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Facile Synthesis of 3-Nitro-2-substituted Thiophenes

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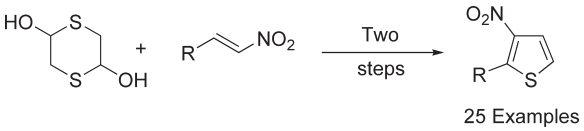

A new approach to 3-nitro-2-substituted thiophenes has been developed. Exposure of commercially available 1,4-dithane-2,5-diol to nitroalkenes in the presence of 20% triethylamine results in a tandem Michael−intramolecular Henry reaction to form the corresponding tetrahydrothiophene. Subsequent microwave irradiation on acidic alumina in the presence of chloranil effects the solvent free dehydration and aromatization to form 3-nitro-2-substituted thiophenes cleanly and rapidly. A simple workup procedure removes the requirement for purification by chromatography in most cases.

Introduction

Thiophene-based materials have emerged as an important class of electrically conducting organic materials.[1−4] The seminal work of Shirakawa, MacDiarmid and Heeger in conducting organic polymers in the late 1970s created a new field of chemistry the growth of which has been nothing short of phenomenal.[5,6] Oligomeric and polymeric thiophenes have generated significant interest with potential applications as organic semiconductors,[7−9] organic light emitting diodes (OLEDs),[10−12] organic field effect transistors (OFETs),[3,13] lasers,[14] sensors, and photovoltaic cells.[13,15−19] Interest in organic electronics stems from the possibility to produce low-cost, large-area, lightweight, and flexible devices with integrated functionalities of conventional silicon-based components.[3,20−25] The electronic properties of oligo- and polythiophenes can be efficiently tuned by varying the

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substitution of the thiophene core. Typically electron-donating substituents tend to produce p-type conducting materials whereas electron-withdrawing substituents such as fluorinated hydrocarbons have a propensity toward n-type behavior.[26] Especially pertinent to the work reported herein is the growing interest in n-type oligothiophenes (as opposed to the more comprehensively studied p-type oligothiophenes).[26,27]

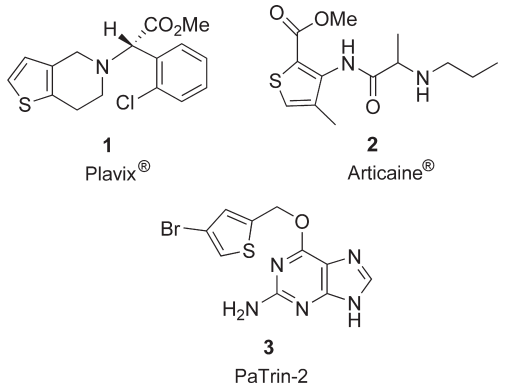
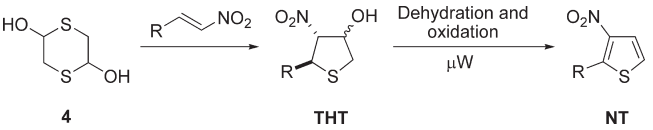


FIGURE 1. Some biologically important thiophenes.

Moreover, thiophenes have significant biological applications: the blockbuster drug Plavix is a potent antiplatelet agent used in the treatment of coronary artery disease;[28] Articaine is the most commonly used dental anesthetic in Europe;[29] and PaTrin-2 is an inhibitor of the DNA repair enzyme O^6-methylguanine-DNA methyl transferase with potential to increase the effectiveness of alkylating agents as cancer therapeutics (Figure 1).[30] Thiophenes have recently been shown to have excellent selective activity at the GLU_{k5} receptor[31] and they also have exhibited potent activity toward CB_1 receptors with good CB_1/CB_2 selectivity.[31,32]

Despite the significant, long-standing interest in aromatic heterocycles, the synthesis of 2,3-disubstituted thiophenes is not always trivial. When possible, electrophilic aromatic substitution (EAS) reactions take place preferentially (although not exclusively) at the 2- and 5-positions often necessitating the use and removal of blocking groups.[33] Note that nitration of thiophene under standard conditions generates an 85:15 ratio of 2-nitro:3-nitrothiophene that is difficult to purify.[33] Ballini et al.[34] have reported the synthesis of 3-nitro-2-substituted thiophenes via addition of Grignard reagents to 3-nitrothiophene; however, the synthesis of

SCHEME 1. Formation of 3-Nitro-2-substituted Thiophenes



3-nitrothiophene in itself is protracted.[35] In an alternative approach, Devarie-Baez et al.[36] reported a "one-pot" synthesis of 2,3-disubstituted thiophenes starting from 3-bromo-2-silylthiophene, which was employed as a 2,3-thienyldianion equivalent. Unfortunately, this methodology requires the synthesis of 3-bromo-2-silylthiophene and the use of strong base. Reported herein is a rapid and general methodology for the preparation of 3-nitro-2-substituted thiophenes from nitroalkenes. This approach involves a tandem Michael−intramolecular Henry reaction between a thiolate anion (formed in situ by dissociation of commercially available dithiane **4**) and a nitroalkene, which led to the formation of a 2,3,4-substituted tetrahydrothiophene (THT). Subsequent dehydration and oxidation provided the 3-nitro-2-substituted thiophene (NT) (Scheme 1).

This route possesses significant advantages over much current methodology as it obviates the need for a blocking group in the 5-position. The final dehydration/oxidation step employed microwave irradiation on a solid support, using solvent free conditions, furnishing the desired products in good yield and high purity without the need for chromatography. Since the appearance of the first article on the application of microwaves for chemical synthesis in polar solvents,[37] the approach has developed considerably and is now considered a general and useful technique for a variety of applications in organic synthesis and functional group transformations.[38−42] In recent years the focus has shifted to solvent-free methods, wherein neat reactants, often in the presence of mineral oxides or supported catalysts, undergo reactions to provide high yields of products thus eliminating or minimizing the use of organic solvents.[38−41] The clear advantages of solvent-free organic syntheses using supported reagents and microwave irradiation has been concisely reviewed by Varma.[42]

Results and Discussion

Initial studies on the formation of the THTs were carried out with the commercially available *trans*-β-nitrostyrene. The first phase of the reaction sequence required the formation of the thiolate anion. This was achieved in situ by treatment of dithiane **4** with a catalytic quantity of triethylamine in the presence of nitroalkene **6** in dichloromethane at room temeperature. The reaction proceeded smoothly and the desired THT **8a** was isolated in excellent 99% yield as a 3:2 mixture of diastereomers.

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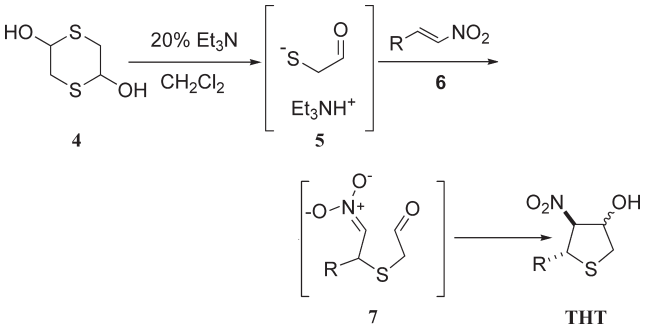
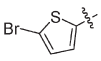
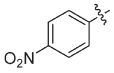
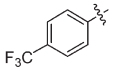
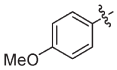
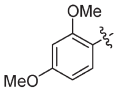
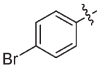
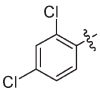
TABLE 1. Substrate Scope for Formation of THTs



THT	R	Yield (%)	THT	R	Yield (%)
8a		99	**21a**		92
9a		99	**22a**		99
10a		77	**23a**		86
11a		97	**24a**		73
12a		80	**25a**	**H**	73[a]
13a		74	**26a**	**Me**	60[a]
14a		71	**27a**		71[a]
15a		88	**28a**		60[a]
16a		77	**29a**		94
17a		99	**30a**		89
18a		99	**31a**		89
19a		84	**32a**		93
20a		99			

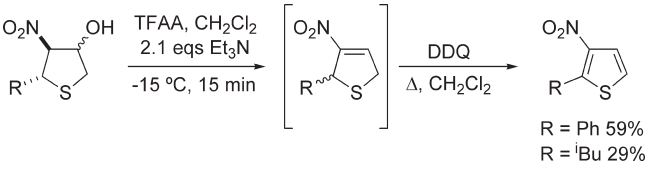
[a]The nitroalkene was generated in situ from the appropriate nitroacetate precursors (see the Supporting Information for the general procedure).

Attempts to expand the scope of the reaction proved successful and a wide range of R groups (H, aromatic, heterocyclic, aliphatic, and CH_2OTBS) are tolerated and the THTs were isolated in good yield (Table 1). Nitroalkenes which were not commercially sourced were prepared according to procedures by Denmark et al.[43] or Kawai et al.[44]

Despite the inevitable loss of the chiral centers upon conversion to 3-nitro-2-phenyl thiopene (**8b**), the diastereomers of **8a** were separated with column chromatography, thereby enabling more facile NMR assignment for subsequent diastereomeric mixtures. A combination of X-ray structural analysis and ^{1}H NMR indicated that there was an *anti* relationship between the nitro group and the R group in both diastereomers (presumably arising from the (*E*)-stereochemistry of the nitroalkenes employed). In the major diastereomer there was an *anti* relationship between the nitro group and the hydroxyl group whereas in the minor diastereomer there was a *syn* relationship between the nitro group and the hydroxyl group. In general, assignment of the major and minor THT diastereomers was possible from the magnitude of the coupling constants between H3 and H4 of the THT ring in each diastereomer and also the separation of the signals arising from the diastereotopic H5 protons. The THTs were formed with diastereomeric ratios between 1:1 and 3:1 for larger R groups (see the Supporting Information for specific ratios); in some cases, NMR data indicated that traces of other isomers were present.

Dehydration and aromatization of the phenyl-substituted THT **8a** was initially attempted by using thermal and solution-based methodologies (Scheme 2). Initial studies involved treatment of a solution of **8a** in dichloromethane with trifluoroacetic anhydride and triethylamine at −15 °C with subsequent addition of DDQ and heating at reflux for 48 h. This gave 3-nitro-2-phenylthiophene after a protracted workup and extensive column chromatography in a maximum yield of 59%. Unfortunately, when this methodology was extended to aliphatic substrates, the yields were considerably lower, < 30%.

SCHEME 2. Two-Pot Dehydration and Aromatization of 8a



Fortunately, it was later discovered that a one-pot dehydration/aromatization procedure employing microwave irradiation and a solid support under solvent-free conditions generated the corresponding 3-nitro-2-phenylthiophene extremely rapidly in good yield.

The reactions were performed by grinding the THT together with acidic alumina and chloranil (using a mortar and pestle) followed by irradiation of the mixture in a laboratory microwave (CEM Discovery series) for 4 min, with the maximum temperature set to 125 °C and maximum power set to 200 W. Table 2 summarizes the studies undertaken to optimize this step of the reaction.

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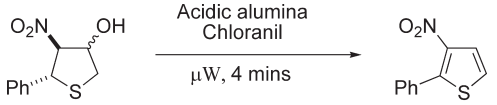
TABLE 2. Optimization Experiments for Dehydration and Aromatization of THT 8a



8a **8b**

entry	alumina (equiv w/w)	chloranil (equiv)	yield **8b** (%)
1	10	1.1	70
2	15	1.1	86
3	20	0	54
4	20	1.1	90
5	20	1.5	91
6	20	2.0	91

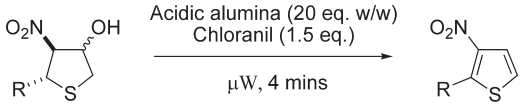
The best yield, cleanest reaction, and most facile workup was achieved employing 20 equiv (w/w) of acidic alumina with 1.5 equiv of chloranil, which gave 3-nitro-2-phenylthiophene in 91% yield. It is worth noting that silica gel and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) provide an alternative solid support and oxidant though yields were reduced.

Fortunately, exposure of the THTs previously prepared with a variety of substituents to the same conditions generated the corresponding 3-nitro-2-substituted thiophenes generally in good yields (Table 3). Surprisingly the majority of the THTs and NTs described are novel compounds. In addition to the incorporation of aromatic, heterocyclic, and aliphatic substituents, formation of the dimeric system **10b**, **25b** (R = H forming 3-nitrothiophene exclusively), and **32b** (R = CH_2OTBS, which provides a functional handle for further manipulation, such as nitroalkene formation) are of particular note.

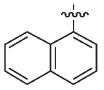
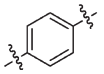
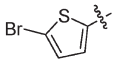
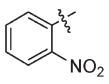
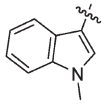
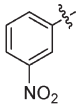
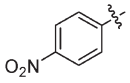
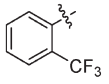
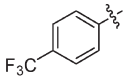
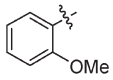
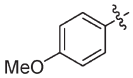
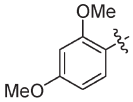
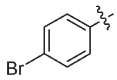
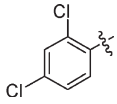
To assess the applicability of this technology to scale-up and the use of a less sophisticated microwave device, the reactions (up to 13 mmol) were also attempted in a conventional 800 W kitchen microwave. Irradiation of the THT **8a** (R = Ph) for 6 min at full power with 10 equiv of acidic alumina and 2 equiv of chloranil in an open vessel gave the expected thiophene **8b** in 83% yield. When R = ^{i}Bu, irradiation of the THT with 20 equiv of alumina and 4 equiv of chloranil for 8 min at full power gave the corresponding thiophene **29b** in 78% yield.

In keeping with the microwave-based philosophy of rapid synthesis we sought to remove the requirement for column chromatography and devised a less labor intensive method of purification. It was found that stirring the crude reaction in dichloromethane for 1 h followed by the addition of solid potassium hydroxide (500 mg/mmol) and activated charcoal (500 mg/mmol) with a further 1 h of stirring followed by filtration through a plug of silica gel gave the desired 3-nitro-2-substituted thiophenes without the requirement for further purification. Alternative solvents proved less successful: diethyl ether gave products with a similar high level of purity but reduced yield while ethyl acetate gave lower purity and yield than dichloromethane.

TABLE 3. Substrate Scope for Formation of NTs



THT **NT**

NT	R	Yield (%)	NT	R	Yield (%)
8b		91	**21b**		56
9b		64	**22b**		78
10b		42[a]	**23b**		81
11b		60	**24b**		28
12b		65	**25b**	**H**	37
13b		70	**26b**	**Me**	54
14b		54	**27b**		52
15b		72	**28b**		57
16b		69	**29b**		85
17b		73	**30b**		78
18b		70	**31b**		64
19b		82	**32b**		57
20b		56			

[a]Poor yield attributed to the limited solubility of **10b** in organic solvent.

Conclusion

In summary, a novel, rapid, and general route to synthetically useful 3-nitro-2-substituted thiophenes bearing a wide range of substituents (aromatic, heterocyclic, aliphatic, H, CH_2OTBS) at the 2-position has been developed. The methodology does not require the use of blocking groups and the rapid workup/isolation procedure precludes the requirement

for chromatography for the majority of postsynthetic applications. The nitro group can serve two further purposes: Its powerful directing effect will ensure exclusive (rather than preferential) electrophilic aromatic substitution reactivity at the 5-position. The nitro group also provides an excellent functional handle to install a variety of other substituents by reduction, diazotization, and substitution with a variety of nucleophiles. We are currently exploring the properties of the NTs produced via this methodology and are examining the possibility of using a similar approach to prepare furans and pyrroles. In addition, we are currently evaluating the medicinal properties of these compounds.

Experimental Section

General Procedure for the Synthesis of Tetrahydrothiophenes from Nitroalkene Precursors, Procedure A. To a stirred solution of the appropriate nitroalkene (2.00 mmol) in CH_2Cl_2 (5.6 mL) were added 2,5-dihydroxy-1,4-dithiane (0.23 g, 1.50 mmol) and triethylamine (56 μL, 0.40 mmol) under an argon atmosphere. The reaction was stirred at room temperature overnight. The reaction was diluted with CH_2Cl_2 (20 mL) and the suspended solid was removed by filtration. A solution of saturated ammonium chloride (20 mL) was added to the filtrate and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL) and then dried over magnesium sulfate. Volatiles were removed at reduced pressure and the resulting residue was purified by column chromatography.

General Procedure for Synthesis of Tetrahydrothiophenes from Nitroacetate Precursors, Procedure B. To a stirred solution of the appropriate nitroacetate (2.16 mmol) in CH_2Cl_2 (6.0 mL) were added 2,5-dihydroxy-1,4-dithiane (170 mg, 1.08 mmol) and triethylamine (330 μL, 2.38 mmol) under an argon atmosphere. Stirring was continued at room temperature overnight. The reaction was diluted with CH_2Cl_2 (20 mL) and the suspended solid was removed by filtration. Water (20 mL) was added to the filtrate and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL) and then dried over magnesium sulfate. Volatiles were removed at reduced pressure and the resulting residue was purified by column chromatography.

General Procedure for the Synthesis of Nitrothiophenes with Use of a Chemical Microwave, Procedure C. The appropriate THT (0.44 mmol) and oven-dried acidic alumina (2.00 g) were ground together in a mortar. (Liquid THTs were adsorbed onto the oven-dried acidic alumina prior to grinding.) Chloranil (0.15 g, 0.61 mmol) was introduced and the solids were further ground together. The pale yellow solids were placed in a microwave sample tube and the sample was irradiated in a chemical microwave (CEM discovery series) at 125 °C for 4 min (maximum power set to 200 W). To the cooled solids was added CH_2Cl_2 (15 mL) and the mixture was stirred for 1 h. Ground charcoal (250 mg) and ground potassium hydroxide powder (250 mg, 4.46 mmol) were added and the mixture was stirred for a further 1 h. The slurry was filtered through a plug of silica (~50 mL) and the solids were washed with CH_2Cl_2 (150 mL). Volatiles were removed at reduced pressure.

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Supporting Information Available: Detailed experimental procedures and full characterization including $^{1}H/^{13}C$ NMR spectra of new compounds in addition to crystal/refinement data and thermal elipsoid plots of compounds **21a**, **29a**, and **19b**. This material is available free of charge via the Internet at http://pubs.acs.org. The crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre; deposition nos. 739460 (**21a**), 739461 (**29a**), and 739459 (**19b**). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK or via www.ccdc.cam.ac.uk/conts/retrieving.html.