developing negative charge over the cyanoalkene function. In **6**, this feature is absent and a similar reaction to that seen with **1** was not likely. As it turned out, no



Michael reaction was observed either, and **6** was recovered unchanged.

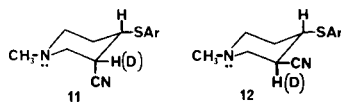
(b) *p*-Chlorothiophenol.

As with **1**, Michael addition occurred readily. Some compounds of type **10** have been prepared previously and have antiulcer properties [7]. In this case, two isomers of **10** were observed, in 70% total isolated yield with the relative proportions depending on the severity of the reaction conditions. For example, with one equivalent of thiophenoxide in ethanol, a 4:1 ratio (from N-Me peaks in the



^1H nmr spectrum) was obtained after 4 hours reflux; with an excess of thiophenoxide in thiophenol at 100° overnight, a 1:1 mixture resulted. Both compounds were isolated and their stereochemistry established by the same methods as for **4**. Little stereochemical information was obtainable from the complex ^1H nmr spectrum. The signals from four protons occurred in the region δ 2.8-3.2 in chloroform but in deuterio dimethylsulfoxide, a doublet of triplets at δ 3.3 was noted for the kinetic product. For the same product obtained from reaction in ethanol-*d*, this became a doublet of doublets ($J = 10, 4$ Hz) and was therefore H-4a. A probable narrow quartet at δ 3.1 disappears in the deuterio compound, *i.e.*, this is H-3, which must be equatorial to give the observed doublet of triplets for H-4 in the protio compound. In the thermodynamic product, only the signal for H-4 at δ 3.28 could be distinguished. This triplet of doublets ($J = 10, 4$ Hz) became a doublet of doublets in the deuterio compound and is therefore H-4a. The loss of a large coupling in this signal from protio to deuterio compounds indicates that H-3

must also be axial. The signal for H-3 would therefore be wide and was not identifiable though a change occurs in the δ 2.4-2.6 region in the deuterio compound.



Thus, the compounds are **11**, the kinetic product (*trans* addition as for the 4-carbonitrile analog, **4**) and **12**, the thermodynamic product, where the difference is in the configuration of the CN group. The essential reversibility of the Michael type reaction was confirmed by heating pure **11** with thiophenoxide/thiophenol. After 24 hours at 100°, the formation of some **12** and the tetrahydropyridine, **6**, was noted by nmr analysis. The ¹³C nmr spectral peaks for **11** and **12** were assigned in the same way as for **4**. Chemical shifts were very similar for the ring carbons, with the major differences being for C-5 (2.4 ppm upfield in **11**). The fact that the C-2 and C-6 signals (β to SAr) were the same in both compounds is additional evidence that the SAr configuration is common (see discussion for **4**).

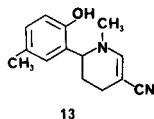
The difference between this reaction and that of the 4-carbonitrile compound is the formation of isomers, with the reason for this difference being not entirely clear. It is reasonable that **11** is destabilised with respect to **4** by diaxial interaction between the cyano function and nitrogen lone pair. However, since **12** was not observed in a greater amount than **11**, there is no significant energy advantage for **12**. As **4** does not have the diaxial interaction referred to above, there is probably even less energy advantage for an equatorial cyano isomer and the fact that this isomer was not formed is therefore not unreasonable.

1,4-Dihydro-1-methylpyridine-3-carbonitrile (**8**).

Extension of these studies to dihydro compounds seemed a logical step and **8** was prepared in high yield by dithionite reduction of **5**.

(a) *p*-Cresol.

Compound **8** contains a similar enamine function proposed for the intermediate **9** in conversion of **1** to **2**. Therefore, useful confirmatory evidence for this general pathway was obtained from the observation that **8** did react in an analogous way. One product only was detected and this, isolated in 26% yield, was assigned structure **13**.

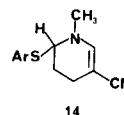


The ¹H nmr spectrum, unlike for previous compounds, was not able to provide definite stereochemical evidence. The spectrum contained a broad singlet at δ 4.65, with no discernable coupling at 90 MHz. This signal is assigned to

H-6, and the absence of axial-axial coupling firstly suggests H-6e. However, we believe this to be misleading because this ring is neither a chair, nor is it rigid, (models indicate considerable flexibility around C-4,5) in the way that a saturated ring is. There seems little doubt about the occurrence of the O-H...N bonding, as in **2**, which necessitates the aryl function being in an equatorial conformation, and H-6 is therefore axial.

(b) *p*-Chlorothiophenol.

A smooth reaction occurred, and one product was detected. This was isolated in 46% yield and assigned the structure **14**. As for the phenol reaction, only the 5,6 double bond reacted, with the low field singlet for H-2 in the ¹H nmr spectrum of **8** also being present in **14** (δ 6.5). The thiophenol ring is joined through sulfur, as evidenced by the doublet of doublets for the aromatic protons. As for **13**, the signal assigned to H-6 is a broad singlet at 4.55 and it seems likely that in this compound too, H-6 is axial.



The ¹H nmr spectrum contained the characteristic OH peak (in carbon tetrachloride) at δ 8.8 and the aromatic pattern was only consistent with linkage of the cresol through carbon. Only one double bond of **8** undergoes reaction, as shown by the occurrence of a single peak for H-2 at δ 6.95.

1,6-Dihydro-1-methylpyridine-3-carbonitrile (**7**).

Borohydride reduction of **5** reportedly gives an approximately equal mixture of **6** and **7** [6], which can be separated by distillation (**6** has the lower bp). We found, however, that the crude mixture (from reduction at 0°) also contained 10% of the 1,4-dihydro compound, **8**, and, after distillation of **6**, the ratio of **8**:**7** was increased. Thermal isomerization of **7** to **8** was therefore quite readily induced and it was not possible to obtain pure **7**. The sample of **7** used was therefore the residue from distillation of **6** at the lowest practicable temperature and pressure and contained 40% of **8**. This was not a problem, since the behaviour of **8** itself was investigated above, and the products from each dihydro compound were separable.

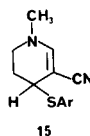
(a) *p*-Cresol.

Compound **7** contains the apparently unreactive C2-C3 double bond and no structural feature to aid isomerization of the C4-C5 double bond to an enamine. Therefore, it was not surprising to find that no reaction with the phenol could be detected.

(b) *p*-Chlorothiophenol.

Reaction occurred readily, and one product from **7** was

detected. This was readily separated from the smaller amount of **14** present by crystallization from methanol (38% yield based on the proportion of **7** in the starting material), and was assigned structure **15**. This orientation



was reported for the product from the base catalyzed addition of phenylacetonitrile to **7** [8], and ^1H and ^{13}C nmr data are compatible with **15**. Once again, the signal for H-4 (δ 3.9) is a broad singlet.

EXPERIMENTAL

The ^1H nmr spectra were recorded on a Perkin Elmer R32 (90 MHz) spectrometer and are in deuteriochloroform solvent unless otherwise stated. The ^{13}C nmr spectra were recorded on a JEOL PFT-100 FT-NMR (25 MHz) spectrometer, also in deuteriochloroform solvent. The assigned ^{13}C peaks (δ ppm) for the heterocyclic ring, and *N*-methyl carbons, of all compounds are listed in Table 1.

1-Methyl-1,2,5,6-tetrahydropyridine-3-carbonitrile (**6**).

This compound, bp 150-155°/25 mm, was prepared by the literature method [6]; ^1H nmr: δ 2.3-2.5 (m, H-5, 2H), 2.4 (s, N-Me, 3H), 2.5-2.6 (m, H-2, 2H), 3.0-3.1 (m, H-6, 2H), 6.65 (m, H-4, 1H).

1-Methyl-1,2,5,6-tetrahydropyridine-4-carbonitrile (**1**).

This compound was prepared likewise and was sufficiently pure for further use without distillation; ^1H nmr: δ 2.2-2.4 (m, H-5, 2H), 2.3 (s, N-Me, 3H), 2.4-2.6 (m, H-2, 2H), 2.9-3.1 (m, H-6, 2H), 6.3 (m, H-3, 1H).

1,4-Dihydro-1-methylpyridine-3-carbonitrile (**8**).

This compound was prepared by dithionite reduction of the quaternary salt (**6**) and was sufficiently pure for further use without distillation; ^1H nmr: δ 3.05 (s, N-Me, 3H), 3.15 (m, H-4, 2H), 4.60 (dt, H-5, 1H, $J = 9, 4$ Hz), 5.70 (dq, H-6, 1H, $J = 9, 1.5$ Hz), 6.45 (s, H-2, 1H).

1,6-Dihydro-1-methylpyridine-3-carbonitrile (**7**).

This compound was not obtained pure, but was the major component (60%), with **8**, in the oil remaining after distillation ($\leq 90^\circ/1.5$ mm) of **6**; ^1H nmr: δ 2.90 (s, N-Me, 3H), 4.2 (m, H-6, 2H), 5.20 (dt, H-5, 1H, $J = 10, 4$ Hz), 5.80 (dq, H-4, 1H, $J = 10, 1.5$ Hz), 6.75 (s, H-2, 1H).

Conditions for Addition Reactions.

(a) *p*-Cresol.

The pyridine (0.02 mole), *p*-cresol (0.03 mole) and sodium (0.004 mole) were heated at 100° for 3 hours. The mixture was taken up in dichloromethane, washed with 5% sodium hydroxide, water, and the organic extract dried and concentrated.

(b) *p*-Chlorothiophenol. Method A.

This was as for the *p*-cresol reactions. The mixture was taken up in dilute hydrochloric acid and extracted with dichloromethane. The product was then obtained by neutralization of the acid solution with ammonium hydroxide. Method B. *p*-Chlorothiophenol (0.01 mole) and the pyridine (0.01 mole) were added to a solution of sodium (0.0008 mole) in ethanol (50 ml) and the mixture was heated under reflux, under nitrogen, for 5 hours. The ethanol was removed, the residue taken up in dichloromethane, washed with 5% sodium hydroxide solution, water, and the organic material dried and concentrated.

3-(*p*-Chlorothiophenoxy)-1-methylpiperidine-4-carbonitrile (**3**).

Both methods gave rise to the same single isomer, with structure **4**.

This was obtained in 40% yield by recrystallization of the crude product from methanol, and had mp 104-105°; ^1H nmr: δ 2.0 (m, H-5, 2H), 2.35 (s, N-Me, 3H), 2.3-2.8 (m, H-2a, 6, 3H), 2.9 (dd, H-2e, 1H, $J = 11, 4$ Hz), 3.07 (q, H-4e, 1H, $J = 4$ Hz), 3.32 (dt, H-3e, 1H, $J = 10, 4$ Hz), 7.25 (d, ArH, 2H, $J = 8$ Hz), 7.45 (d, ArH, 2H).

Anal. Calcd. for $\text{C}_{13}\text{H}_{15}\text{ClN}_2\text{S}$: C, 58.5; H, 5.7; N, 10.5; S, 12.0. Found: C, 58.4; H, 5.6; N, 10.4; S, 12.2.

4-(*p*-Chlorothiophenoxy)-1-methylpiperidine-3-carbonitrile (**10**).

The crude product from method B was recrystallized from methanol to give isomer **11**, mp 81-82°, in 50% yield; ^1H nmr: δ 1.6-2.3 (m, H-2a, 5, 6a, 4H), 2.35 (s, N-Me, 3H), 2.8-3.2 (m, H-2e, 3e, 4a, 6e, 4H), 7.3 (d, ArH, 2H, $J = 8$ Hz), 7.5 (d, ArH, 2H); ^1H nmr (DMSO- d_6): δ 3.3 (dt, H-4a, 1H, $J = 10, 4$ Hz).

Anal. Calcd. for $\text{C}_{13}\text{H}_{15}\text{ClN}_2\text{S}$: C, 58.5; H, 5.7; N, 10.5; S, 12.0. Found: C, 58.5; H, 5.6; N, 10.4; S, 12.2.

Method A (heated for 16 hours) afforded two isomers in approximately equal amounts. Isomer **11** was separated by crystallization from light petroleum and the filtrate yielded isomer **12** as an oil; ^1H nmr: δ 1.8-3.2 (m, all ring H, 8H), 2.20 (s, N-Me, 3H), 7.3 (d, ArH, 2H, $J = 8$ Hz), 7.45 (d, ArH, 2H); ^1H nmr (DMSO- d_6): δ 3.28 (td, H-4a, 1H, $J = 10, 4$ Hz). The methiodide of **12** had mp 237-238° (methanol).

Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{ClIN}_2\text{S}$: C, 40.7; H, 4.4; N, 6.8; S, 7.8. Found: C, 41.1; H, 4.5; N, 6.8; S, 8.1.

6-(2-Hydroxy-5-methylphenyl)-1-methyl-1,4,5,6-tetrahydropyridine-3-carbonitrile (**13**).

Crystallization of the crude product from methanol gave **13**, mp 212-214°, in 26% yield; ^1H nmr (carbon tetrachloride): δ 1.9 (bs, H-4,5, 4H), 2.2 (s, ArMe, 3H), 2.85 (s, N-Me, 3H), 4.55 (bs, H-6, 1H), 6.5-6.8 (m, ArH, 3H), 6.95 (s, H-2, 1H), 8.8 (bs, OH, 1H).

Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}$: C, 73.6; H, 7.1; N, 12.3. Found: C, 73.4; H, 7.1; N, 12.2.

6-(*p*-Chlorothiophenoxy)-1-methyl-1,4,5,6-tetrahydropyridine-3-carbonitrile (**14**).

Reaction of **8** with *p*-chlorothiophenol by method B gave this compound, mp 48-50° (from benzene-light petroleum) in 46% yield; ^1H nmr (carbon tetrachloride): δ 1.9-2.6 (m, H-4,5, 4H), 2.90 (s, N-Me, 3H), 4.55 (bs, H-6, 1H), 6.5 (s, H-2, 1H), 7.2 (d, ArH, 2H, $J = 8$ Hz), 7.4 (d, ArH, 2H).

Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{ClN}_2\text{S}$: C, 59.0; H, 5.0; N, 10.6; S, 12.1. Found: C, 59.2; H, 5.2; N, 10.7; S, 11.9.

4-(*p*-Chlorothiophenoxy)-1-methyl-1,4,5,6-tetrahydropyridine-3-carbonitrile (**15**).

The mixture of **7** and **8** was reacted according to method B. Recrystallization of the residue from methanol gave **15**, mp 140-142°, in 38% yield, with the product from **8**, i.e., **14**, remaining in the filtrate; ^1H nmr: δ 1.8-2.0 (m, H-5, 2H), 2.95 (s, N-Me, 3H), 3.1-3.6 (m, H-6, 2H), 3.90 (bs, H-4, 1H), 6.75 (s, H-2, 1H), 7.2 (d, ArH, 2H, $J = 8$ Hz), 7.4 (d, ArH, 2H).

Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{ClN}_2\text{S}$: C, 59.0; H, 5.0; N, 10.6; S, 12.1. Found: C, 58.7; H, 5.0; N, 10.5; S, 12.1.

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