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# Synthesis of some Novel Imidate Derivatives of Thiophene and Furan: Investigations of their Metallation Properties and some Synthetic Applications

**Richard A. Barcock,[1] Derek J. Chadwick[2] and Richard C. Storr**

Department of Chemistry, University of Liverpool, P.O. Box 147,
Liverpool L69 3BX, U.K.

**Lance S. Fuller and John H. Young**

Synthetic Chemicals Ltd., Four Ashes, Wolverhampton,
West Midlands WV10 7BP, U.K.

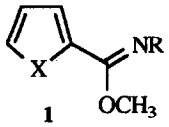
***Abstract:*** *Methyl N-methyl- and methyl N-(2,4,6-trimethyl)phenyl-2-carboximidates of thiophene and furan have been synthesized in excellent yields by the reaction of sodium methoxide in methanol with the corresponding N-methyl- and N-(2,4,6-trimethyl)phenyl-2-carboximidoyl chlorides, which in turn, were obtained from their respective secondary amides by refluxing in neat thionyl chloride. A thorough investigation into the directed lithiation properties of the these heteroaryl-2-imidates with various lithiating agents, solvents, and reaction conditions revealed almost exclusive C5-lithiation. This regioselectivity is in contrast to the C3-lithiation reported for the oxazolino functionality (a cyclic imidate). The synthetic utility of the C5-lithiated intermediate of methyl N-methyl-thiophene-2-carboximidate with various electrophiles is demonstrated. C3-Lithiation has been effected in the case of methyl N-methylthiophene-2-carboximidate when the C5-position is blocked with a removable trimethylsilyl group. Methyl thiophene-2-carboximidate, an N-unsubstituted imidate, was found to eliminate methoxide ion and undergo subsequent C5-lithiation to give 5-lithiothiophene-2-carbonitrile with LDA. n-Butyllithium gave rise predominantly to products resulting from nucleophilic addition to the nitrile group.*

## INTRODUCTION

The five-membered heteroaromatics, thiophene, furan, and *N*-alkyl pyrrole undergo electrophilic substitution and metallation predominantly at the α-positions. This reactivity pattern makes the syntheses of the β-substituted derivatives a challenging problem. Much work has been done in our laboratories on utilizing suitable groups at an α-position of a heteroaromatic to direct metallation into the adjacent β-position with high regioselectivity, thus providing a new route to the particularly awkward 2,3-disubstitution pattern.

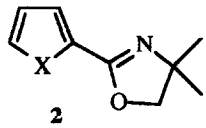
In continuance of the search for functional groups capable of directing lithiation into the C3-position of five-membered heterocycles, the imidate functionality **1** has been thoroughly investigated. Work carried out in our laboratories has amply demonstrated that the oxazolinyl functionality **2** (a cyclic imidate) can be used to successfully direct *ortho*-lithiation in thiophene, furan and pyrrole ring systems.[3-5] In principle, the imidate functionality possesses two important properties which make it a potential *ortho*-director of lithiation; i) a ligating

(Lewis basic) center and ii) an ability to interact electronically to reduce the electron density of an attached heteroaromatic ring.



1

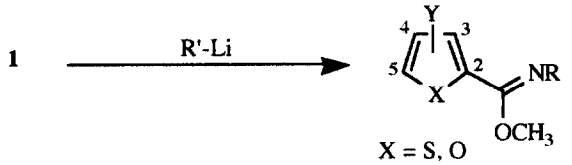
X = S, O
R = H, alkyl, aryl



2

X = S, O, NR'

Some functional groups which have been found to be highly selective in *ortho*-lithiation, for example, the secondary amido functionality, are to some extent vitiated by subsequent transformation difficulties. For example, hydrolysis of secondary amides by aqueous base is exceedingly slow and removal under acidic conditions requires extended heating under reflux.[6] Such vigorous conditions can be incompatible with certain other substituents and, in general, with the furan and pyrrole ring systems. However, the imidate functionality can be readily and easily transformed into other groups. For example, hydrolysis to an ester can be readily effected under mildly acidic conditions;[7] the ester can then be subsequently hydrolyzed to the carboxylic acid. Hydrolysis of the imidate functionality under mildly basic conditions gives secondary amido derivatives.[5] Imidates also have the potential to undergo Chapman-type rearrangements,[8] especially in the presence of a catalytic amount of an alkyl halide, to yield tertiary amides.[9,10] Thus, we were interested in how tolerant the imidate functionality **1** was to organolithium reagents under various reaction conditions and in the regiochemistry of lithiation (either C3- or C5-) of some 2-substituted imidates of thiophene and furan (Figure 1).



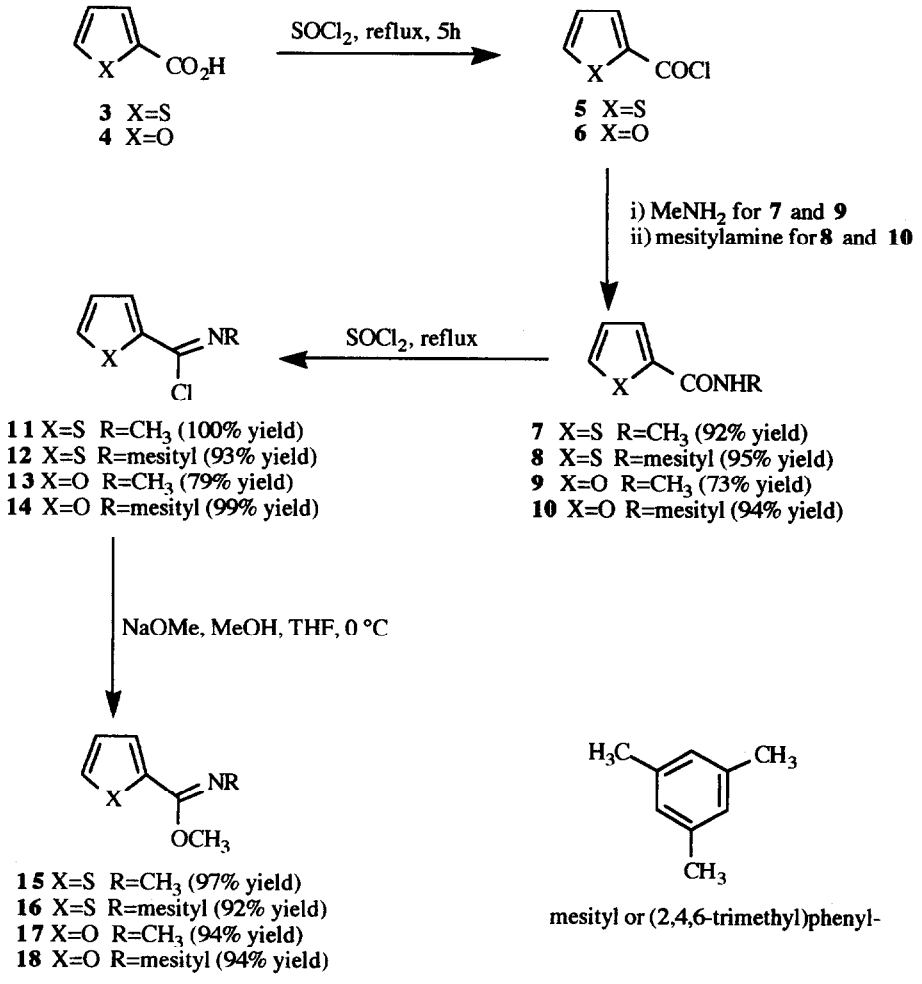
X = S, O
Y = C3-Li or C5-Li

Figure 1.

***Synthesis of Compounds.*** The novel alkyl and aryl imidate derivatives of thiophene and furan were synthesized in high yields as shown in Scheme 1. Thiophene-2-carbonyl chloride (**5**) and furan-2-carbonyl chloride (**6**) were prepared from their respective carboxylic acid (**3** and **4**) by refluxing with neat thionyl chloride. Treatment of the acid chlorides with an aqueous solution of methylamine gave the secondary amides **7** and **9**, respectively, in high yields, and with 2,4,6-trimethylaniline (mesitylamine) gave the secondary amides **8** and **10**, respectively, also in high yields. Treatment of the secondary amides (**7**, **8**, **9**, and **10**) with refluxing thionyl chloride under an argon atmosphere gave the imidoyl chlorides **11**, **12**, **13**, and **14**, respectively, in excellent yields.

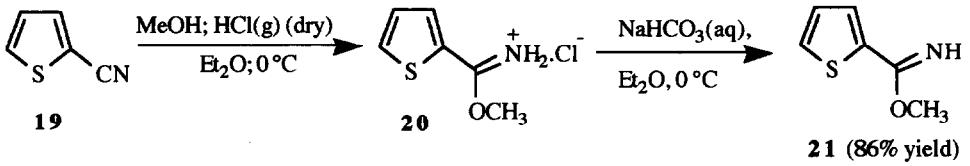
The imidoyl chlorides are lachrymatory and are very susceptible to hydrolysis by atmospheric moisture and so must be handled under anhydrous conditions. Treatment of the imidoyl chlorides (**11**, **12**, **13** and **14**) with

sodium methoxide in anhydrous methanol in tetrahydrofuran at 0 °C yielded the imidates **15**, **16**, **17** and **18**, respectively, in very high yields.[11]




Scheme 1.

Methyl thiophene-2-carboximidate (**21**) was synthesized by application of the Pinner synthesis.[12,13] Passage of dry HCl gas into an ethereal solution of thiophene-2-carbonitrile (**19**), containing an equimolar amount of methanol for 1 hour gave the hydrochloride salt (**20**). This was isolated as a crystalline solid and treated with sodium bicarbonate solution in ether at 0 °C to provide the free imidate **21** in high overall yield (86%) as a mobile oil (Scheme 2).




**19** **20** **21** (86% yield)

Scheme 2.

***Lithiation Studies on Methyl N-Methylthiophene-2-carboximidate (15) and Methyl N-(2,4,6-trimethyl)phenylthiophene-2-carboximidate (16).*** In Tables 1 and 2 are presented the results of a range of experiments designed to elucidate the factors affecting regioselectivity of metallation for the thiophene imidate derivatives (**15** and **16**). The extent of lithiation was generally estimated, as in previous work,[14] by quenching of the reaction mixtures with an excess of either methyl alcohol-*d* or deuterium oxide and comparing the integration of the C5- and C3- protons versus the C4- proton of the heteroaryl rings. This analysis assumes that deprotonation at C4 does not occur. The two electrophiles gave identical results to within experimental error (± 5%) (*cf.* entries 1.2, 1.3 and 1.1, 1.9 in Table 1) and, therefore, we believe that these deuteriation experiments provide a simple yet sufficiently reliable monitoring technique for our present purposes. Our assignment of the C3- and C5- protons was confirmed by an ambiguous synthesis of the 5-deuteriated derivatives of **7** and **8**, based on an earlier lithiation study on 2-substituted heteroaromatic amides.[6] These 5-deuteriated amides of **7** and **8** were then transformed to the 5-deuteriated imidates of **15** and **16** using the procedure outlined in Scheme 1.

The initial lithiation study was carried out on methyl *N*-methylthiophene-2-carboximidate (**15**) (Table 1). It is evident from these results that exclusive, and virtually quantitative α-lithiation is observed using *n*-butyllithium and tetrahydrofuran as solvent (entries 1.1-1.6). These deprotonation reactions presumably go *via* the 'acid-base' mechanism.[15] Employing shorter reaction times (entries 1.2, 1.3) yielded high levels (≥90%) of C5-lithiation. This short reaction time (0.25 h) supported our belief that initial β-lithiation with subsequent transmetallation of the lithium to the C5 position was not involved. Increasing the temperature of the reaction to -20 °C (entry 1.4) also gave exclusive C5-lithiation. An excess of *n*-butyllithium (2.2 equivalents) (entry 1.5) led solely to quantitative C5-lithiation. Inclusion of the $Li^+$-complexing diamine *N,N,N',N'*-tetramethylethylenediamine (TMEDA) at -78 °C (entry 1.8) led to no observable reaction. It is apparent that TMEDA complexes with the *n*-butyllithium deactivating it towards further deprotonation reactions. The reason for this is not clear. Change of lithiating agent to *sec*-butyllithium (a kinetically stronger base) (entry 1.7) gave exclusive and virtually quantitative C5-lithiation. Use of lithium diisopropylamide in tetrahydrofuran at -78 °C (entry 1.10) gave quantitative C5-lithiation. This was anticipated as lithium diisopropylamide has been described as a 'coordinatively saturated' reagent;[15] as such it would be expected to eschew imidate coordination preferring acid-base controlled α-lithiation, as is observed. Changing solvent to 1,2-dimethoxyethane (entry 1.9) and employing 1.1 equivalents of *sec*-butyllithium did not change the outcome of the reaction and gave quantitative C5-lithiation. However, changing the solvent to diethyl ether (entry 1.11) only gave reduced levels (15%) of C5-lithiation.

The virtual absence of any C3-lithiation may be due to the preferential coordination of solvent, rather than imidate, with the organolithium reagent. This effectively removes the directing force that the imidate group exerts and, thus, C5-lithiation *via* an acid-base mechanism is more favoured. In a non-polar solvent like hexane, the imidate functionality might be expected to coordinate with the lithiating agent giving rise to a lower order oligomer capable of initiating protophilic attack into the C3-position. However, only negligible levels of C3- and C5-lithiation were obtained at -78 °C (entry 1.12) and only low levels of lithiation were seen at -20 °C (entry 1.13).

**Table 1. Lithiation of Methyl *N*-Methylthiophene-2-carboximidate (15).**

| Entry | Solvent [a] | Temp(°C) | RLi [b] | Time (h) | $E^+$ | Product Composition (%) [c] derived from 5-lith | 3-lith | Total Recovered yield (%) [d] |
|---|---|---|---|---|---|---|---|---|
| 1.1 | A | -78 | X(1.1) | 1 | MeOD | 100 | 0 | 97 |
| 1.2 | A | -78 | X(1.1) | 0.25 | MeOD | 90 | 0 | 96 |
| 1.3 | A | -78 | X(1.1) | 0.25 | $D_2O$ | 91 | 0 | 97 |
| 1.4 | A | -20 | X(1.1) | 1 | MeOD | 100 | 0 | 90 |
| 1.5 | A | -78 | X(2.2) | 1 | MeOD | 100 | 0 | 98 |
| 1.6 | A | -78 | X(1.1) | 1 | $D_2O$ | 100 | 0 | 100 |
| 1.7 | A | -78 | Y(1.1) | 1 | MeOD | 100 | 0 | 98 |
| 1.8 [e] | A | -78 | X(1.1) | 1 | MeOD | 0 | 0 | 98 |
| 1.9 | B | -78 | Y(1.1) | 1 | $D_2O$ | 100 | 0 | 100 |
| 1.10 | A | -78 | Z(1.1) | 1 | MeOD | 100 | 0 | 100 |
| 1.11 | D | -78 | X(1.1) | 0.5 | MeOD | 15 | 0 | 94 |
| 1.12 | C | -78 | X(1.1) | 0.5 | MeOD | 3 | 3 | 96 |
| 1.13 | C | -20 | X(1.1) | 0.5 | MeOD | 34 | 4 | 100 |

[a] A = tetrahydrofuran; B = 1,2-dimethoxyethane; C = hexane; D = diethylether

[b] X = *n*-butyllithium; Y = *sec*-butyllithium; Z = lithium diisopropylamide. The figures in parenthesis refer to the number of equivalents of organolithium reagent with respect to substrate.

[c] Estimated by NMR analysis (see text) and expressed as a percentage of recovered yield. Starting imidate constitutes balance to 100%.

[d] With respect to starting material.

[e] *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was present in equimolar ratio to the base.

We next focused our attention on an aryl imidate, methyl *N*-(2,4,6-trimethyl)phenylthiophene-2-carboximidate (**16**), in order to determine whether an *N* aryl substituent was more influential on the regioselectivity of lithiation than the *N*-methyl substituent. The results of a range of lithiations are given in Table 2. From these results it is evident that exclusive and virtually quantitative α-lithiation occurred in tetrahydrofuran solution using *n*-butyllithium, *sec*-butyllithium or lithium diisopropylamide (entries 2.1-2.4), *via* an 'acid-base' mechanism.[15] Changing the solvent to 1,2-dimethoxyethane, also gave C5-lithiation with *n*-butyllithium at -78 °C, but the overall level of lithiation was reduced due to the heterogenous nature of the reaction mixture in this solvent (entry 2.6).

**Table 2. Lithiation of Methyl *N*-(2,4,6-Trimethyl)phenylthiophene-2-carboximidate (16).**

| Entry | Solvent [a] | Temp(°C) | RLi [b] | Time (h) | $E^+$ | Product Composition (%) [c] derived from | | Total Recovered yield (%) [d] |
|---|---|---|---|---|---|---|---|---|
| | | | | | | 5-lith | 3-lith | |
| 2.1 | A | -78 | X(1.1) | 1 | MeOD | 90 | 0 | 99 |
| 2.2 | A | -78 | Y(1.1) | 1 | MeOD | 93 | 0 | 90 |
| 2.3 | A | -78 | Y(2.2) | 1 | $D_2O$ | 95 | 0 | 98 |
| 2.4 | A | -78 | Z(1.1) | 1 | MeOD | 90 | 0 | 96 |
| 2.5 [e] | A | -78 | X(1.1) | 1 | MeOD | 0 | 0 | 98 |
| 2.6 | B | -78 | X(1.1) | 1 | MeOD | 70 | 0 | 98 |
| 2.7 [e] | B | -78 | X(1.1) | 1 | MeOD | 0 | 0 | 100 |
| 2.8 | C | -78 | X(1.1) | 1 | MeOD | 0 | 0 | 100 |
| 2.9 | C | -20 | X(1.1) | 0.5 | MeOD | 9 | 3 | 96 |
| 2.10 | C | 20 | X(1.1) | 0.5 | MeOD | 8 | 4 | 100 |
| 2.11 | C | -20 | Y(1.1) | 0.5 | MeOD | 0 | 0 | 94 |
| 2.12 | C | 20 | X(3.0) | 0.5 | MeOD | 6 | 10 | 100 |

The conventions of Table 1 apply.

The use of an excess of *sec*-butyllithium (entry 2.4) slightly increased the level of C5-lithiation. As seen above, the inclusion of TMEDA in reactions in tetrahydrofuran (entry 2.5) and 1,2-dimethoxyethane (entry 2.7) led to no observable lithiation. In hexane with *n*-butyllithium at -78 °C, there was no observable lithiation at all, due to the insolubility of the substrate in this medium at this temperature (entry 2.8). Repeating this reaction at increased temperatures (-20 to 20 °C) increased the solubility of the substrate, but the regioselectivity and overall level of lithiation were poor (entries 2.9 and 2.10). Change of lithiating agent from *n*-butyllithium to *sec*-butyllithium at -20 °C in hexane (entry 2.11), led to no reaction. Employing an excess of *n*-butyllithium (3.0 equivalents) in hexane at 20 °C gave low levels of lithiation and poor regioselectivity (entry 2.12).

***Lithiation Studies on Methyl N-Methylfuran-2-carboximidate (17) and Methyl N-(2,4,6-Trimethyl)phenylfuran-2-carboximidate (18).*** In Tables 3 and 4 are presented the results of a range of experiments designed to elucidate the factors affecting regioselectivity of metallation for the furan imidate derivatives (**17** and **18**).

**Table 3. Lithiation of Methyl *N*-Methylfuran-2-carboximidate (17).**

| Entry | Solvent [a] | Temp(°C) | RLi [b] | Time (h) | $E^+$ | Product Composition (%) [c] derived from 5-lith | 3-lith | Total Recovered yield (%) [d] |
|---|---|---|---|---|---|---|---|---|
| 3.1 | A | -78 | X(1.1) | 0.5 | MeOD | 100 | 0 | 87 |
| 3.2 | A | -78 | Y(1.1) | 0.5 | MeOD | 91 | 0 | 94 |
| 3.3 | A | -78 | Z(1.1) | 0.5 | MeOD | 91 | 0 | 94 |
| 3.4 [e] | A | -78 | X(2.2) | 0.5 | MeOD | 0 | 0 | 96 |
| 3.5 [e] | A | -78 | Y(1.1) | 0.5 | MeOD | 0 | 0 | 100 |
| 3.6 | C | -78 | X(1.1) | 0.5 | MeOD | 11 | 0 | 98 |

The conventions of Table 1 apply.

**Table 4. Lithiation of Methyl *N*-(2,4,6-Trimethyl)phenylfuran-2-carboximidate (18).**

| Entry | Solvent [a] | Temp(°C) | RLi [b] | Time (h) | $E^+$ | Product Composition (%) [c] derived from 5-lith | 3-lith | Total Recovered yield (%) [d] |
|---|---|---|---|---|---|---|---|---|
| 4.1 | A | -78 | X(1.1) | 0.5 | MeOD | 86 | 0 | 96 |
| 4.2 | A | -78 | X(2.2) | 0.5 | MeOD | 96 | 0 | 100 |
| 4.3 | A | -78 | Y(1.1) | 0.5 | MeOD | 90 | 0 | 94 |
| 4.4 | A | -78 | Z(1.1) | 0.5 | MeOD | 77 | 0 | 92 |
| 4.5 | A | -78 | Y(2.2) | 0.5 | MeOD | 100 | 0 | 100 |
| 4.6 [e] | A | -78 | X(1.1) | 0.5 | MeOD | 0 | 0 | 98 |
| 4.7 | B | -78 | X(1.1) | 0.5 | MeOD | 97 | 0 | 98 |

The conventions of Table 1 apply.

It is immediately clear from these results that for methyl *N*-methylfuran-2-carboximidate **17** (see Table 3) exclusive and high yielding α-lithiation occurred in tetrahydrofuran solution using *n*-butyllithium, *sec*-butyllithium or lithium diisopropylamide (entries 3.1-3.3), *via* an 'acid-base' mechanism,[15] probably enhanced by the greater electronegativity of the oxygen heteroatom of the furan ring. As observed above, the inclusion of TMEDA in reactions in tetrahydrofuran (entries 3.4 and 3.5) led to no observable lithiation. In hexane with *n*-butyllithium at -78 °C for 0.5 h (entry 3.6) there was little C5 lithiation observed. A similar pattern of results was observed for methyl *N*-(2,4,6-trimethyl)phenylfuran-2-carboximidate **18** with α-lithiation being predominant (see Table 4). Other lithiation experiments in the non-polar solvent hexane, were not attempted due to the insolubility of the substrate in this medium at low temperatures (-20 °C and -78 °C). These observations closely parallel those obtained with the thiophene imidates **15** and **16** and the same interpretation of the results applies here.

It is clear that the directing force (coordinative and / or inductive) of the *N*-substituted imidate functionality for C3-lithiation is poor. Thus, C5-lithiation is favoured over C3-lithiation. In contrast, the oxazolino functionality (cyclic imidate) has been shown to be a highly effective directing group for β-lithiation.[3-5] The oxazolines have a rigid conformation and configuration, termed Z-anti-periplanar [Z (ap)]: Z- refers to the configuration about the carbon-nitrogen double bond; anti-periplanar refers to the $OCH_2$- / heteroaryl ring arrangement about the C-O single bond (Figure 2). The lone electron-pair on the nitrogen, required to coordinate and de-oligomerize the organolithium reagent, is exposed in the vicinity of the C3-position. This produces the high molarity of 'activated' lithiating agent in close proximity to the C3-proton and leads to protophilic attack at this position. In contrast to the oxazolines, simple acyclic imidates appear to exist predominantly in the E (ap) form (Figure 3).

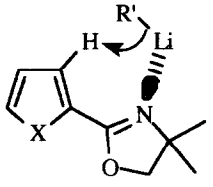
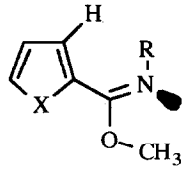
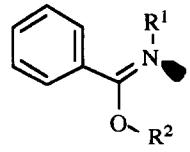



Figure 2.




R = H, $CH_3$, (2,4,6-trimethyl)phenyl

Figure 3.



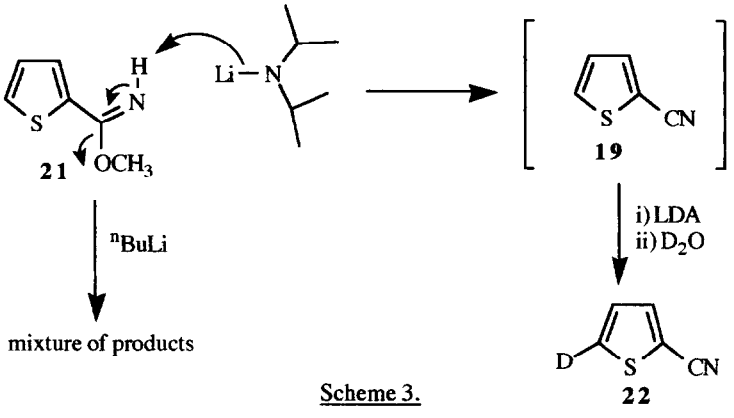

$R^1$ = H, alkyl, aryl
$R^2$ = alkyl

Figure 4.

Thus, Exner and Schindler have carried out a complete dipole moment and molecular refraction study on some *N*-unsubstituted and *N*-substituted imidates[16] and found the E-configuration to be generally valid for simple *N*-substituted alkyl and aryl imidates (*cf.* Figure 4). The preference for the E-configuration was attributed to the conformation at the $R^2$-O bond ($R^2$ = alkyl). Walter confirmed these findings using nmr techniques.[17] If this E (ap) configuration is indeed predominant for the heteroaryl imidate (figure 3) under these reaction conditions, it can be imagined that the lone pair on the nitrogen of the imidate functionality (essential for coordination of the organolithium reagent) is directed away from the ring, and so exerts no directing force (*via* a 'coordinative' mechanism) for *ortho*-lithiation. Therefore, since there is no competition from the 'coordination-only' mechanism, the 'acid-base' mechanism is preferred and exclusive α-lithiation prevails.

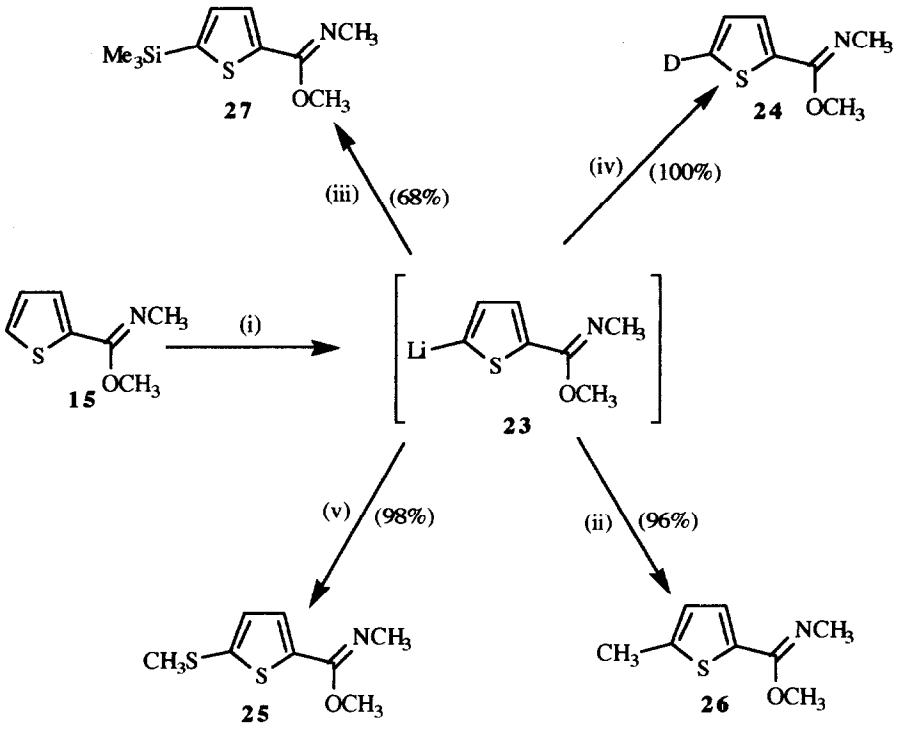
To finalize the lithiation studies on some heteroaryl-2-imidates, the tolerance of an *N*-unsubstituted imidate with organolithium reagents was briefly investigated. Reaction of imidate **21** with 2.0 equivalents of *n*-butyllithium in tetrahydrofuran at -78 °C for 0.5 hour, followed by electrophilic quench with deuterium oxide yielded a mixture of products as evidenced by tlc. Infra-red analysis indicated the presence of a nitrile functionality and the $^1$H nmr spectra confirmed the presence of thiophene-2-carbonitrile (**19**), its 5-deuterio isomer (**22**), and products resulting from nucleophilic addition of the organolithium reagent to the nitrile derivatives.

Treatment of imidate **21** with 2.0 equivalents of the more sterically hindered base, lithium diisopropylamide, gave an excellent yield of 5-deuterio thiophene-2-carbonitrile (**22**) (80% by $^1$H nmr analysis). No products resulting from nucleophilic addition reactions of the organolithium reagent to the nitrile were observed. In this reaction, presumably the first equivalent of lithium diisopropylamide removes the acidic NH proton of **21**, with concomitant elimination of methoxide, to form thiophene-2-carbonitrile (**19**). The C5-proton is subsequently removed with the second equivalent of lithium diisopropylamide by an 'acid-base' type mechanism[15] (scheme 3).




Scheme 3.

***Synthetic Applications of Lithiated Imidates.*** Although no significant levels of β-lithiation were obtainable employing the imidate functionality as a directing group, high levels of α-lithiation were achieved on the thiophene ring. Thus, methyl *N*-methyl-5-lithio-thiophene-2-carboximidate (**23**) can be generated in 100% yield by using, for example, *n*-butyllithium in tetrahydrofuran at -78 °C for 1 hour. Work-up of the thiophene anion (**23**) with a range of electrophiles at this temperature yielded a range of 5-substituted thiophene-2-imidates (Scheme 4). Thus, with an excess of methyl alcohol-*d* a quantitative yield of the 5-deuterio imidate **24** was obtained. With five equivalents of methyl disulfide the methylthio imidate **25** was obtained in excellent yield (98%). Five equivalents of methyl iodide yielded the 5-methylimidate **26** also in excellent yield (96%). Addition of 1.1 equivalent of trimethylsilyl chloride gave the 5-silyl-imidate **27** in 68% yield.

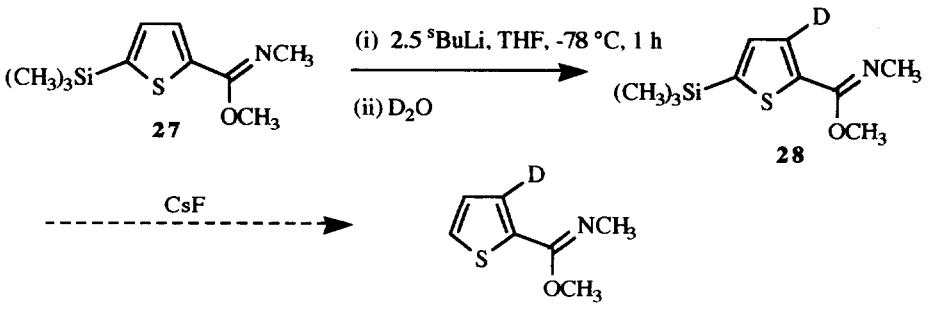



Reagents: (i) $^{n}$BuLi, THF, -78 °C, 1 h; (ii) MeI; (iii) TMSCl; (iv) MeOD; (v) $Me_2S_2$

Scheme 4.

***Lithiation of Methyl N-Methyl-5-trimethylsilylthiophene-2-carboximidate (27): the use of Silicon Blocking Groups.*** It was of interest to determine whether any β-lithiation could be seen when the C5-position of the thiophene-2-imidate **15** was blocked with a trimethylsilyl group. Successful lithiation would lead to trisubstituted thiophenes and the subsequent removal of the blocking group with a source of fluoride (for example, cesium fluoride) is potentially a route to 2,3-disubstituted thiophene derivatives.

A short lithiation / deuteriation study undertaken on imidate **27** (Table 5) demonstrated that 1.1 equivalents of *n*-butyllithium in tetrahydrofuran at -78 °C for 1 h gave no C3-lithiation (entry 5.1). Indeed, 2.5 equivalents of *sec*-butyllithium in tetrahydrofuran at -78 °C was required for quantitative β-lithiation to give **28** (entry 5.3). Thus, when the C5-position of the thiophene ring is blocked, lithiation can be achieved at the C3-position (Scheme 5). Since an excess of *sec*-butyllithium, a kinetically stronger base, was required for complete deprotonation it seems more probable that the 'inductive' effect rather than the 'coordinative' effect of the imidate functionality is influencing the reaction here, *via* an 'acid-base' type mechanism.




Scheme 5.

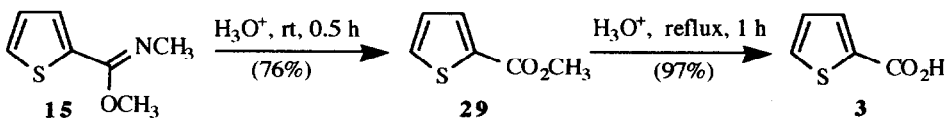
**Table 5. C3-Lithiation of Methyl *N*-Methyl-5-trimethylsilylthiophene-2-carboximidate (27)**

| Entry | Solvent [a] | Temp(°C) | R-Li [b] | Time (h) | $E^+$ | Product Composition (%) [c] Derived from C3-Lithiation | Total Recovered Yield (%) [d] |
|---|---|---|---|---|---|---|---|
| 5.1 | A | -78 | X(1.1) | 1 | $D_2O$ | 0 | 100 |
| 5.2 | A | -78 | Y(1.1) | 1 | $D_2O$ | 50 | 96 |
| 5.3 | A | -78 | Y(2.5) | 1 | $D_2O$ | 100 | 98 |

The conventions of Table 1 apply.

***Transformations of the Imidate Moiety.*** Ease of subsequent transformation is an important factor when the overall utility of a metallation directing group is being assessed. The synthetic potential of a directed metallation group is seriously undermined if such transformations cannot be achieved readily. The imidate functionality is synthetically equivalent to the carboxylate and carboxylic acid functionalities, and this is of particular importance as many ester type substrates themselves undergo nucleophilic addition reactions with alkyllithium reagents.

Treatment of methyl *N*-methylthiophene-2-carboximidate (**15**) with an aqueous solution of HCl at room temperature yielded methyl thiophene-2-carboxylate (**29**) as a colourless oil in good yield (76%), which was then readily hydrolysed further with aqueous HCl to thiophene-2-carboxylic acid (**3**, 97%) (Scheme 6).




Scheme 6.

## CONCLUSIONS

The work described herein demonstrates that the *N*-substituted imidate functionality is indeed tolerant to organolithium reagents. C5-Lithiation is predominant; the directing ability of this functionality for lithiation into the β- position of thiophene and furan is low. This is in contrast to that observed for the oxazolino functionality (a cyclic imidate). However, quantitative levels of C5 lithiation can be achieved and this permits access, through reactions of the lithiated intermediate with various electrophiles, to 2,5-disubstituted derivatives. β-Lithiation can be effected for methyl *N*-methyl-thiophene-2-carboximidate when the C5-position is blocked with a trimethylsilyl group, and an excess of *sec*-butyllithium is used. This opens up a route to 2,3,5-trisubstituted derivatives and with the potential for the easy removal or replacement of the trimethylsilyl group, a route to 2,3-disubstituted derivatives. In the presence of LDA, methyl thiophene-2-carboximidate, an *N*-unsubstituted imidate, is converted into thiophene-2-carbonitrile which undergoes subsequent C5-deprotonation. Nucleophilic addition to the resulting nitrile group occurs with *n*-butyllithium.

## EXPERIMENTAL SECTION

Product purity was checked by thin layer chromatography (tlc) on Merck 10 x 2 cm aluminium-backed plates with a 0.2 mm layer of Kieselgel 60 $F_{254}$. Melting points (mp) were determined on a Kofler block and are uncorrected. Microanalyses were performed at the University of Liverpool Microanalyses Laboratory. $^1H$ nmr spectra were recorded on either a Bruker AC 200 (200 MHz) or a Perkin Elmer R34 (220 MHz) spectrometer in $CDCl_3$ using TMS as the internal reference. Infrared spectra were recorded either on an AEI MS902 VG analytical 7070E or a Mattson Centauri Spectrometer. Solvents were dried prior to use: diethyl ether ($Et_2O$), 1,2-dimethoxyethane (DME), and tetrahydrofuran (THF) from sodium benzophenone ketyl; hexane, diisopropylamine, *N*, *N*, *N'*, *N'*-tetramethylethylenediamine (TMEDA) from calcium hydride. MeOH was distilled from magnesium methoxide. Argon gas was used to provide an inert atmosphere. The concentrations of solutions of commercial *n*-butyllithium and *sec*-butyllithium were determined by titration against diphenylacetic acid in THF.[18]

*N-Methylthiophene-2-carboxamide (7):* Thiophene-2-carboxylic acid (40.0 g, 0.31 mol), and $SOCl_2$ (112 ml, 1.55 mol) were heated under reflux for 5 h. The excess of $SOCl_2$ was removed under reduced pressure and the crude acid chloride added dropwise to a solution of commercial aqueous $MeNH_2$ (41 ml, 0.31 mol) in aqueous 10% NaOH (50 ml). After addition of the acid chloride the mixture was stirred for a further 12 h and extracted with ethyl acetate (5 x 30 ml) and washed with aqueous HCl (5% v/v, 30 ml), water (2 x 30 ml) and brine (30 ml). The organic layer was dried ($MgSO_4$) and evaporated to give the crude product which was purified by recrystallisation (ethyl acetate-light petroleum) to give the amide (7) (36.28 g, 83%) as colourless crystals, mp 111-113 °C (lit.,[19] 110-112 °C).

*N-(2,4,6-Trimethyl)phenylthiophene-2-carboxamide (8):* Thiophene-2-carbonyl chloride (22.34 g, 0.152 mol) in $CH_2Cl_2$ (50 ml) was added dropwise to a solution of 2,4,6-trimethylaniline (20.62 g, 0.15 mol), $Et_3N$ (31.80 ml, 0.23 mol) and $CH_2Cl_2$ (100 ml) at room temperature. The mixture was then refluxed for 12 h, washed with water (2 x 50 ml), and dried ($MgSO_4$). The organic layer was evaporated under reduced pressure to

yield the crude product which was purified by recrystallisation (ethyl acetate-light petroleum) to give the amide (**8**) (33.58 g, 95%) as colourless crystals, mp 180-181 °C (lit.,[20] 164-165 °C); Anal. Calcd. for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.17. Found: C, 68.50; H, 6.16; N, 5.57.

*N-Methylfuran-2-carboxamide (**9**):* 2-Furoic acid (10.19 g, 91.0 mmol), and $SOCl_2$ (19.8 ml, 0.27 mol) were heated under reflux for 5 h. The excess of $SOCl_2$ was removed under reduced pressure and the crude acid chloride added dropwise to a solution of commercial aqueous $MeNH_2$ (10.22 ml, 91.0 mmol) in aqueous 10% NaOH (50 ml). After addition of the acid chloride the mixture was stirred for a further 12 h and extracted with ethyl acetate (5 x 30 ml) and washed with aqueous HCl (5% v/v, 30 ml), water (2 x 30 ml) and brine (30 ml). The organic layer was dried ($MgSO_4$) and evaporated to give the crude product which was purified by distillation to give the amide (**9**) (36.28 g, 83%) as a viscous colourless oil, bp 142 °C / 3 mmHg. On cooling a colourless crystalline solid was formed, m.p., 59-61 °C (lit.,[21] 62-64.5 °C).

*N-(2,4,6-Trimethyl)phenylfuran-2-carboxamide (**10**):* Furan-2-carbonyl chloride (15.0 g, 0.115 mol) in $CH_2Cl_2$ (50 ml) was added dropwise to a solution of 2,4,6-trimethylaniline (15.54 g, 0.115 mol), $Et_3N$ (24 ml, 0.172 mol) and $CH_2Cl_2$ (80 ml) at room temperature. The mixture was then refluxed for 12 h, washed with water (2 x 50 ml), and dried ($MgSO_4$). The organic layer was evaporated under reduced pressure to yield the crude product which was purified by recrystallisation (ethyl acetate-light petroleum) to give the amide (**10**) (24.86 g, 94%) as colourless crystals, mp 162-163 °C; $\nu_{max}$ (Nujol): 3280, 2950, 1660 (C=O), 1590, 1490, 1340, 1040 and 870 $cm^{-1}$; $^1H$ nmr: δ 7.64 (br. s, 1H, NH), 7.48 (d, J = 1.7 Hz, 1H, furan 5-H), 7.17 (d, J = 3.9 Hz, 1H, furan 3-H), 6.90 (2H, s, aryl H), 6.50 (dd, J = 3.9, 1.7 Hz, 1H, furan 4-H), 2.27 (s, 3H, aryl $CH_3$), 2.21 (6H, s, 2 x aryl $CH_3$); MS: *m/z* 229($M^+$, 37%), 200(7), 134(100), 95(74), 77(8), 65(7), 45(40). Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.24; H, 6.57; N, 6.00.

*N-Methylthiophene-2-carboximidoyl Chloride (**11**):* *N*-Methylthiophene-2-carboxamide (5.50 g, 39.0 mmol) was heated under reflux with $SOCl_2$ (15 ml, 0.21 mol) for 18 h. Excess of $SOCl_2$ was removed *in vacuo* and the residue was distilled under reduced pressure to give the pure imidoyl chloride (**11**) (6.00 g, 96%) as a colourless oil, bp 88 °C, 15 mmHg; $\nu_{max}$ (film): 3090, 2950, 1660 (C=N), 1590, 1490, 1340, 1040 and 870 $cm^{-1}$; $^1H$ nmr: δ 7.71 (dd, J = 3.8, 1.0 Hz, 1H, thiophene 3-H), 7.43 (dd, J = 4.9, 1.0 Hz, 1H, thiophene 5-H), 7.03 (dd, J = 4.9, 3.8 Hz, 1H, thiophene 4-H), 3.40 (s, 3H, $NCH_3$); MS: *m/z* 159($M^+$, 19%), 143(20), 124(54), 109(100), 102(22), 75(31), 45(40). Anal. Calcd. for $C_6H_6NSCl$: C, 45.14; H, 3.79; N, 8.77. Found: C, 44.79; H, 3.70; N, 8.66.

*N-(2,4,6-Trimethyl)phenylthiophene-2-carboximidoylchloride (**12**):* *N*-(2,4,6-Trimethyl)phenylthiophene-2-carboxamide (5.0 g, 20 mmol) was heated under reflux with $SOCl_2$ (25 ml, 0.35 mol) for 3 h. Excess of $SOCl_2$ was removed *in vacuo* and the residue was distilled under reduced pressure to give the pure imidoyl chloride (**12**) (5.0 g, 93%) as a viscous oil, bp 138 °C, 3 mmHg. On cooling a light yellow solid was obtained, mp 63-65 °C; $\nu_{max}$ (film): 3080, 2900, 1655 (C=N), 1630, 1480, 1140, 1050 and 850 $cm^{-1}$; $^1H$ nmr: δ 7.78 (dd, J = 3.9, 1.1 Hz, 1H, thiophene 3-H), 7.50 (dd, J = 5.2, 1.1 Hz, 1H, thiophene 5-H), 7.10 (dd, J = 5.2, 3.9 Hz, 1H, thiophene 4-H), 6.88 (s, 2H, aryl H), 2.27 (s, 3H, aryl $CH_3$), 2.07 (s, 6H, 2 x aryl $CH_3$); MS:

*m/z* 263($M^+$, 8%), 228(24), 110(28), 91(36), 77(38), 44(58), 36(100). Anal. Calcd. for $C_{14}H_{14}NSCl$: C, 63.75; H, 5.53; N, 5.31. Found: C, 63.70; H, 5.29; N, 5.18.

*N-Methylfuran-2-carboximidoyl Chloride (13):* *N*-Methylfuran-2-carboxamide (5.0 g, 40 mmol) was heated under reflux with $SOCl_2$ (25 ml, 0.34 mol) for 12 h. Excess of $SOCl_2$ was removed *in vacuo* and the residue was distilled under reduced pressure to give the pure imidoyl chloride (**13**) (4.53 g, 79%) as a pale yellow oil, bp 37 °C, 0.06 mmHg; $\nu_{max}$ (film): 3180, 2950, 1705 (C=N), 1500, 1180, and 850 $cm^{-1}$; $^1H$ nmr: δ 7.52 (d, J = 1.7 Hz, 1H, furan 5-H), 7.00 (d, J = 3.4 Hz, 1H, furan 3-H), 5.46 (dd, J = 3.4, 1.7 Hz, 1H, furan 4-H), 3.44 (s, 3H, $NCH_3$); MS: *m/z* 145($M^+$, 3%), 143(9), 108(100), 93(82) and 64(41). Anal. Calcd. for $C_6H_6NOCl$: C, 50.20; H, 4.21 N, 9.76. Found: C, 50.06; H, 4.23; N, 9.67.

*N-(2,4,6-Trimethyl)phenylfuran-2-carboximidoylchloride (14):* *N*-(2,4,6-Trimethyl)phenylfuran-2-carboxamide (1.0 g, 4.04 mmol) was heated under reflux with $SOCl_2$ (15 ml, 0.21 mol) for 3 h. Excess of $SOCl_2$ was removed *in vacuo* and the residue was distilled under reduced pressure to give the pure imidoyl chloride (**14**) (1.07 g, 99%) as a viscous oil, bp 115 °C, 0.1 mmHg. On cooling a light yellow waxy solid was obtained, mp 46-47 °C; $\nu_{max}$ (film): 3180, 2950, 1680 (C=N), 1490, 1220, 1040 and 870 $cm^{-1}$; $^1H$ nmr: δ 7.65 (d, J = 1.6 Hz, 1H, furan 5-H), 7.25 (d, J = 3.9 Hz, 1H, furan 3-H), 6.90 (s, 2H, aryl H), 6.59 (dd, J = 3.9, 1.6 Hz, 1H, furan 4-H), 2.30 (s, 3H, aryl $CH_3$), 2.10 (s, 6H, 2 x aryl $CH_3$); MS: *m/z* 247($M^+$, 38%), 212(100), 197(21), 168(6), 134(9), 119(11), 91(24), 77(19). Anal. Calcd. for $C_{14}H_{14}NOCl$: C, 67.88; H, 5.70; N, 5.65. Found: C, 67.52; H, 5.63; N, 5.64.

*Methyl N-Methylthiophene-2-carboximidate (15):* A solution of sodium methoxide (1.0 g, 18.52 mmol) in MeOH (15 ml) was added dropwise to *N*-methylthiophene-2-carboximidoyl chloride (1.02 g, 6.39 mmol) in THF (10 ml) at 0 °C. The solution was stirred at 0 °C for 0.5 h and allowed to reach room temperature and stirred for 12 h. The bulk of the MeOH and THF was removed *in vacuo* and the residue was diluted with $Et_2O$ (40 ml) and washed with aqueous sodium bicarbonate (2 x 20 ml), water (20 ml), and brine (20 ml). The organic phase was dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a pale yellow oil which was purified by distillation under reduced pressure to give the pure imidate (**15**) (0.93 g, 97%) as a colourless oil, bp 60 °C, 1.0 mmHg; $\nu_{max}$ (film): 3090, 2950, 1665 (C=N), 1440, 1365, 1220, 1025 (C-O), and 860 $cm^{-1}$; $^1H$ nmr: δ 7.48 (dd, J = 3.8, 1.1 Hz, 1H, thiophene 3-H), 7.43 (dd, J = 5.0, 1.1 Hz, 1H, thiophene 5-H), 7.09 (dd, J = 5.0, 3.8 Hz, 1H, thiophene 4-H), 3.78 (s, 3H, $OCH_3$), 3.34 (s, 3H, $NCH_3$); MS: *m/z* 155 ($M^+$, 40%), 154(41), 141(9), 124(86), 111(100), 97(44), 83(14), 72(10), 57(11). Anal. Calcd. for $C_7H_9NOS$: C, 54.17; H, 5.84; N, 9.02. Found: C, 53.93; H, 5.86; N, 8.82.

*Methyl N-(2,4,6-Trimethyl)phenylthiophene-2-carboximidate (16):* A solution of sodium methoxide (4.0 g, 74.10 mmol) in MeOH (20 ml) was added dropwise to *N*-(2,4,6-trimethyl)phenylthiophene-2-carboximidoyl chloride (4.0 g, 15.20 mmol) in THF (25 ml) at 0 °C. The solution was stirred at 0 °C for 1 h and allowed to reach room temperature and stirred for 12 h. Work-up as for (**15**) gave the pure imidate (**16**) (3.61 g, 92%) as a viscous, yellow oil, bp 133 °C, 2.0 mmHg. On cooling a pale yellow solid was obtained, mp 70.5-71.5 °C; $\nu_{max}$ (Nujol): 3050, 2900, 1655 (C=N), 1455, 1355, 1260, 1100, 1070 (C-O), 980 and 860 $cm^{-1}$; $^1H$ nmr: δ 7.22 (dd, J = 3.9, 1.1 Hz, 1H, thiophene 5-H), 7.02 (dd, J = 5.0, 1.1 Hz, 1H, thiophene 3-H), 6.86 (s, 2H,

aryl H), 6.83 (dd, J = 5.0, 3.9 Hz, 1H, thiophene 4-H), 4.00 (s, 3H, $OCH_3$), 2.29 (s, 3H, aryl $CH_3$), 1.98 (s, 6H, 2 x aryl $CH_3$); MS: *m/z* 259 ($M^+$, 23%), 228(28), 160(18), 119(22), 111(100), 91(60), 77(51), 65(29), 51(28). Anal. Calcd. for $C_{15}H_{17}NOS$: C, 69.46; H, 6.61; N, 5.40. Found: C, 69.19; H, 6.52; N, 5.28.

*Methyl N-Methylfuran-2-carboximidate (17):* A solution of sodium methoxide (3.50 g, 24.39 mmol) in MeOH (20 ml) was very slowly added dropwise to *N*-methylfuran-2-carboximidoyl chloride (0.50 g, 3.48 mmol) in THF (30 ml) at 0 °C. The solution was stirred at 0 °C for 2 h and allowed to reach room temperature and stirred for 5 h. Work-up as for (**15**) gave a pale yellow oil which was purified by distillation under reduced pressure to give the pure imidate (**17**) (0.42 g, 94%) as a colourless oil, bp 70 °C, 20 mmHg; $\nu_{max}$ (film): 3150, 2950, 1690 (C=N), 1500, 1300, 1220, 1050 (C-O), and 990 $cm^{-1}$; $^1H$ nmr: δ 7.50 (d, J = 1.7 Hz, 1H, furan 5-H), 6.82 (d, J = 3.6 Hz, 1H, furan 3-H), 6.46 (dd, J = 3.6, 1.7 Hz, 1H, furan 4-H), 3.75 (s, 3H, $OCH_3$), 3.36 (s, 3H, $NCH_3$); MS: *m/z* 139 ($M^+$, 23%), 125(25), 108(17), 95(100), 82(13). Anal. Calcd. for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.22; H, 6.57; N, 10.03.

*Methyl N-(2,4,6-Trimethyl)phenylfuran-2-carboximidate (18):* A solution of sodium methoxide (12.0 g, 0.22 mol) in MeOH (25 ml) was added dropwise to *N*-(2,4,6-trimethyl)phenylfuran-2-carboximidoyl chloride (10.84 g, 43.8 mmol) in THF (30 ml) at 0 °C. The solution was stirred at 0 °C for 2 h and allowed to reach room temperature and stirred for 12 h. Work-up as for (**15**) gave the pure imidate (**18**) (3.61 g, 92%) as a viscous, colourless oil, bp 115 °C, 0.3 mmHg. On cooling a waxy colourless solid was obtained, mp 46-47 °C; $\nu_{max}$ (Nujol): 3150, 2950, 1660 (C=N), 1470, 1290, 1240, 1180, 1030 (C-O), 860 and 760 $cm^{-1}$; $^1H$ nmr: δ 7.36 (d, J = 1.7 Hz, 1H, furan 5-H), 6.89 (s, 2H, aryl H), 6.22 (dd, J = 3.9, 1.7 Hz, 1H, furan 3-H), 5.88 (d, J = 3.9 Hz, 1H, furan 3-H), 4.05 (s, 3H, $OCH_3$), 2.28 (s, 3H, aryl $CH_3$), 1.99 (s, 6H, 2 x aryl $CH_3$); MS: *m/z* 243.1263 ($M^+$, 4%, $C_{15}H_{17}NO_2$ requires 243.1259), 229(48), 194(12), 149(34), 134(100), 95(93). Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.42; H, 7.03; N, 5.58.

*Methyl Thiophene-2-Carboximidate (21):* An excess of HCl gas (dry) was passed for 1 h through a solution of thiophene-2-carbonitrile (1.0 g, 9.16 mmol) and anhydrous MeOH (0.37 ml, 9.16 mmol) in $Et_2O$ (15 ml) at 0 °C. A colourless crystalline solid precipitated out. After standing for 48 h at room temperature, the hydrochloride salt was shaken vigorously with a saturated solution of sodium bicarbonate (20 ml) and $CH_2Cl_2$ (40 ml) at 0 °C. The organic layer was separated and dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a brown oil, which was purified by distillation under reduced pressure to give the pure imidate (**21**) (0.87 g, 67%) as a pale yellow oil, bp 90 °C at 15 mmHg; $\nu_{max}$ (film): 3280 (NH), 3060, 2920, 1625 (C=N) and 1065 (C-O) $cm^{-1}$; $^1H$ nmr: δ 7.45 (dd, J = 3.6, 1.1 Hz, 1H, thiophene 3-H), 7.35 (dd, J = 5.0, 1.1 Hz, 1H, thiophene 5-H), 7.01 (dd, J = 5.0, 3.6 Hz, 1H, thiophene 4-H), 3.87 (s, 3H, $OCH_3$); MS: *m/z* 141 ($M^+$, 36%), 110(100), 97(21), 84(77), 69(24) and 58(24).

**Lithiation and Deuteration Studies of Thiophene- and Furan-2-Carboximidates: General Procedures.**

*Method A: n-Butyllithium or sec-butyllithium with hexane or $Et_2O$ as solvent:* To the imidate (0.50 g) in hexane (30 ml) or $Et_2O$ (30 ml) was added commercial *n*-butyllithium in hexane or *sec*-butyllithium in cyclohexane at the specified temperature (see Tables). The reaction mixture was stirred under an inert atmosphere

for the stated time. The electrophile (MeOD or $D_2O$) was added and the mixture was allowed to warm to room temperature, and then stirred for a further 12 h unless otherwise stated. Water (10 ml) and then $Et_2O$ (60 ml) were added. The organic layer was separated, washed with water (2 x 20 ml), brine (10 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield the products which were analyzed by nmr; the results are shown in their respective Tables.

*Method B: 1,2-Dimethoxyethane or THF as solvent:* The procedure was the same as for Method A, except that the solvent was removed under reduced pressure prior to the addition of water. $Et_2O$ (60 ml) was then added to the mixture.

*Method C: Lithiation reactions with LDA*: An equimolar quantity of *n*-butyllithium was added to diisopropylamine in the required solvent at room temperature and left for 0.25 h. The reaction vessel was then cooled to the specified temperature and the imidate derivatives, in the required solvent (10 ml), were then added and the experiment was continued as in Methods A or B.

*Methyl N-Methyl-5-deuteriothiophene-2-carboximidate (**24**):* *n*-Butyllithium (2.43 ml, 3.55 mmol) was added to methyl *N*-methylthiophene-2-carboximidate (**15**) (0.50 g, 3.23 mmol) in THF (30 ml) at -78 °C and the mixture stirred for 1 h, after which methyl alcohol-*d* (1 ml, excess) was added and the reaction mixture allowed to reach room temperature. The solvent was removed under reduced pressure and the residue suspended in water (10 ml) and extracted with diethyl ether (2 x 30 ml). The combined organic extracts were washed with water (10 ml) and brine (10 ml), dried ($MgSO_4$) and the solvent was evaporated *in vacuo* to yield the 5-deuterio-imidate (**24**) as a pale yellow oil (0.50 g, 100%); $^1H$ nmr: δ 7.48 (d, J = 3.9 Hz, 1H, thiophene 3-H), 7.09 (d, J = 3.9 Hz, 1H, thiophene 4-H), 3.78 (s, 3H, $OCH_3$), 3.34 (s, 3H, $NCH_3$).

*Methyl N-Methyl-5-methylthiothiophene-2-carboximidate (**25**):* *n*-Butyllithium (2.43 ml, 3.55 mmol) was added to methyl *N*-methylthiophene-2-carboximidate (0.50 g, 3.23 mmol) in THF (30 ml) at -78 °C and the mixture stirred for 1 h, after which $Me_2S_2$ (1.45 ml, 16.15 mmol) was added and the reaction mixture allowed to reach room temperature. Work-up as for **24** gave the product (**25**) as a yellow oil (0.64 g, 98%); $\nu_{max}$ (film): 2945, 1665 (C=N), 1435, 1330, 1310, 1085 (C-O), 1045 (C-S) and 805 $cm^{-1}$; $^1H$ nmr: δ 7.34 (d, J = 3.8 Hz, 1H, thiophene 3-H), 6.99 (d, J = 3.8 Hz, 1H, thiophene 4-H), 3.75 (s, 3H, $OCH_3$), 3.33 (s, 3H, $NCH_3$), 2.54 (s, 3H, $SCH_3$). MS: *m/z* 201.0280 ($M^+$, 80%, $C_8H_{11}NOS_2$ requires 201.0282), 186(9), 170(100), 155(56), 143(41), 114(32), 94(8).

*Methyl N-Methyl-5-methylthiophene-2-carboximidate (**26**):* *n*-Butyllithium (2.43 ml, 3.55 mmol) was added to methyl *N*-methylthiophene-2-carboximidate (0.50 g, 3.23 mmol) in THF (30 ml) at -78 °C and the mixture stirred for 1 h, after which time MeI (1.01 ml, 16.15 mmol) was added and the reaction mixture allowed to reach room temperature over 7 hours. Work-up as for **24** gave the spectroscopically pure product (**26**) as a pale yellow oil (0.52 g, 96%); $\nu_{max}$ (film): 3050, 2930, 2850, 1650 (C=N), 1455, 1390, 1250, 1060 (C-O), and 805 $cm^{-1}$; $^1H$ nmr: δ 7.28 (d, J = 3.7 Hz, 1H, thiophene 3-H), 6.75 (d, J = 3.7 Hz, 1H, thiophene 4-H), 3.74 (s, 3H, $OCH_3$), 3.32 (s, 3H, $NCH_3$), 2.49 (s, 3H, thiophene-$CH_3$). MS: *m/z* 169.0563 ($M^+$, 45%, $C_8H_{11}NOS$ requires 169.0561), 138(100), 124(70), 111(55), 97(14).

*Methyl N-Methyl-5-trimethylsilylthiophene-2-carboximidate (27):* *n*-Butyllithium (2.43 ml, 3.55 mmol) was added to methyl *N*-methylthiophene-2-carboximidate (0.50 g, 3.23 mmol) in THF (30 ml) at -78 °C and the mixture stirred for 1 h, after which TMSCl (0.45 ml, 3.55 mmol) was added and the reaction mixture allowed to reach room temperature over 8 h. Work-up as for **24** gave the product as a pale brown oil which was purified by Kugelrohr distillation to yield the pure product (**27**) as a pale yellow oil (0.50 g, 68%); $\nu_{max}$ (film): 2950, 1650 (C=N), 1430, 1390, 1300, 1190, 1065 (C-O), 970 and 740 $cm^{-1}$; $^1H$ nmr: δ 7.49 (d, J = 3.9 Hz, 1H, thiophene 3-H), 7.20 (d, J = 3.9 Hz, 1H, thiophene 4-H), 3.74 (s, 3H, $OCH_3$), 3.32 (s, 3H, $NCH_3$), 0.33 (s, 9H, $Si(CH_3)_3$). MS: *m/z* 227 ($M^+$, 58%), 212(92), 183(100), 166(25), 115(15), 73(60), 59(14).

*Acid-Catalyzed Hydrolysis of Methyl N-Methylthiophene-2-Carboximidate (15) to Thiophene-2-Carboxylic Acid (3):* Aqueous 10% HCl (20 ml) was added to methyl *N*-methylthiophene-2-carboximidate (0.50 g, 3.23 mmol) and the reaction was stirred at room temperature for 0.5 h. After this period of time, the reaction mixture was extracted with $Et_2O$ (3 x 20 ml). The combined organic extracts were washed with water (30 ml), dried ($MgSO_4$) and the solvent was evaporated to yield a colourless oil (0.35 g, 76%) which was confirmed by $^1H$ nmr analysis to be methyl thiophene-2-carboxylate (**29**). The ester **29** was then treated further with aqueous 10% HCl (20 ml) in dioxane (40 ml) under reflux for 1 h. Work-up as above yielded thiophene-2-carboxylic acid (**3**) as a white solid (0.30 g, 97%). An analytical sample was purified by sublimation to give white needles, mp 127-129 °C (lit.,[22] 129-130 °C).

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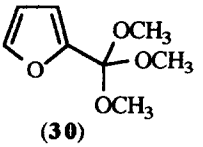
11. Preparation of imidate (**17**) was successfully achieved by the very slow addition of sodium methoxide in methanol at 0 °C. Too rapid an addition always yielded a significant amount (<20%) of a side-product, showing a characteristic singlet at δ 3.21 ppm in the $^1$H nmr spectrum, suggesting the presence of the orthoester of furoic acid (**30**). It is noteworthy that no similar products were observed in the synthesis of the other imidates (**15**, **16** and **18**).

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