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Highly Selective 5-Substitution of 3-Methylthiophene via Directed Lithiation

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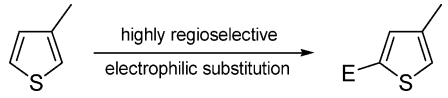

Lithiation of 3-methylthiophene with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) is highly selective at the 5-position, and reaction with a range of electrophiles gives high yields of the corresponding 2,4-disubstituted thiophenes, even when unhindered electrophiles are used.

Substituted thiophenes are important building blocks for pharmaceuticals,[1] conductive polymers,[2,3] photochromic dithienylethene molecular switches,[4,5] liquid crystals,[6] molecular machines,[7] etc. In light of the ubiquity of thiophenes, we were surprised to find that the synthesis of simple 2,4-disubstituted thiophenes from monosubstituted thiophenes has generally not been straightforward.[8] As recently as 2002, unselective reactions of this type, leading to the need for eventual separation of isomers and the waste of products, have been reported.[1c] In response to this problem, we now report a convenient and highly selective one-pot synthesis of a range of 2-substituted 4-methylthiophenes via lithiation of commercially available 3-methylthiophene with lithium 2,2,6,6-tetramethylpiperidide (LiTMP).

Reactions of electrophiles with 3-substituted thiophenes generally give predominantly 2,3-disubstituted products.[8] Only when the original substituent is either highly sterically hindered or strongly electron withdrawing does substitution take place preferentially at the 5-position (to give a 2,4-disubstituted product). This approach is therefore not appropriate for the general synthesis of simple 2,4-disubstituted thiophenes.

Lithiation of thiophene is highly α-selective.[9] For 3-substituted thiophenes with a substituent that directs metalation (e.g., dimethylaminocarbonyl, dimethylaminomethyl, methanethiyl), lithiation is directed to the 2-position, α- to both the substituent and the ring sulfur atom.[9,10] For 3-substituted thiophenes with a substituent that does not direct metalation, for example, 3-methylthiophene, lithiation occurs at both the 2- and 5-positions, but the 5-position usually predominates.[9] More sterically hindered 3-substituents increase the predominance.[11] However, to our knowledge, the only exclusively 5-selective substitutions of 3-methylthiophene reported until now have been those of its lithiated derivative with extremely hindered electrophiles, and in such cases, the reported yields of products are low to moderate.[1d,7] There is therefore still a great need for a high-yielding general method for highly regioselective 5-substitution of simple 3-substituted thiophenes with unhindered electrophiles.

In connection with an ongoing research project, we needed a convenient and high-yielding synthesis of 2,4-dimethylthiophene (**2**). Published syntheses of **2** and potentially adaptable syntheses of other 2,4-disubstituted thiophenes often involved several steps, required costly or unavailable starting materials, or gave low yields.[6,12,13] The simplest method, reported by Sicé in 1954, involved lithiation of 3-methylthiophene (**1**) with *n*-BuLi, which is not very selective,[1c,14] followed by reaction with dimethylformamide and subsequent reduction.[15]

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(1) Recent examples: (a) Denton, T. T.; Zhang, X.; Cashman, J. R. *J. Med. Chem.* **2005**, *48*, 224. (b) Conde, S.; Pérez, D. I.; Martínez, A.; Perez, C.; Moreno, F. J. *J. Med. Chem.* **2003**, *46*, 4631. (c) Collins, I.; Moyes, C.; Davey, W. B.; Rowley, M.; Bromidge, F. A.; Quirk, K.; Atack, J. R.; McKernan, R. M.; Thompson, S.-A.; Wafford, K.; Dawson, G. R.; Pike, A.; Sohal, B.; Tsou, N. N.; Ball, R. G.; Castro, J. L. *J. Med. Chem.* **2002**, *45*, 1887. (d) Espaze, F.; Hamon, J.; Hirbec, H.; Vignon, J.; Kamenka, J.-M. *Eur. J. Med. Chem.* **2000**, *35*, 323.

(2) Recent reviews: (a) Guernion, N. J. L.; Hayes, W. *Curr. Org. Chem.* **2004**, *8*, 637. (b) Roncali, J. *J. Mater. Chem.* **1999**, *9*, 1875. (c) Kraft, A.; Grimsdale, A. C.; Holmes, A. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 402.

(3) Recent examples: (a) Jiang, X.; Patil, R.; Harima, Y.; Ohshita J.; Kunai, A. *J. Phys. Chem. B* **2005**, *109*, 221. (b) Buga, K.; Kepczynska, K.; Kulszewicz-Bajer, I.; Zagórska, M.; Demadrille, R.; Pron, A.; Quillard, S.; Lefrant, S. *Macromolecules* **2004**, *37*, 769. (c) Berlin, A.; Zotti, G.; Zecchin, S.; Schiavon, G.; Vercelli, B.; Zanelli, A. *Chem. Mater.* **2004**, *16*, 3667. (d) Albertin, L.; Bertarelli, C.; Gallazzi, M. C.; Meille, S. V.; Capelli, S. C. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1752.

(4) Recent reviews: (a) Matsuda, K.; Irie, M. *J. Photochem. Photobiol. C* **2004**, *5*, 169. (b) Raymo, F. M.; Tomasulo, M. *J. Phys. Chem. A* **2005**, *109*, 7343. (c) Irie, M. *Chem. Rev.* **2000**, *100*, 1685. (d) Feringa, B. L.; van Delden, R. A.; Koumura, N.; Geertsema, E. M. *Chem. Rev.* **2000**, *100*, 1789.

(5) Recent examples: (a) de Jong, J. J. D.; Browne, W. R.; Walko, M.; Lucas, L. N.; Barrett, J.; McGarvey, J. J.; van Esch, J. H; Feringa, B. L. *Org. Biomol. Chem.* **2006**, *4*, 2387. (b) Asano, Y.; Murakami, A.; Kobayashi, T.; Goldberg, A.; Guillaumont, D.; Yabushita, S.; Irie, M.; Nakamura S. *J. Am. Chem. Soc.* **2004**, *126*, 12112. (c) Jukes, R. T. F.; Adamo, V.; Hartl, F.; Belser, P.; De Cola, L. *Inorg. Chem.* **2004**, *43*, 2779. (d) Peters, A.; Branda, N. R. *Chem. Commun.* **2003**, 954. (e) Kim, M.-S.; Sakata, T.; Kawai T.; Irie, M. *Jpn. J. Appl. Phys.* **2003**, *42*, 3676.

(6) Kim, E. K.; Lee, K. U.; Cho, B. Y.; Kim, Y. B.; Kang, K.-T. *Liquid Crystals* **2001**, *28*, 339.

(7) Lomas, J. S.; Lacroix, J.-C.; Vaissermann, J. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2001.

(8) Meth-Cohn, O. *Comp. Org. Chem.* **1979**, *4*, 789.

(9) (a) Gschwend, H. W.; Rodriguez, H. R. *Org. Reactions* (*NY*) **1979**, *26*, 35. (b) Ramanathan, V.; Levine, R. *J. Org. Chem.* **1962**, *27*, 1667. (c) Catoni, G.; Galli, C.; Mandolini, L. *J. Org. Chem.* **1980**, *45*, 1906.

(10) (a) Slocum, D. W.; Gierer, P. L. *J. Org. Chem.* **1976**, *41*, 3668. (b) Taylor, E. C.; Vogel, D. E. *J. Org. Chem.* **1985**, *50*, 1002.

(11) (a) Götz, G.; Sheib, S.; Klose, R.; Heinze, J.; Bäuerle, P. *Adv. Funct. Mater.* **2002**, *12*, 723. (b) Detty, M. R.; Hayes, D. S. *Heterocycles* **1995**, *40*, 925. (c) O'Donovan, A. R. M.; Shepherd, M. K. *Tetrahedron Lett.* **1994**, *35*, 4425.

(12) (a) Morton, A. A. *The Chemistry of Heterocyclic Compounds*, 3rd ed.; McGraw-Hill: New York, 1946; pp 39−55. (b) Joule, J. A.; Mills, K.; Smith, G. *Heterocyclic Chemistry*, 3rd ed.; Chapman & Hall: Oxford, 1995; pp 368−377. (c) Gilchrist, T. L. *Heterocyclic Chemistry*, 2nd ed.; Longman: London, 1992; pp 214−223. (d) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491.

(13) (a) Hartough, H. D. *J. Am. Chem. Soc.* **1951**, *73*, 4033. (b) Parham, W. E.; Mayo, G. L. O.; Gadsby, B. *J. Am. Chem. Soc.* **1959**, *81*, 5993. (c) Nishimura, H.; Mizutani, J. *J. Org. Chem.* **1975**, *40*, 1567. (d) Takeshita, M.; Tashiro, M. *J. Org. Chem.* **1991**, *56*, 2837. (e) Belen'kii, L. I.; Yakubov, A. P. *Tetrahedron* **1984**, *40*, 2471. (f) Kang, K.-T.; Hwang, Y. B.; Kim, M. Y.; Lee, S. K.; Lee, J. G. *Bull. Korean Chem. Soc.* **2002**, *23*, 1333.

(14) Boelens, M. P.; de Valois, J.; Wobben, H. J.; van der Gen, A. *J. Agric. Food. Chem.* **1971**, *19*, 984.

(15) Sicé, J. *J. Org. Chem.* **1954**, *19*, 70.

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SCHEME 1. Lithiation and Methylation of 3-Methylthiophene (1)

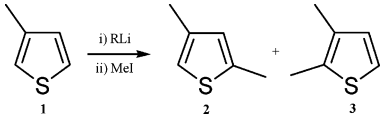

TABLE 1. Variation of Selectivity with Lithiating Reagent According to Scheme 1[a]

	RLi	2:3	Total yield 2 + 3 (%)[b]
1	methyllithium[c]	3:1	87
2	*n*-butyllithium	4.4:1	56[d]
3	*tert*-butyllithium	5:1	91
4	*tert*-butyllithium/TMEDA	7:1	96
5	lithium diisobutylamide	9:1	40[d]
6	lithium piperidide	10:1	42[d]
7	lithium dicyclohexylamide	15:1	48[d]
8	lithium di-*sec*-butylamide	16:1	95
9	LiTMP	79:1	99

[a] Lithiation at −78 °C, 1 h. More detailed conditions are in the Experimental Section. [b] Measured by GC with reference to tetradecane as internal standard. [c] Methyllithium reaction carried out at room temperature. No lithiation observed at −78 °C. [d] Significant quantities of unconsumed 3-methylthiophene were observed. Thiophene mass balances were all around 100%.

However, based on our experience in selective lithiation reactions,[16] we felt that it ought to be possible to develop a more regioselective lithiation of **1**, to enable synthesis of **2** in high yield by simple quenching of the 4-methyl-2-thienyllithium with iodomethane, despite the unhindered nature of the electrophile. We now report success in this endeavor.

Lithiation of **1** with *n*-butyllithium for 1 h at room temperature in THF followed by quenching with iodomethane gave two products (Scheme 1, R = *n*-Bu). GC and NMR analyses showed that the products were **2** and 2,3-dimethylthiophene (**3**), formed in 99% yield and 3.5:1 ratio. Selectivity increased to 4:1 at 0 °C and to 4.4:1 (though in lower yield because reaction was not complete in the allowed time) at −78 °C.

In order to investigate the influence of the base, experiments were conducted with a variety of lithiating agents having different steric demands. Reactions were conducted at −78 °C in order to maximize selectivity. The results (Table 1) showed that selectivity generally increased with increasing bulkiness of the base, and dramatically so, to a ratio of 79:1, with LiTMP.

To demonstrate the value of the new procedure as a general method for regioselective 5-substitution of **1** and to create a range of precursor compounds for further work, the lithiated intermediate was treated with a range of different electrophiles (Scheme 2).

As the results (Table 2) show, each reaction led to a high yield of the corresponding 2-substituted 4-methylthiophene (**2** and **4**−**9**). To the knowledge of the authors, compounds **4** and **9** have not previously been reported, and the only previous report of compound **8** was as a byproduct, without characterization data.[17] 4-Methyl-2-thiophenecarboxaldehyde (**6**) has previously been reported as the minor product of direct formylation of **1**[18] and as the major product of lithiation of **1** followed by reaction with DMF, but the best ratio of **1** to its 2,3-disubstituted isomer previously achieved is around 8:1.[1c,11b] In the present work, lithiation of **1** with LiTMP and reaction with 2 molar equiv of DMF produced **6** in almost quantitative yield and with a selectivity of 35.5:1 (GC/NMR).

SCHEME 2. Highly Selective 5-Substitution of 3-Methylthiophene

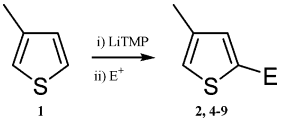

TABLE 2. Yields of 2-Substituted 4-Methylthiophenes Prepared According to Scheme 2[a]

product	electrophile (E^+)	E	yield (%)[b]
2	iodomethane	Me	97
4	benzophenone	Ph_2COH	98
5	benzonitrile	PhCO	99
6	*N*,*N*-dimethylformamide (DMF)	CHO	97
7	carbon dioxide	COOH	(75)[c]
8	benzaldehyde	PhCHOH	(74)[c]
9	phenyl isothiocyanate	PhNHCS	(76)[c]

[a] Reaction conditions are given in the Experimental Section. [b] Measured by GC with reference to tetradecane as internal standard. [c] The product was not amenable to determination by GC, and the yield given is therefore of isolated purified material. There was no evidence for formation of a significant quantity of the corresponding 2,3-disubstituted isomer.

(4-Methyl-2-thienyl)phenylmethanone (**5**) has been reported[19,20] as one product of benzoylation of **1**, but separation from its 5-thienyl isomer may not always be easy.[20] In the present work, lithiation of **1** with LiTMP and reaction with benzonitrile produced **5** in almost quantitative yield. There was no evidence, either in the GC or NMR analyses, for the unwanted 2,3-disubstituted isomer, possibly due to the combined effects of the bulkiness of the lithiating reagent and the relative bulkiness of the electrophile.

4-Methylthiophene-2-carboxylic acid (**7**) has been prepared from other 2-substituted 4-methylthiophenes[15,21,22] and via metalation of **1** followed by reaction with CO_2,[23] but the latter reactions were said to give low yields. Compound **7** has recently become commercially available, but the method of preparation is not in the public domain. In the present work, lithiation of **1** with LiTMP and reaction with solid CO_2 slurried in THF followed by aqueous workup produced **7** in high yield. There was no evidence in the NMR analyses for the unwanted 2,3-disubstituted isomer, possibly due to combined effects of a bulky

(16) (a) Smith, K.; Lindsay, C. M.; Pritchard, G. J. *J. Am. Chem. Soc.* **1989**, *111*, 665. (b) Smith, K.; Pritchard, G. J. *Angew Chem., Int. Ed. Engl.* **1990**, *29*, 282. (c) Smith, K.; El-Hiti, G. A.; Abdel-Megeed, M. F.; Abdo, M. A. *J. Org. Chem.* **1996**, *61*, 647. (d) Smith, K.; El-Hiti, G. A.; Abdel-Megee, M. F.; Abdo, M. A. *J. Org. Chem.* **1996**, *61*, 656. (e) Smith, K.; Anderson, D.; Matthews, I. *J. Org. Chem.* **1996**, *61*, 662. (f) Smith, K.; Hou, D. *J. Org. Chem.* **1996**, *61*, 1530. (g) Smith, K.; El-Hiti, G. A.; Pritchard, G. J.; Hamilton, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2299. (h) Smith, K.; El-Hiti, G. A.; Shukla, A. P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2305. (i) Smith, K.; El-Hiti, G. A.; Hawes, A. C. *Synthesis* **2003**, 2047. (j) Smith, K.; El-Hiti, G. A. *Curr. Org. Synth.* **2004**, *1*, 253. (k) Smith, K.; El-Hiti, G. A.; Abdel-Megeed, M. F. *Synthesis* **2004**, 2121. (l) Smith, K.; El-Hiti, G. A.; Hegazy, A. S. *J. Sulfur Chem.* **2005**, *26*, 121. (m) Smith, K.; El-Hiti, G. A.; Hegazy, A. S. *Synthesis* **2005**, 2951.

(17) Agarwal, N.; Ravikanth, M. *Tetrahedron* **2004**, *60*, 4739.
(18) Meth-Cohn, O.; Ashton, M. *Tetrahedron Lett.* **2000**, *41*, 2749.
(19) Spurlock, J. J. *J. Am. Chem. Soc.* **1953**, *75*, 1115.
(20) Barrett, A. G. M.; Bouloc, N.; Braddock, D. C.; Chadwick, D.; Henderson, D. A. *Synlett* **2002**, *10*, 1653.
(21) Farrar, M. W.; Levine, R. *J. Am. Chem. Soc.* **1950**, *72*, 3695.
(22) Perweew, K. *Zh. Obsch. Khim.* **1953**, *23*, 976.
(23) (a) Schick, J. W.; Hartough, H. D. *J. Am. Chem. Soc.* **1948**, *70*, 1646. (b) Blanchette, J. A.; Brown, E. V. *J. Am. Chem. Soc.* **1952**, *74*, 1848.

lithiating reagent and a low reaction temperature resulting from use of solid CO_2 as electrophile.

In conclusion, it is now possible to substitute 3-methylthiophene highly regioselectively at the 5-position with a variety of electrophiles following lithiation with LiTMP. The method greatly improves syntheses of several known compounds and allows preparation of some novel ones. The approach should interest both academe and industry, and a patent application has been filed.

Experimental Section

Melting point (mp) and boiling point (bp) determinations are reported uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) chemical shifts are referenced to tetramethylsilane. Data for electrospray (ES), electron impact (EI), and chemical ionization (CI) mass spectra are presented first with the high-resolution analysis of the molecular or pseudo molecular ion and its calculated value followed by the most abundant peaks of each measured spectrum with relative intensities in parentheses. Microanalytical data are given as measured percentage values compared to calculated values. Column chromatography was carried out with silica gel 60 A (35−70 μm particle size) or activated neutral alumina (Brockmann I, standard grade, approximately 150 mesh, 58 Å) as indicated in the individual procedures. TLC analyses were carried out on aluminum silica gel plates and visualized by ultraviolet light. Chemicals were used as supplied unless GC analysis showed appreciable impurities. Alkyllithiums were estimated by the Gilman double titration method.[24] Tetrahydrofuran was dried by filtration through activated alumina, stirring overnight with calcium hydride and distillation from sodium benzophenone ketyl. Reduced pressure distillations were carried out using a water aspirator (15 mmHg). Quantitative GC analyses were carried out using tetradecane as an internal standard.[25]

Lithiation of 3-Methylthiophene with Alkyllithiums. 3-Methylthiophene (**1**, 0.294 g, 3.00 mmol) was dissolved in dry distilled THF (10 mL) in a septum-sealed 25 mL round-bottom flask which had previously been flushed with argon. The mixture was cooled in a dry ice/acetone bath for 30 min, then the commercial organolithium reagent solution (3.20 mmol) was added dropwise by syringe to the mixture, which was stirred for 1 h. Excess iodomethane (0.680 g, 4.79 mmol) was added dropwise by syringe, and the mixture was stirred for 30 min, after which the cooling bath was removed and the mixture stirred for a further 90 min. An internal standard solution (5.00 mL of a 0.292 mol dm^{-3} solution of tetradecane in diethyl ether, 1.46 mmol) was added, followed by hydrochloric acid (2M, 20 mL) to quench the reaction. The mixture was swamped with diethyl ether (50 mL) and washed with saturated sodium hydrogen carbonate solution (20 mL) and saturated sodium chloride solution (20 mL). The organic phase was dried over anhydrous magnesium sulfate. An aliquot of the supernatant sample solution was analyzed by GC to determine yield and the ratio of dimethylthiophenes (**2** and **3**). The results are shown in Table 1.

Lithiation of 3-Methylthiophene with Lithium Amides. The appropriate dialkylamine (3.20 mmol) was dissolved in dry distilled THF (10 mL) in a septum-sealed 25 mL round-bottom flask which had previously been flushed with argon. The mixture was cooled in a dry ice/acetone bath for 30 min; *tert*-butyllithium (2.00 mL of a 1.70 mol dm^{-3} solution in pentane, 3.40 mmol) was added dropwise by syringe, and the reaction mixture was stirred for 1 h. 3-Methylthiophene (**1**, 0.294 g, 3.00 mmol) was added by syringe, and the mixture was stirred for 1 h. Excess iodomethane (0.680 g, 4.79 mmol) was added dropwise by syringe, and the mixture was then treated in exactly the same way as for reactions with alkyllithiums. The results are also shown in Table 1.

Scaled-up Synthesis and Purification of 2,4-Dimethylthiophene. 2,2,6,6-Tetramethylpiperidine (HTMP, 8.20 g, 58.0 mmol) was dissolved in dry distilled THF (100 mL) in a septum-sealed 250 mL round-bottom flask that had previously been flushed with argon. The mixture was cooled in a dry ice/acetone bath for 30 min; *tert*-butyllithium (35.0 mL of a 1.70 mol dm^{-3} solution in pentane, 59.5 mmol) was added dropwise by syringe, and the reaction mixture was stirred for 1 h. 3-Methylthiophene (**1**, 5.40 g, 55.0 mmol) was added by syringe, and the mixture was stirred for 1 h. Excess iodomethane (12.5 g, 88.0 mmol) was added dropwise by syringe, and the mixture was stirred for 30 min, after which the cooling bath was removed and the mixture stirred for a further 90 min. Hydrochloric acid (2 M, 80 mL) was added to quench the reaction. The mixture was swamped with diethyl ether (120 mL) and washed with saturated sodium hydrogen carbonate solution (80 mL) and saturated sodium chloride solution (80 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered, evaporated, and made up to 200 mL in a volumetric flask. A 1 mL aliquot was taken; internal standard solution (1 mL of a 0.30 mol dm^{-3} solution of tetradecane in diethyl ether, 0.30 mmol) was added to the aliquot, and the yield was determined by GC with reference to a standard solution made up with purified **2** and tetradecane. The remaining dark brown solution was treated three times with decolorizing charcoal and evaporated to give a light green oil (6.15 g, 54.9 mmol, 99% yield). The oil was distilled at atmospheric pressure to give **2** as a colorless liquid (bp 139 °C, lit.[15] 139 °C, 4.50 g, 73%).

Immediately upon removal from the organic phase, the HCl phase (pH = 1) was treated with 2 M aqueous sodium hydroxide until the pH reached 14, at which point HTMP separated out as an oil. After being allowed to cool to room temperature, the mixture was extracted with diethyl ether (4 × 50 mL). The ether phase was washed with saturated aqueous sodium chloride solution and dried with magnesium sulfate. Upon evaporation and distillation under reduced pressure, HTMP was recovered as a colorless oil in 87% yield (7.13 g, 50.5 mmol).

Reactions with Different Electrophiles. 2,2,6,6-Tetramethylpiperidine (0.452 g, 3.20 mmol) was dissolved in dry distilled THF (15 mL) in a sealed 50 mL round-bottom flask which had previously been flushed with argon. The mixture was cooled in a dry ice and acetone bath for 30 min to ensure thorough cooling. *tert*-Butyllithium (2.00 mL of a 1.70 mol dm^{-3} solution in pentane, 3.40 mmol) was added dropwise by syringe, and the reaction mixture was stirred for 1 h. 3-Methylthiophene (**1**, 0.294 g, 3.00 mmol) was added by syringe, and the mixture was stirred for 1 h. Electrophile (3.70 mmol; 7.40 mmol in the case of DMF; for further details, see individual examples) was added dropwise by syringe or, if solid, dissolved in dry distilled THF (10 mL) and added dropwise by syringe. The mixture was stirred overnight, warming to room temperature in the process. Aqueous hydrochloric acid (2 M, 20 mL) was added to quench the reaction (for exceptions to this, see individual examples). The mixture was swamped with diethyl ether (50 mL) and washed with saturated sodium hydrogen carbonate solution (20 mL) and saturated sodium chloride solution (20 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered, and made up to 100 mL in a volumetric flask. If the product was amenable to analysis by GC, a 1 mL aliquot was taken, internal standard solution (0.50 mL of a 0.30 mol dm^{-3} solution of tetradecane in diethyl ether, 0.15 mmol) was added and the yield was determined by GC (with reference to a standard solution of the purified product and tetradecane). The remaining product solution was evaporated, and the mixture was separated by column chromatography where necessary (see individual examples for details). The purified product was characterized as

(24) Wakefield, B. J. *Organolithium Methods*; Academic Press: London, 1988.

(25) Scott, R. P. W. *Introduction to Analytical Gas Chromatography*, 2nd ed.; Marcel Dekker: New York, 1998.

reported. Where no selectivity is given, there was no indication of the unwanted isomer. The results are shown in Table 2.

2,4-Dimethylthiophene (2): Purified by distillation; colorless liquid; bp 139 °C (lit.[15] 139 °C); purity 97.2% (GC); GC yield = 98%; isolated yield = 73% (4.50 g, 40.2 mmol); selectivity = 79:1 (2:3, GC, NMR).

(4-Methyl-2-thienyl)diphenylmethanol (4): Reagent = benzophenone (Ph_2CO, 0.674 g, 3.70 mmol); purified by column chromatography (SiO_2, gradient elution, hexane up to10% Et_2O/hexane) and recrystallization (Et_2O/hexane); GC yield = 98%; isolated yield = 85% (0.701 g, 2.51 mmol); off-white solid, mp 81.7−83.2 °C; purity = 97% (GC); crystals turn purple over time, so they are unsuitable for microanalysis; ν_{max} (film)/cm^{-1} 3419; δ_H (400 MHz; $CDCl_3$) 2.09 (3H, s), 2.83 (1H, s, D_2O exch.), 6.44 (1H, s), 6.74 (1H, s), 7.15−7.30 (10H, m); δ_C (100 MHz; $CDCl_3$) 16.3, 80.4, 121.4, 127.7, 128.0, 128.4, 129.7, 137.5, 147.0, 152.3; *m*/*z* (EI$^+$) = 280.0917 ([M]$^+$; $C_{18}H_{16}OS$ requires 280.0916); *m*/*z* (EI$^+$) = 280 (23%), 263 (24), 247 (23), 203 (73), 175 (72), 125 (69), 105 (87), 97 (27), 77 (100); *m*/*z* (CI$^+$(NH_3) 280 (10%), 263 (100).

(4-Methyl-2-thienyl)phenylmethanone (5): Reagent = PhCN (0.382 g, 3.70 mmol); GC yield 99%; isolated yield 91% (0.545 g, 2.70 mmol); purified by chromatography (alumina, 10% Et_2O/hexane) and recrystallization (Et_2O/hexane); white solid, mp 90.0−91.4 °C (lit.[19] 91−92 °C); purity 96% (GC).

4-Methyl-2-thiophenecarboxaldehyde (6): Reagent = *N*,*N*-dimethylformamide (DMF, 0.546 g, 7.48 mmol); purified by passing through a short alumina plug with 50% Et_2O/hexane and then reduced pressure distillation; clear, colorless liquid, bp 224 °C (lit.[15] 84−86 °C, 8 Torr); purity 97.3% (GC); selectivity 35.5:1 (GC); GC yield = 97%; isolated yield = 89% (0.335 g. 2.67 mmol).

4-Methylthiophene-2-carboxylic acid (7): Reagent = excess solid CO_2 (ca. 2.5 g, slurried in THF (15 mL), to which the THF solution of lithiated **1** was added); isolated by treating the NH_4Cl phase with 2 M HCl to pH = 1, when a solid precipitated. Et_2O (100 mL) was added to dissolve the solid. The aqueous layer was extracted with Et_2O (2 × 100 mL). The organic extracts were combined and treated as in the general procedure. Evaporation and recrystallization (Et_2O/hexane) gave the product: isolated yield = 75% (0.319 g, 2.25 mmol); white solid, mp 119.7−121.5 °C (lit.[15] 123−124 °C).

(4-Methyl-2-thienyl)phenylmethanol (8): Reagent = PhCHO (0.393 g, 3.70 mmol); purified by chromatography (silica, eluted with 10% Et_2O/hexane); isolated yield = 79% (0.483 g, 2.37 mmol); light orange solid, mp 46.7−48.0 °C; unsuitable for microanalysis as it darkens and loses solidity over a few days; ν_{max} (film)/cm^{-1} 3310; δ_H (400 MHz; $CDCl_3$) 2.10 (3H, s), 2.29 (1H, s, D_2O exch.), 5.94 (1H, s), 6.15 (1H, s), 6.77 (1H, s), 7.20−7.45 (5H, m); δ_C (100 MHz; $CDCl_3$) 16.2, 76.9, 121.0, 127.3, 127.8, 128.3, 129.6, 137.4, 141.6, 146.3; *m*/*z* (EI$^+$) = 203.0521 ([M − H]$^+$, $C_{12}H_{11}OS$ requires 203.0525); *m*/*z* (EI$^+$) = 204 (26%), 203 (62), 187 (65), 171 (51), 127 (45), 105 (80), 99 (100), 77 (91); *m*/*z* (CI$^+$(NH_3)) 203 (10%), 189 (77), 87 (100).

4-Methyl-2-thiophenecarbothioic acid phenylamide (9): Reagent = PhNCS (0.50 g, 3.70 mmol); purified by a short column (SiO_2, 20% Et_2O/hexane) to remove colored impurities and recrystallization (Et_2O/hexane); isolated yield 76% (0.531 g, 2.28 mmol); bright yellow solid, mp 104.2−105.0 °C. Anal. Calcd for $C_{12}H_{11}NS_2$: C 61.81, H 4.75, N 6.00%. Found: C 61.60, H 4.69, N 5.88%; ν_{max} (film)/cm^{-1} 3231, 1142; δ_H (400 MHz; $CDCl_3$) 2.18 (3H, s), 7.06 (1H, s), 7.18 (1H, t, J = 8 Hz), 7.29 (3H, m), 7.55 (2H, appt t, J = 8 Hz), 8.84 (1H, s, D_2O exch.); δ_C (100 MHz; $CDCl_3$) 16.2, 124.6, 127.4, 129.0 129.4, 139.0, 139.2, 188.3; *m*/*z* (ES$^+$) 234.0406 ([M + H]$^+$ $C_{12}H_{12}NS_2$ requires 234.0406); *m*/*z* (EI$^+$) = 233 (62%), 200 (41), 141 (100), 110 (28), 97 (40), 77 (52); *m*/*z* (CI$^+$) 234 (100%), 202 (22).

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