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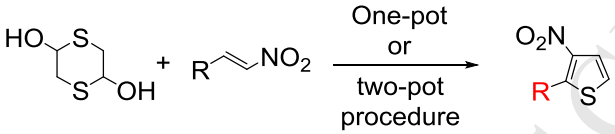
Neasa McNabola,[a] Cornelius J. O'Connor,[a] Mark D. Roydhouse,[a] Michael D. Wall[b] and J. Mike Southern,*[a]

[a] Trinity Biomedical Sciences Institute, School of Chemistry, Trinity College Dublin, Dublin 2, Ireland. [b] Discovery Medicinal Chemistry, GlaxoSmithKline, Gunnels Wood Rd, Stevenage, SG1 2NY, UK; Current address: Medicinal Chemistry (Early Discovery) Charles River Laboratories Chesterford Research Park, CB10 1XL, U.K.



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A one-pot synthesis of 3-nitrothiophene and 3-nitro-2-substituted thiophenes

Neasa McNabola,[a] Cornelius J. O'Connor,[a] Mark D. Roydhouse,[a] Michael D. Wall[#b] and J. Mike Southern,*[1a]

[a] *Trinity Biomedical Sciences Institute, School of Chemistry, Trinity College Dublin, Dublin 2, Ireland.*
[b] *Discovery Medicinal Chemistry, GlaxoSmithKline, Gunnels Wood Rd, Stevenage, SG1 2NY, UK,*

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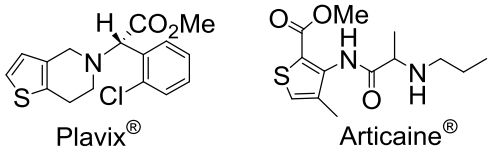
ABSTRACT

A one-pot approach to the synthesis of 3-nitrothiophene and 3-nitro-2-substituted thiophenes has been developed. Exposure of 1,4-dithane-2,5-diol to nitroacetates or nitroalkenes in the presence of 25% triethylamine and subsequent treatment with molecular sieves and combinations of silica gel or acidic alumina with DDQ or chloranil formed 3-nitrothiophene or a number of 3-nitro-2-substituted thiophenes with complete regiocontrol. A simple work-up procedure removes the requirement for purification by chromatography for most post-synthetic applications.

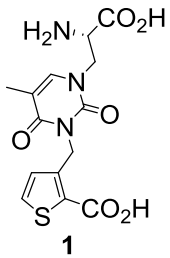
1.1. Introduction

Thiophene is an important heterocycle that features in numerous biologically active compounds. For example, Plavix® (Clopidogrel bisulfate) is a medication that inhibits ADP induced platelet aggregation and is used to prevent the formation blood clots particularly in patients who have recently suffered from a heart attack or stroke.[1]



Plavix®

Articaine®



1

Glu_{K5} Antagonist

Figure 1 Some important thiophenes

A 2,3-disubstituted thiophene also features in the selective Gluk5 receptor antagonist **1** developed by Jane and co-workers.[2] Articaine® is a voltage gated sodium channel blocker and a popular dental anaesthetic in Europe[3] and displays a 2,3,4-trisubstituent pattern. Thiophenes are also found in polymeric form in materials conferring interesting electronic and optical properties Oligomeric and polymeric thiophenes have been shown to have a variety of uses, including as organic semiconductors, organic light emitting diodes (OLEDs), organic field effect transistors (OFETs), lasers, sensors and photovoltaic cells.[4]

Although many methods of producing thiophenes have been reported each has drawbacks, particularly with respect to formation of a 2,3-disubstitution pattern. Elegant methodologies have been devised to prepare thiophenes from acyclic starting materials such as condensations with dicarbonyl compounds and the Gewald Synthesis but providing the 2-substituted-3-nitro pattern by these methods is not simple.[5] Electrophilic aromatic substitution reactions have a preference for the 2- and 5-positions which means that producing the 2,3-substitution pattern, described herein, requires the use of blocking groups.[5] Although there is a preference for the 2- and 5-positions reaction at these positions is not completely selective; the nitration of thiophene via a S_EAr process results in an 85:15 mixture of 2-nitrothiophene:3-nitrothiophene that is troublesome to separate.[5]

* *Corresponding Author Tel. +35318963411; Fax. +3531 6772274, email address southerj@tcd.ie
#Current address: Medicinal Chemistry (Early Discovery), Charles River Laboratories, Chesterford Research Park, CB10 1XL, U.K.

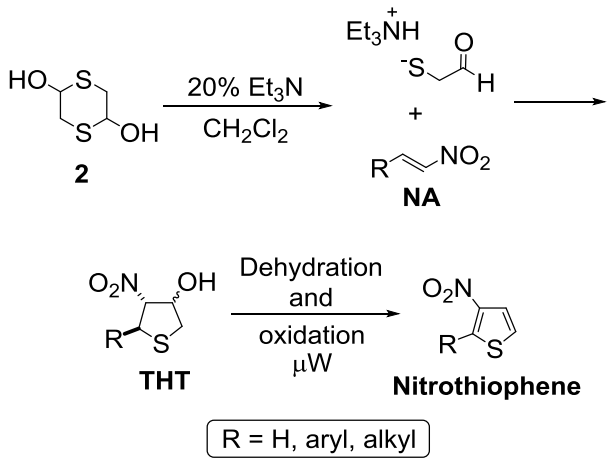
Ballini and co-workers have reported the addition of Grignard reagents to 3-nitrothiophene to produce a number of 3-nitro-2-substituted thiophenes.[6] This method requires the synthesis of 3-nitrothiophene and is limited to reagents suitable to Grignard formation. Devarie-Baez and co-workers have reported the use of 3-bromo-2-silylthiophene as a 2,3-dithienylanion equivalent that can serve as a precursor to 3-nitro-2-substituted thiophenes.[7] However, this synthetic approach does not circumvent the initial problem of installing the 2,3-pattern and also requires the use of strong base.

Despite the long and distinguished history associated with the chemistry of thiophenes,[5] the ongoing development of new, elegant synthetic strategies and methodologies to produce thiophenes is testament to their importance and requirement for improved synthetic options.[8]

We have recently reported a microwave based method to produce 2-substituted-3-nitrothiophenes[9] but we felt that a complimentary thermal based strategy would be useful. A thermal approach has clear advantages in removing the requirement for microwave equipment and potentially offering a one-pot protocol, both of which are advantageous when considering the production of compounds on a large scale.

1.2. Results and discussion

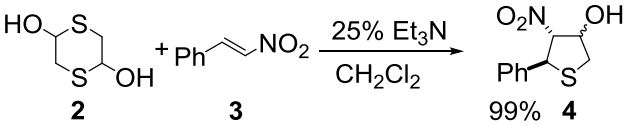
The previously described microwave based approach[9] involved the preparation of a tetrahydrothiophene (THT) by treatment of 1,4-dithiane-2,5-diol **2**, a dimeric mercaptoacetaldehyde equivalent[10] with 20 mol% of triethylamine and a nitroalkene (NA) in dichloromethane. A tandem conjugate-addition/nitroaldol ring closure reaction gave the corresponding THT as a mixture of diastereoisomers in high yields. Dehydration and subsequent oxidative aromatisation under microwave irradiation formed the corresponding 3-nitro-2-substituted thiophene in good yields.



Scheme 1 A microwave based approach

When considering the development and optimisation of the process for a thermal approach, the initial reaction to form the THTs was high yielding. The quantity of triethylamine was increased from 20 mol% to 25 mol% for this study but further investigation was not required. To optimise the dehydration and oxidiation reactions we chose to employ the commercially available β-nitrostyrene and the THT **4** was formed in 99% yield.

Initial studies aimed at nitrothiophene formation involved the treatment of the THT with trifluoroacetic anhydride, two equivalents of base, then DDQ as the oxidant. Although this approach was successful it was troublesome experimentally, requiring anhydrous conditions at -15 ºC and provided low yields (particularly in the case of aliphatic substituents) so a more efficient approach was investigated. Ballini and co-workers reported the dehydration of nitroalcohols using basic alumina in dichloromethane at reflux.[11] We found that treatment of THT **4** with basic alumina (4 eq. w/w with respect to the starting material) in dichloromethane at reflux for 41 hours provided the desired nitrothiophene **6** (by aerobic oxidative aromatisation), however the starting material was not completely consumed and 2-phenyl thiophene **7** (aromatisation by loss of HNO_2) was also produced as a competing side product in approximately equimolar quantities (Table 1). Neutral alumina (4 eq. w/w) gave similar results (a 1:1 ratio of **6**:**7**) whereas acidic alumina (4 eq. w/w) gave a more promising **2**:1 ratio after 41 hours.



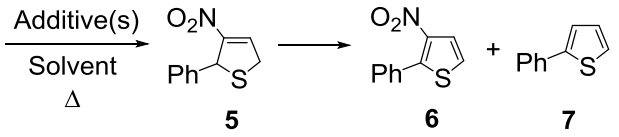
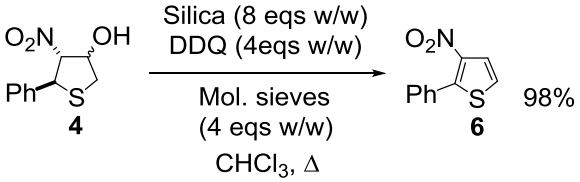


Table 1: Optimisation of the dehydration and aromatisation of **4**

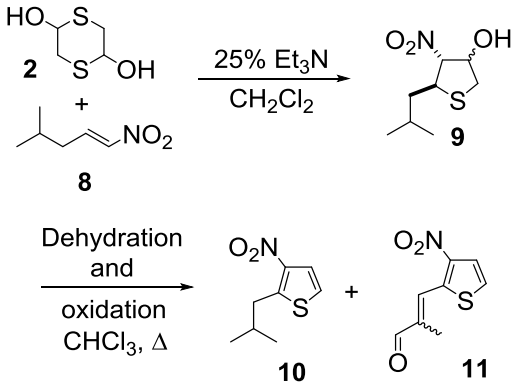
Additive (eqs)	**Solvent**	**4 Consumed**	**6:7 (% yield)**
Basic alumina (4)	CH_2Cl_2	No	1:1
Neutral alumina (4)	CH_2Cl_2	No	1:1
Acidic alumina (4)	CH_2Cl_2	No	2:1
Acidic alumina (4) and DDQ (2)	CH_2Cl_2	No	1:0
Acidic alumina (4) and DDQ (2)	$CHCl_3$	No	1:0
Acidic alumina (4), DDQ (2) and 4Å mol. sieves (2)	$CHCl_3$	Yes	1:0 (88)
Silica gel (8), DDQ (4) and 4 Å mol. sieves (4)	$CHCl_3$	Yes	1:0 (98)

It was postulated that the addition of DDQ would facilitate rapid aromatisation and suppress the loss of HNO_2 from dihydrothiophene **5**. Indeed, repeating the reaction in the presence of DDQ (2 eq.) did prevent the aromatisation through loss of HNO_2. Although nitrothiophene **6** was cleanly formed after 62 hours it was evident that THT **4** had not been completely consumed. Heating at reflux in the higher boiling chloroform gave a slightly improved 30:70 ratio of **4**:**7** after 40 hours and it was postulated that the removal of water from THT **4** was reversible. Repetition of the reaction in the presence of 4Å activated molecular sieves (2 eq. w/w) generated 3-nitro-2-phenylthiophene (**6**) exclusively in 88% yield after 64 hours at reflux. Finally, exchanging acidic alumina for silica gel (8 eq. w/w) and using DDQ (4 eq.) and molecular sieves (4 eq. w/w) allowed the isolation of **6** in 98% yield after heating at reflux for 24 hours. This was considered the preferred protocol and is herein referred to as **Method A** (Scheme 2).



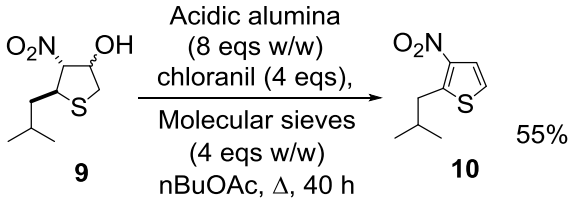
Scheme 2 Method A dehydration and aromatisation

Having established methodology to prepare **6** we turned our attention to the installation of alkyl substituents at the 2-position. Treating nitroalkene **8** under the conditions optimised for β-nitrostyrene did produce the expected nitrothiophene **10** but in addition approximately 20% of an aldehyde, tentatively assigned as **11**, was isolated (Scheme 3).



Scheme 3 Early problems with aliphatic substituents

Screening a range of solvents in order to eliminate this side-product indicated that **10** could be produced cleanly, albeit slowly, in ethyl acetate. Screening higher boiling esters, different supports and conditions allowed us to isolate the desired nitrothiophene **10** in 55% yield when employing acidic alumina (8 eq. w/w), molecular sieves (4 eq. w/w) and chloranil (4 eq.) in butyl acetate (b.pt 126 ºC) at reflux for 40 hours. This was the preferred protocol for the inclusion of alkyl substituents and is herein referred to as **Method B** (Scheme 4).



Scheme 4 Method B dehydration and aromatisation

In our previous work employing microwave irradiation we developed a rapid work up/purification procedure in which the crude reaction mixture was stirred with 500 mg/mmol KOH (based on the mass of the starting THT) and 500 mg/mmol activated charcoal, for 1 hour.[9] Subsequent filtration through a pad of silica and washing with DCM gave the nitrothiophene without the requirement for further purification by column chromatography. We applied the same isolation protocol when employing the thermal methodology and were pleased to find that further purification was not required for most post synthetic applications.

Having secured the two step process, we turned our attention to the further development of the methodology to provide a "one-pot" protocol for preparation of 2-substituted-3-nitrothiophenes directly from the appropriate nitroalkene.

For aromatic substituents, the one-pot **Method C** was developed. In this case, the nitroalkene was stirred overnight with dithiane **2** and 25% triethylamine in chloroform before the addition of silica gel (8 equivalents w/w), DDQ (4 equivalents) and molecular sieves (4 equivalents w/w) and heating at reflux for 24 hours.

In the case of aliphatic substituents we were pleased to discover that the initial addition/cyclisation reactions proceeded smoothly in butyl acetate and this led to the development of **Method D**. The appropriate nitroalkene, dithiane **2** and 25% triethylamine were stirred overnight in butyl acetate before the addition of acidic alumina (8 equivalents w/w), chloranil (4 equivalents) and molecular sieves (4 equivalents w/w) and heating at reflux for 40 hours. In Method D acidic alumina can be replaced with 8 equivalents of silica gel with a small reduction in yield.

The same isolation protocol (stirring with 500 mg/mmol KOH and charcoal) was attempted using the one-pot methodology and were pleased to find that for the majority of post-synthetic uses further purification was not required. The results for a range of 3-nitro-2-substituents are shown in Table 2.

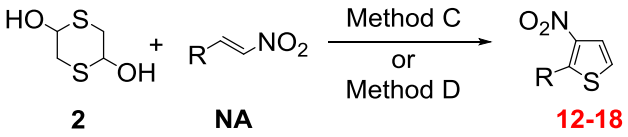
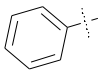
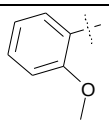
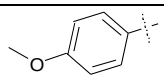
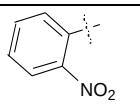
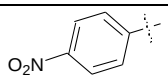
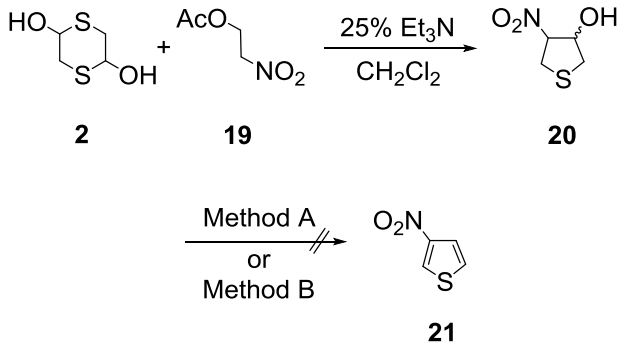


Table 2: One-pot formation of nitrothiophenes

Nitro-thiophene	R =	Method	Yield
12		C	42%
13		C	37%
14		C	23%
15		C	27%
16		C	77%
17		D	45%
18		D	46%

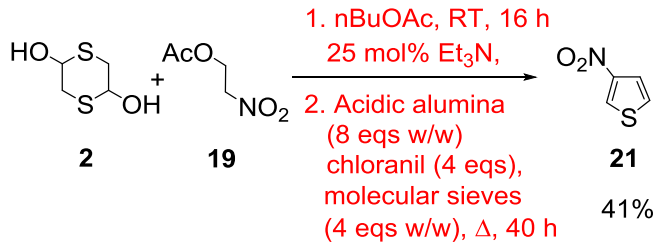
Having developed chemistry to prepare alkyl or aromatic 2-substituted-3-nitrothiophenes we turned our attention to the preparation of 3-nitrothiphene itself. In order to achieve this using the methodology described, the use of volatile and reactive nitroethene would have been required required. Fortunately, chemistry developed by De Rosi *et al*[12] allowed us to circumvent the use of nitroethene by employing a nitroacteate precursor **19**. Treatment of the dithiane **2** with nitroacetate **19** in the presence of 25 mol% of triethylamine formed THT **20** in 73% yield. Unfortunately attempts to induce dehydration/aromatisation reaction using either Method A or Method B failed to provide any 3-nitrothiophene (**21**,

Scheme 5).



Scheme 5 A failed attempt to prepare 3-nitrothiophene

Despite the failure of the two-pot method in the synthesis of 3-nitrothiophene we wanted to assess utilisation of the nitroacetate methodology in a one-pot reaction (Scheme 6). Nitroacetate **19,** dithiane **2** and triethylamine (25 mol%) were stirred for 16 hours in butyl acetate at room temperature, before acidic alumina (8 equivalents w/w), chloranil (4 equivalents) and molecular sieves (4 equivalents w/w) were added. The resultant mixture was heated at reflux for 40 hours which gave 3-nitrothiophene (**21**) in 41% yield. Once again the rapid isolation protocol (stirring with 500 mg/mmol KOH and charcoal) was successful and further purification was not required. Surprisingly, if the reaction was attempted with 1.25 equivalents of triethylamine (to provide an extra equivalent to facilitate the elimination of acetate) the yield for the reaction dropped to 14%.



Scheme 6 The synthesis of 3-nitrothiophene

1.3. Conclusions

A simple one-pot procedure which allows for the completely regioselective formation of 3-nitrothiophene as well as a range of 2-sustituted-3-nitrothiophenes from easily accessible starting materials is reported. To access thiophenes with this substitution pattern would usually require the use of a blocking group strategy. Exploitation of the powerful directing effect of the nitro group in addition to its further manipulation by reduction and diazotization are ongoing.

General Experimental section

Melting points were determined using a standard melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory. Proton nuclear magnetic resonance (NMR) spectra were recorded on: Bruker Avance III 400 MHz, Bruker DPX400 400 MHz and Bruker Avance II 600 MHz spectrometers (^{1}H NMR spectra were recorded at 400.23 MHz, 400.13 MHz and 600.13 MHz respectively). Chemical shifts are reported in ppm relative to tetramethylsilane and coupling constants (*J*) are quoted in Hertz. Carbon NMR spectra were recorded on the previously mentioned instruments (100.64 MHz, 100.61 MHz & 150.9 MHz, respectively) with total proton decoupling. Fluorine NMR spectra were recorded on the Bruker DPX400 machine at 376.5 MHz). HSQC, HMBC, TOCSY and nOe NMR experiments were used to aid assignment of NMR peaks when required. A Waters micromass LCT-tof mass spectrometer was used in ES positive and ES negative modes for electrospray mass spectrometry. Electron impact mass spectra were determined on a Quatro-II mass spectrometer in the EI mode. Mass spectra were recorded in CSCB Trinity College Dublin, CSCB University College Dublin. Flash chromatography was performed using Merk Kiesegel 60 (art. 9385) and aluminium oxide 90, standardized (activity II-III). Merk precoated Kiesegel 60F_{254} were used for thin-layer chromatography and slides were visualised by UV irradiation, $KMnO_4$, or anisaldehyde staining. Toluene, CH_2Cl_2, and triethylamine were distilled from calcium hydride.

Method A – general aromatic two-pot procedure

Step 1: To a stirred solution of the appropriate nitroalkene (1.0 eq.) in CH_2Cl_2 (0.1 M) were added 2,5-dihydroxy-1,4-dithiane (0.75 eq.) and triethylamine (0.25 eq) under an inert atmosphere. The reaction was stirred at room temperature overnight. The reaction was diluted with CH_2Cl_2 and the suspended solid was removed by filtration. A solution of saturated ammonium chloride was added to the filtrate and the aqueous layer was twice extracted with CH_2Cl_2. The combined organic layers were washed with water and brine and then dried over magnesium sulfate. Volatiles were removed at reduced pressure and the crude reaction product used directly in step 2.
Step 2: To a solution of the appropriate aromatic substituted THT in anhydrous chloroform (0.1 M) were added DDQ (4 eq), silica gel (8 eq w/w) and 4 Å molecular sieves (4 eq w/w). The reaction mixture was heated at reflux and stirred for approximately 24 hours until TLC indicated that the starting material had been consumed. After this time, the reaction was allowed to cool to room temperature and charcoal (500 mg/mmol, with respect to the THT) and powdered KOH (500 mg/mmol, with respect to the THT) were added. The mixture was stirred for an hour before being filtered through a pad of silica which was then rinsed with CH_2Cl_2. The volatiles were removed at reduced pressure to give the desired 3-nitro-2-substituted-thiophene.

Method B – general aliphatic two-pot procedure

Step 1: To a stirred solution of the appropriate nitroalkene (1.0 eq.) in CH_2Cl_2 (0.1 M) were added 2,5-dihydroxy-1,4-dithiane (0.75 eq.) and triethylamine (0.25 eq) under an inert atmosphere. The reaction was stirred at room temperature overnight. The reaction was diluted with CH_2Cl_2 and the suspended solid was removed by filtration. A solution of saturated ammonium chloride was added to the filtrate and the aqueous layer was twice extracted with CH_2Cl_2. The combined organic layers were washed with water and brine and then dried over magnesium sulfate. Volatiles were removed at reduced pressure and the crude reaction product used directly in step 2.
Step 2: To a solution of the appropriate aliphatic THT in anhydrous butyl acetate (0.1 M) was added chloranil (4 eq), acidic alumina (8 eq w/w) and 4 Å molecular sieves (4 eq w/w). The reaction mixture was heated at reflux and stirred for approximately 40 hours until TLC indicated that the starting material had been consumed. After this time, the reaction was allowed to cool to room temperature and charcoal (500 mg/mmol) and powdered KOH (500 mg/mmol) were

added. The mixture was stirred for an hour before being filtered through a pad of silica which was then rinsed with CH_2Cl_2. The volatiles were removed at reduced pressure to give the desired 3-nitro-2-substituted-thiophene.

Method C – general aromatic one-pot procedure

A solution of an aromatic nitroalkene (1.0 eq.), 2,5-dihydroxy-1,4-dithiane (0.75 eq.) and triethylamine (0.25 eq.) in chloroform (0.1 M) was stirred overnight at room temperature under an inert atmosphere, and monitored by TLC. When the nitroalkene had been consumed (typically around 16 hours) DDQ (4.0 eq.), acidic alumina (8.0 eq. w/w) and 4 Å molecular sieves (4.0 eq. w/w) were then added and the resulting mixture was heated to reflux for 48 hours. The reaction mixture was allowed to cool to room temperature before charcoal (500 mg/mmol, with respect to the THT (assuming 100% yield)) and powdered KOH (500 mg/mmol, with respect to the THT (assuming 100% yield)) were added. The mixture stirred for 1 hr before being filtered through a thick pad of silica which was then rinsed with CH_2Cl_2. The volatiles were removed at reduced pressure to give the desired 3-nitro-2-substituted-thiophene.

Method D – general aliphatic one-pot procedure

A solution of an aliphatic nitroalkene (1.0 eq.), 2,5-dihydroxy-1,4-dithiane (0.75 eq.) and triethylamine (0.25 eq.) in butyl acetate (0.1 M) was stirred overnight at room temperature under an inert atmosphere, monitored by TLC. When the nitroalkene had been consumed (approximately 16 hours), chloranil (4.0 eq.), acidic alumina (8.0 eq. w/w) and 4 Å molecular sieves (4.0 eq. w/w) were then added and the resulting mixture was heated at reflux for 48 hours. The reaction mixture was allowed to cool to room temperature before charcoal (500 mg/mmol, with respect to the THT (assuming 100% yield)) and powdered KOH (500 mg/mmol, with respect to the THT (assuming 100% yield)) were added. The mixture stirred for 1 hr before being filtered through a thick pad of silica which was then rinsed with CH_2Cl_2. The volatiles were removed at reduced pressure to give the desired 3-nitro-2-substituted-thiophene.

Method A: Two pot aromatic - 3-Nitro-2-phenyl-thiophene (6):

Prepared via Method A using using β-nitrostyrene (333 mg, 2.23 mmol), 2,5-dihydroxy-1,4-dithiane (255 mg, 1.67 mmol) and triethylamine (78 µL, 0.56 mmol) in chloroform under an inert atmosphere. The crude THT was treated with silica gel (2.60 g), 4 Å molecular sieves (1.30 g) and DDQ (2.02 g, 8.92 mmol) in chloroform which gave **6** as a yellow solid (450 mg, 2.19 mmol, 98%)

m.p. 101-103 ºC, lit.[13] 101.5-102.5 ºC; R_f (10% EtOAc/hexane) 0.33; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, J = 5.5 Hz, 1H), 7.45-7.54 (m, 5H), 7.68 ppm (d, J = 5.5 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 123.6, 124.5, 128.0, 129.15, 129.19, 130.1, 142.5, 145.1 ppm; IR υ_{max}: 2926, 1546, 1506, 1372, 1331, 1261, 752 cm^{-1}; HRMS: (*m/z*-EI) calcd for $C_{10}H_8NO_2S$ $(M+H)^+$ 206.0276, found 206.0270.

Method B: Two-pot aliphatic - 2-Isobutyl-3-nitrothiophene (10)

Prepared via Method B using *(E)*-4-methyl-1-nitropent-1-ene (72 mg, 0.56 mmol), chloroform, 2,5-dihydroxy-1,4-dithiane (65 mg, 0.42 mmol) and triethylamine (20 µL, 0.14 mmol) under an inert atmosphere. The crude THT was treated with acidic alumina (720 mg), 4 Å molecular sieves (360 mg) and chloranil (550 mg, 2.24 mmol) in butyl acetate which gave **10** as a yellow oil (42 mg, 0.29 mmol, 52%)

R_f (10% EtOAc/hexane) 0.63; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.99 (d, J = 6.7 Hz, 6H), 2.05 (nonet, J = 6.7 Hz, 1H), 3.09 (d, J = 6.7 Hz, 2H), 7.08 (d, J = 5.8 Hz, 1H), 7.57 ppm (d, J = 5.8 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 21.9, 29.5, 37.3, 121.1, 124.1, 143.7, 148.0 ppm; IR υ_{max}: 3122, 3105, 2959, 1539, 1500, 1374, 1327, 1182, 841, 703 cm^{-1}; HRMS: (*m/z*-EI) calcd for $C_8H_{11}NO_2S$ $(M)^+$ 185.0511, found 185.0512.

Method C: One-pot aromatic - 3-Nitro-2-phenyl-thiophene (6):

Prepared via method C using *trans*-β-nitrostyrene (300 mg, 2.01 mmol), 2,5-dihydroxy-1,4-dithiane (230 mg, 1.51 mmol) and triethylamine (70 µL, 0.51 mmol) in chloroform. After consumption of the nitroalkene (monitored by TLC), DDQ (1.80 g, 7.93 mmol), silica gel (2.40 g) and 4 Å molecular sieves (1.20 g) were added and the reaction mixture heated for the appropriate time. After treatment with KOH, charcoal and filtration through a pad of silica gel, **6** was obtained as a yellow solid (173 mg, 0.84 mmol, 42%).

Method C: One-pot aromatic - 3-Nitro-2-(4-nitrophenyl)-thiophene (16)

Prepared via method C using *p*-nitro-*trans*-β-nitrostyrene (50 mg, 0.26 mmol), 2,5-dihydroxy-1,4-dithiane (30 mg, 0.20 mmol) and triethylamine (9 µL, 0.07 mmol) in chloroform. After consumption of the nitroalkene (monitored by TLC), DDQ (236 mg, 1.04 mmol), silica gel (400 mg) and 4 Å molecular sieves (200 mg) were added and the reaction mixture heated for the appropriate time. After treatment with KOH, charcoal and filtration through a pad of silica gel, **16** was obtained as a yellow solid (50 mg, 0.20 mmol, 77%).

m.p.153-155 ºC, lit.[13] 146-148 ºC; R_f (20% CH_2Cl_2/hexane) 0.18; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, J = 5.5 Hz, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 5.5 Hz, 1H), 8.34 ppm (d, J = 8.0 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 123.6, 125.3, 125.5, 130.8, 137.0, 142.0, 143.9, 148.3 ppm; IR υ_{max}: 3140, 3121, 1593, 1540, 1509, 1497, 1340, 1313, 1103, 851, 840, 747, 704, 691 cm^{-1}; HRMS: (*m/z*-EI) calcd for $C_{10}H_6N_2NaO_4S$ $(M+Na)^+$ 272.9946, found 272.9939.

Method C: One-pot aromatic - 3-nitro-2-(2-nitrophenyl)thiophene (15)

Prepared via method C using *o*-nitro-*trans*-β-nitrostyrene (150 mg, 0.77 mmol), 2,5-dihydroxy-1,4-dithiane (88 mg, 0.58 mmol) and triethylamine (26 µL, 0.19 mmol) in chloroform. After consumption of the nitroalkene (monitored by TLC), DDQ (700 mg, 3.01 mmol), silica gel (1.2 g) and 4 Å molecular sieves (600 mg) were added and the reaction mixture heated for the appropriate time. After treatment with KOH, charcoal and filtration through a pad of silica gel, **15** was obtained as an orange solid (52 mg, 0.21 mmol, 27%).

m.p. 142-143 ºC, lit.[9] 142-143 ºC; R_f (hexane-CH_2Cl_2 1:1) 0.45; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, J = 5.7 Hz, 1H), 7.47 (d, J = 7.4 Hz, 1H), 7.64-7.73 (m, 3H), 8.24 ppm (d, J = 8.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 124.2, 125.0, 125.2, 126.2, 130.7, 132.5, 133.1, 140.6, 144.1, 148.5 ppm; IR υ_{max}: 3110, 3096, 1547, 1518 (NO_2), 1501 (NO_2), 1349, 1323, 855, 729, 698 cm^{-1}; HRMS: (*m/z*-ES) calcd for $C_{10}H_5N_2O_4S$ $(M-H)^-$ 248.9976, found 248.9966.

Method C: One-pot aromatic - 2-(4-Methoxyphenyl)-3-nitrothiophene (14)

Prepared via method C using *p*-methoxy-*trans*-β-nitrostyrene (100 mg, 0.58 mmol), 2,5-dihydroxy-1,4-dithiane (64 mg, 0.42 mmol) and triethylamine (20 μL, 0.15 mmol) in chloroform. After consumption of the nitroalkene (monitored by TLC), DDQ (510 mg, 2.24 mmol), silica gel (800 mg) and 4 Å molecular sieves (400 mg) were added and the reaction mixture heated for the appropriate time. After treatment with KOH, charcoal and filtration through a pad of silica gel, **14** was obtained as a yellow solid (28 mg, 0.12 mmol, 23%).
m.p. 93-94 ºC, lit.[9] 93-94 ºC; R_f (10% EtOAc/hexane) 0.33; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.88 (s, 3H), 6.99 (d, *J* = 8.9 Hz, 2H), 7.23 (d, *J* = 5.7 Hz, 1H), 7.47 (d, *J* = 8.9 Hz, 2H), 7.65 ppm (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 55.2, 113.8, 122.5, 123.2, 124.9, 131.0, 142.4, 145.6, 160.6 ppm; IR υ_{max}: 3103, 2966, 2836, 1609 (NO_2), 1507 (NO_2), 1455, 1328, 1243, 1027, 835, 700 cm^{-1}; HRMS: (*m/z*-EI) calcd for $C_{11}H_9O_3NS$ $(M)^+$ 235.0303, found 235.0294.

Method C: One-pot aromatic - 2-(2-Methoxyphenyl)-3-nitrothiophene (13)

Prepared via method C using *o*-methoxy-*trans*-β-nitrostyrene (25 mg, 0.14 mmol), 2,5-dihydroxy-1,4-dithiane (15 mg, 0.10 mmol) and triethylamine (5 μL, 0.05 mmol) in chloroform. After consumption of the nitroalkene (monitored by TLC), DDQ (118 mg, 0.52 mmol), silica gel (200 mg) and 4 Å molecular sieves (100 mg) were added and the reaction mixture heated for the appropriate time. After treatment with KOH, charcoal and filtration through a pad of silica gel, **13** was obtained as a pale green solid (12 mg, 0.05 mmol, 37%).
m.p. 79-81, lit[9] 80-82 ºC; R_f (20% EtOAc/hexane) 0.58; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.81 (s, 3H), 7.00 (dd, *J* = 1.1, 8.4 Hz, 1H), 7.04-7.08 (m, 1H), 7.30 (d, *J* = 5.5 Hz, 1H), 7.37 (dd, *J* = 1.5, 7.3 Hz, 1H), 7.44-7.48 (m, 1H), 7.65 ppm (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 55.4, 111.0, 119.8, 120.4, 123.8, 124.3, 130.6, 131.0, 140.7, 144.3, 156.7 ppm; IR υ_{max}: 3112, 3096, 2926, 1543, 1503, 1488, 1462, 1456, 1375, 1329, 1248, 1018, 757, 724 cm^{-1}; HRMS: (*m/z*-EI) calcd for $C_{11}H_9NO_3S$ $(M)^+$ 235.0303, found 235.0298.

Method D: One-pot aliphatic - 2-cyclohexyl-3-nitrothiophene (17)

Prepared via method D using *(E)*-(2-nitrovinyl)cyclohexane (150 mg, 0.96 mmol), 2,5-dihydroxy-1,4-dithiane (110 mg, 0.72 mmol) and triethylamine (34 μL, 0.24 mmol) in butylacetate. After consumption of the nitroalkene (monitored by TLC), chloranil (950 mg, 3.86 mmol), acidic alumina (1.20 g) and 4 Å molecular sieves (600 mg) were added and the reaction mixture heated for the appropriate time. After treatment with KOH, charcoal and filtration through a pad of silica gel, **17** was obtained as a pale yellow solid (93 mg, 0.44 mmol, 45%).
m.p. 65-66 ºC, lit[9] 65-66; R_f (10% EtOAc/hexane) 0.68; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.19-1.33 (m, 1H), 1.33-1.42 (m, 2H), 1.42-1.54 (m, 2H), 1.73-1.81 (m, 1H), 1.81-1.89 (m, 2H), 2.09 (m, 2H), 3.74 (tt, *J* = 3.4, 11.3 Hz, 1H), 7.07 (d, *J* = 5.9 Hz, 1H), 7.55 ppm (d, *J* = 5.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 25.7, 26.4, 34.8, 38.5, 121.2, 124.5, 143.1, 156.7 ppm; IR υ_{max}: 3101, 2920, 2850, 1531 (NO_2), 1496, 1448, 1374, 1312, 841, 775, 712 cm^{-1}; HRMS: (*m/z*-EI) calcd for $C_{10}H_{13}NO_2S$ $(M)^+$ 211.0667, found 211.0676.

Method D: One-pot aliphatic - 2-heptyl-3-nitrothiophene (18)

Prepared via method D using (E)-1-nitronon-1-ene (75 mg, 0.44 mmol), 2,5-dihydroxy-1,4-dithiane (50 mg, 0.33 mmol) and triethylamine (15 μL, 0.11 mmol) in butylacetate. After consumption of the nitroalkene (monitored by TLC), chloranil (432 mg, 1.76 mmol), acidic alumina (600 mg) and 4 Å molecular sieves (300 mg) were added and the reaction mixture heated for the appropriate time. After treatment with KOH, charcoal and filtration through a pad of silica gel, **18** was obtained as a yellow oil (46 mg, 0.23 mmol, 46%).
R_f (4% EtOAc/hexane on neutral alumina plates) 0.85; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.0 Hz, 3H), 1.24-1.50 (m, 8H), 1.76 (p, *J* = 7.7 Hz, 2H), 3.24 (t, *J* = 7.7 Hz, 2H), 7.08 (d, *J* = 5.8 Hz, 1H), 7.60 ppm (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 114.1, 22.6, 28.9, 29.3, 29.5, 30.3, 31.7, 121.2, 124.6, 143.8, 150.4 ppm; IR υ_{max}: 3121, 3103, 2954, 2924, 2854, 1538, 1500, 1458, 1374, 1331, 840, 776, 701 cm^{-1}; HRMS: (*m/z*-EI) calcd for $C_{11}H_{17}NO_2S$ $(M)^+$ 227.0980, found 227.0984.

3-Nitrothiophene (21)

A solution of 2-nitro-ethyl acetate (200 mg, 1.50 mmol), 2,5-dihydroxy-1,4-dithiane (171 mg, 1.12 mmol) and triethylamine (52 μl, 0.38 mmol) in butyl acetate (0.1 M) was stirred overnight at room temperature under an inert atmosphere. After consumption of the 2-nitro-ethyl acetate (as monitored by TLC, approximately 16 hours) chloranil (1.48 g, 6.02 mmol), acidic alumina (1.6g) and 4 Å molecular sieves (800 mg) were added. The resultant mixture was heated at reflux for 40 hours. The reaction mixture was allowed to cool to room temperature before charcoal (500 mg/mmol based on starting nitroaceate) and powdered KOH (500 mg/mmol based on starting nitroaceate) were added. The mixture was stirred for 1 hr before being filtered through a pad of silica. The volatiles were removed at reduced pressure to yield **21** (80 mg, 0.62 mmol, 41% yield) as a white solid.
m.p. 77-79 ºC, lit.[14] 76-77 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31(dd, *J* = 3.5, 5.3 Hz, 1H), 7.66 (d, *J* = 5.3 Hz, 1H), 8.31 ppm (d, *J* = 3.5 Hz, 1H), ^{13}C NMR (151 MHz, $CDCl_3$): δ = 122.9, 127.0, 127.6 ppm, HRMS (*m/z*-EI) calcd for $C_4H_3NO_2S$ $(M)^+$ 128.9885, found 128.9884.

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