Organic Process Research & Development **2010**, *14*, 1427–1431

Practical Access to Metallo Thiophenes: Regioselective Synthesis of 2,4-Disubstituted Thiophenes

Sylvie M. Asselin,*,† Matthew M. Bio, Neil F. Langille,* and Ka Yi Ngai

Chemical Process R&D, Amgen, Inc., 360 Binney Street, Building 1000, Cambridge, Massachusetts 02142, United States

Abstract:

This report describes a protocol for functionalization of thiophenes, utilizing a regioselective magnesiation mediated by commercial Grignard reagents and catalytic 2,2,6,6-tetramethylpiperidine. This metalation provides practical access to metallo thiophenes, avoiding cryogenic conditions, prolonged reaction times, and prohibitively expensive reagents. Application to a target thiophene-phthalazinone 6 was accomplished by addition of 2-magnesio-4-methylthiophene to phthalic anhydride, providing the product with >40:1 regioselectivity. This also solved a chemoselectivity issue encountered with analogous lithio-thiophene reagents and cyclic anhydrides, or with magnesio-thiophene generated by simultaneous lithium-to-magnesium transmetalation/anhydride acylation. These alternative *in situ* transmetalation sequences were plagued by an age effect dictated by the kinetic solubility of $MgCl_2$/THF complexes.

Introduction

A recent project required a practical synthetic preparation of thiophene-phthalazinone **6**.[1,2] A logical precursor to this molecule is keto acid **4**, formed through union of 3-methylthiophene **1** and phthalic anhydride **3** (Scheme 1). Upon subjection of **1** and **3** to Friedel−Crafts conditions[3] ($AlCl_3$, CH_2Cl_2, −10 °C), the more electron-rich alkene reacted selectively to form the undesired 2,3-keto acid regioisomer **4′** (8:1 ratio, **4′**:**4**). Therefore, preformed 2-metallo-4-methylthiophene **2** was explored as a nucleophile to form keto acid **4**, where steric factors could promote the desired 2,4-regioisomer. A successful sequence would require practical, scalable conditions to address regioselective deprotonation to form a 2,4-thiophene isomer (**2** vs **2′**) and subsequent chemoselective monoaddition to the anhydride (**4** vs **5**) to provide this key intermediate.

Li-Based Deprotonation. The deprotonation of 3-methylthiophene has been the subject of previous research studies.[4] Smith and co-workers reported excellent regioselectivity in the deprotonation of 3-methylthiophene (>35:1) using *n*-BuLi and 2,2,6,6-tetramethylpiperidine (TMP-H).[4c] However, the reported regioselectivity could only be achieved at −78 °C. A practical, although under-utilized, lithium amide formation involves dropwise addition of an alkyllithium to a substoichiometric amount of amine in the presence of the acidic reactant.[5] Application of this method to 3-methylthiophene produced the desired lithio-thiophene **2a** (Scheme 2) with useful levels of thiophene regioselectivity (12:1)[6] using 10 mol % TMP-H at −20 °C.

However, direct addition of lithio-thiophene **2a** to phthalic anhydride **3** gave a 1:2 mixture of desired keto acid **4** and undesired bis-thiophene **5**.[7] Alternatively transmetalation of lithio-thiophene **2a** with $MgCl_2$ produced magnesio-thiophene **2b**, which reacted with **3** to produce the desired product **4** in 88% assay yield with >30:1 chemoselectivity (**4**/**5**). The deprotonation/transmetalation/acylation sequence provided keto acid **4** via preformed Mg-thiophene **2b**; however this procedure represented a tedious three-vessel operation.

If Li-to-Mg transmetalation (**2a** to **2b**) occurred faster than addition of **2a** to phthalic anhydride, Mg-thiophene **2b** could potentially be generated *in situ* in the presence of the electrophile, accomplishing two steps of the process simultaneously in a single vessel. Slow addition of Li-thiophene **2a** could be utilized to exploit this rate difference. If this proposed sequence were successful, the resulting Mg-thiophene **2b** would react to form the stabilized Mg-alkoxide **7b**, chemoselectively producing the desired keto acid **4**. To test this hypothesis, Li-thiophene **2a** was generated via the catalytic TMP-H method and added dropwise to a phthalic anhydride/$MgCl_2$/THF mixture at −20 °C, producing the desired keto acid **4** in 80% assay yield, with a 10:1 ratio of mono- to bis-thiophene products (Table 1, entry 1). In preparation for scaling, slurries of phthalic anhydride/$MgCl_2$/THF were aged at 20 °C prior to introduction of Li-thiophene **2a**. This age time had a dramatic effect: when phthalic

* Authors to whom correspondence may be sent. E-mail: sylvie.asselin@amgen.com; neil.langille@amgen.com.

† Current address: Chemical Process R&D, Amgen, Inc., One Amgen Center Drive, Thousand Oaks, California 91320, United States

(1) Cee, V. J.; Deak, H. L.; Du, B.; Geuns-Meyer, S. D.; Hodous, B. L.; Nguyen, H. N.; Olivieri, P. R.; Patel, V. F.; Romero, K.; Schenkel, L. *Chem. Abstr.* **2007**, *147*, 235186. Preparation of Substituted Phthalazinamines as Aurora Kinase Modulators. PCT Int. Appl. WO/2007/087276, 2007.

(2) For alternate synthesis, see: (a) Iwase, N.; Morinaka, Y.; Tamao, Y.; Kanayama, T.; Yamada, K. *Chem. Abstr.* **1993**, *119*, 249963. 3,6-Disubstituted Pyridazine Derivative Blood Platelet Aggregation Inhibitors. Eur. Pat. Appl. EP 534443 19920924, 1993.

(3) Weinmayr, V. *J. Am. Chem. Soc.* **1952**, *74*, 4353–4357.

(4) (a) Ramanathan, V.; Levine, R. *J. Org. Chem.* **1962**, *27*, 1667–1670. (b) Gronowitz, S.; Cederlund, B.; Hornfeldt, A.-B. *Chem. Scr.* **1974**, *5*, 217–226. (c) Smith, K.; Barrat, M. L. *J. Org. Chem.* **2007**, *72*, 1031–1034.

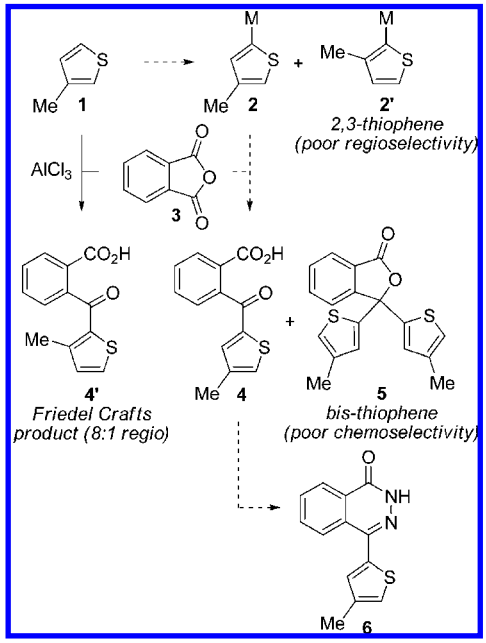
(5) (a) Alorati, A. D.; Bio, M. M.; Brands, K. M. J.; Cleator, E.; Davies, A. J.; Wilson, R. D.; Wise, C. S. *Org. Process Res. Dev.* **2007**, *11*, 637–641. (b) Klingensmith, L. M.; Bio, M. M.; Moniz, G. A. *Tetrahedron Lett.* **2007**, *48*, 8242–8245.

(6) Regioisomeric ratio upon reaction with phthalic anhydride (not a direct measurement of deprotonation).

(7) Analysis by ^{13}C NMR indicates that isolated keto acid **4** exists as the open form shown in Scheme 2 and side product **5** exists as the closed lactone form.

10.1021/op100226k
Published on Web 10/13/2010

Scheme 1. **Plausible synthetic routes to phthalazinone 6**



anhydride/$MgCl_2$/THF mixtures were used immediately or aged longer than 6 h, significant amounts of undesired side product **5** were formed (entries 2−3).

The effect shown in Table 1 can be explained by kinetic solubility of $MgCl_2$/THF complexes,[8] where competing crystal forms have been shown to drastically alter solubility (eq 1).

$$MgCl_2 \xrightarrow{\text{fast}} \underset{\text{highly soluble}}{MgCl_2\cdot(THF)_2} \xrightarrow{\text{slow}} \underset{\text{sparingly soluble}}{MgCl_2\cdot(THF)_4} \qquad (1)$$

Our trend suggests that the highly soluble $MgCl_2\cdot(THF)_2$ complex promotes the desired Li-to-Mg transmetalation, while side-product formation competes in the presence of the less soluble $MgCl_2\cdot(THF)_4$ complex. Given the longer cycle times anticipated on scale, it would be difficult to rely on a transient kinetic form in a manufacturing environment. For this reason, lithiation/transmetalation protocols were abandoned in favor of a direct magnesiation of 3-methylthiophene.[9]

Scheme 2. **Divergent reactivity of Li- and Mg-thiophenes**

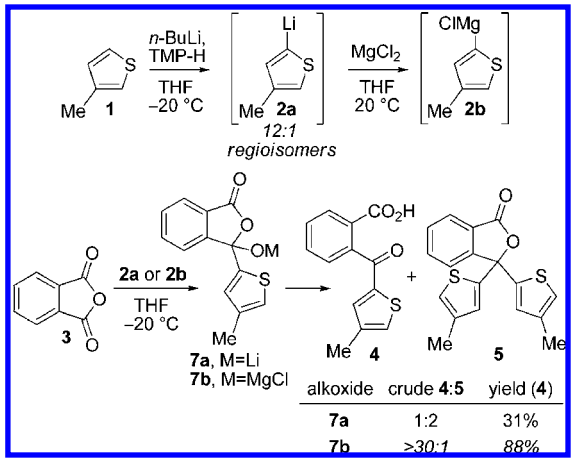
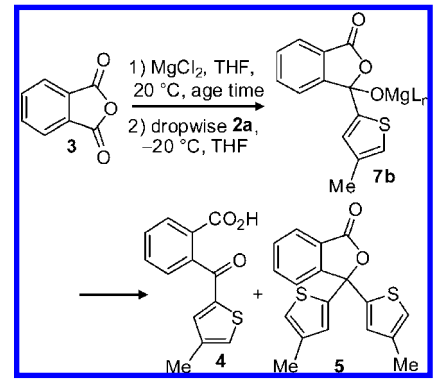


Table 1. **Transmetalation dynamics and effect on acylation**



entry	age time[a]	yield of **4**[b] (%)	(**4**:**5**)[c]
1	1 h	80 (14:1)	10:1
2	5 min	38 (12:1)	1:1.5
3	18 h	54 (14:1)	1.2:1

[a] $MgCl_2$ was allowed to precomplex with THF and phthalic anhydride at 20 °C for the age time. [b] Assay yield of desired regioisomer by quantitative HPLC (thiophene regioselectivity in parentheses). [c] Molar ratio by quantitative HPLC.

A Direct Magnesiation Approach. A more direct approach to **2b** which would circumvent issues with transmetalation would be the use of a Mg-TMP amide generated directly from a magnesium base such as *i*-PrMgCl. This approach has been designed for magnesiation of functionalized aryl[10] and heteroaryl[11] rings, including thiophene itself. However, the specialized complex base *i*-PrMgCl·LiCl and stoichiometric levels of TMP-H are impractical, and reaction times are typically in excess of 48 h, precluding the use of this system on large scale. Control experiments indicated that *i*-PrMgCl could not deprotonate 3-methylthiophene by itself.[12]

The simultaneous Mg-TMP formation/deprotonation of 3-methylthiophene was investigated as a one-pot process (Scheme 3). Mg-thiophene formation proceeded with catalytic (10 mol %) TMP-H;[13] however the deprotonation was slow and incomplete, achieving only 85% conversion after 36 h at 66 °C.[14] Once formed, the resulting Mg-thiophene **2b** reacted with phthalic anhydride **3** to produce keto acid **4** in 81% assay yield with *>40:1* regioselectivity favoring the 2,4-disubstituted thiophene. As expected, exclusive chemoselectivity was maintained in this magnesiation/acylation.

(8) Handlíř, K.; Holeček, J.; Beneš, L. *Collect. Czech. Chem. Commun.* **1985**, *50*, 2422–2430.
(9) Using the solvent DME resulted in a 1:1.4 ratio of **4**:**5**, possibly indicating a destabilization of alkoxide **7b**.
(10) (a) Lin, W.; Baron, O.; Knochel, P. *Org. Lett.* **2006**, *8*, 5673–5676. (b) Stoll, A. H.; Knochel, P. *Org. Lett.* **2008**, *10*, 113–116. (c) Rohbogner, C. J.; Clososki, G. C.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1503–1507.
(11) (a) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958–2961. (b) Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7681–7684. (c) Mosrin, M.; Knochel, P. *Org. Lett.* **2008**, *10*, 2497–2500. (d) Piller, F. M.; Knochel, P. *Org. Lett.* **2009**, *11*, 445–448.
(12) For a relevant discussion, see: Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2007**, *63*, 1568–1576.
(13) Extent of deprotonation measured by ^{1}H NMR upon quenching with CD_3OD. Similar experiments with iodine were inconsistent with CD_3OD, indicating competitive electrophilic iodination of the Me-substituted alkene.
(14) No change in rate was observed with *i*-PrMgCl·LiCl instead of *i*-PrMgCl.

Scheme 3. **Design of a catalytic Mg-TMP-promoted deprotonation/acylation of 3-methylthiophene**

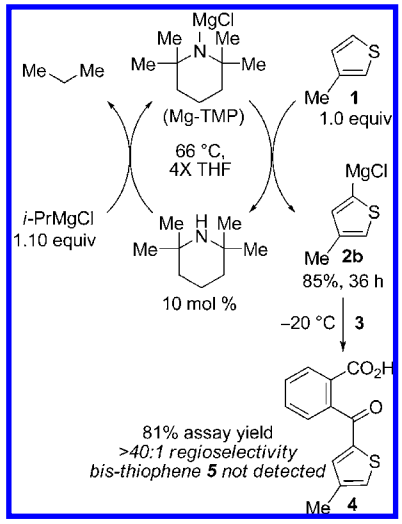
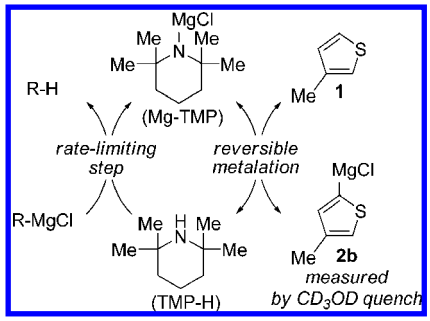


Table 2. **Mechanism and optimization**



entry	RMgCl (equiv)	equiv of TMP-H	% deprotonation[a] (h)
1	*i*-PrMgCl (1.1)	0.1	85 (36)
2	*i*-PrMgCl (1.0)	0.2	83 (15)
3	*i*-PrMgCl (1.3)	0.1	80 (18)
4	*t*-BuMgCl (1.0)	0.2	9 (18)
5	*n*-HexMgCl (1.0)	0.2	90 (8)
6	*i*-PrMgCl (1.1)	1.1	44 (18)
7	*i*-PrMgCl (0.85[b])	0.1	>95 (18)[c]

[a] Measured by ^{1}H NMR after quenching with CD_3OD. [b] Equals 1.2 equiv of 3-methylthiophene, relative to *i*-PrMgCl. [c] Based on conversion of *i*-PrMgCl.

With proof of principle in hand, a detailed study was initiated to optimize the 3-methylthiophene magnesiation. Increasing the amount of TMP-H or *i*-PrMgCl (Table 2, entries 2 and 3) also increased the deprotonation rate but failed to promote full conversion. Altering the sterics of the Grignard had a more profound effect: *t*-BuMgCl (entry 4) resulted in minimal deprotonation, while the less-hindered *n*-HexMgCl promoted 90% conversion to **2b** in 8 h.[15] This indicates that Mg-TMP formation may be the rate-limiting step in the catalytic cycle. Even with an accelerated rate, however, full conversion was not observed, suggesting that thiophene metalation might be a reversible process.[16] Employing stoichiometric TMP-H supported this hypothesis, resulting in only 44% conversion (entry 6).

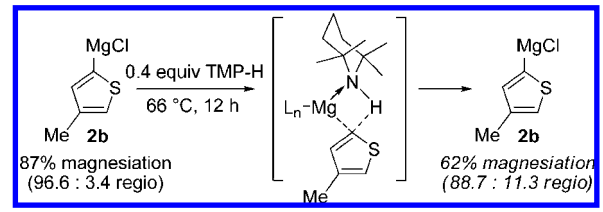


Figure 1. **Simplified model for proton transfer via coordination to TMP-H.**

Ultimately, excess 3-methylthiophene (1.2 equiv, or 0.85 equiv of *i*-PrMgCl, entry 7) drove this equilibrium to product, resulting in >95% conversion of *i*-PrMgCl to Mg-thiophene **2b**. The excess 3-methylthiophene showed no detrimental effects on the acylation step and could be removed during workup through distillation.[17]

Additional experimental evidence supports the reversibility of the magnesiation of 3-methylthiophene. Charging 0.4 equiv of TMP-H to a reaction at 87% conversion resulted in partial reversion of **2b** to the protonated 3-methylthiophene **1** (accompanied by a loss of regioselectivity, see Figure 1). On the basis of pK_a measurements this would be impossible (in DMSO/TMP-H = 37, unsubstituted thiophene = 32[12]). However, coordination of a metal complex (in the simplest case, **2b**) could lower the pK_a of TMP-H, providing a means for proton transfer.[18] In this hypothesis, the 2-Mg-3-Me-thiophene isomer would be less likely to participate, providing a rationale for the observed decay in regioselectivity.

Application of this two-pot magnesiation/acylation to the synthesis of thiophene-phthalazinone **6** is illustrated in Scheme 4. Treatment of 147 g of 3-methylthiophene with *i*-PrMgCl as limiting reagent at 66 °C in the presence of catalytic TMP-H resulted in 98% conversion to Mg-thiophene **2b**.[19] Mg-thiophene **2b** (1.10 equiv) was added dropwise to a −20 °C slurry of phthalic anhydride in THF to provide crude keto acid **4** in 94% assay yield[20] (>40:1 thiophene regioisomers). Removal of solvent and residual 3-methylthiophene was accomplished through a distillative solvent switch into EtOH. Intermediate **4** was crystallized from EtOH/water in 89.7% adjusted yield.

Alternatively, the crude EtOH solution proved competent in a through-process conversion to phthalazinone **6**. The EtOH solution of **4** was treated with excess aqueous hydrazine at 80 °C. After consumption of the starting material, the precipitated product was filtered directly from the reaction at 20 °C. This process provided thiophene-phthalazinone **6** in 84.7% yield over the two steps.

(15) Residual *n*-hexane complicated the through-process synthesis of phthalazinone **6** (oiling during crystallization) and was abandoned for the synthesis of this particular target. Further investigation of *n*-hexylmagnesium chloride in similar applications is underway.

(16) For reversible metalation of other heterocycles, see: (a) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1988**, *29*, 773–776. (b) Trécourt, F.; Mallet, M.; Marsais, F.; Quéguiner, G. *J. Org. Chem.* **1988**, *53*, 1367–1371. (c) Viciu, M. S.; Gupta, L.; Collum, D. B. *J. Am. Chem. Soc.* **2010**, *132*, 6361–6365.

(17) Use of excess *i*-PrMgCl (≥1.3 equiv) is detrimental to phthalic anhydride addition, producing a side product from isopropyl incorporation into keto acid product **4**.

(18) Magnesium or lithium aggregates have been implicated in reversible metallations of this type. See references 16a−c and references within for more details.

(19) The 98% conversion is calculated on the basis of the limiting reagent *i*-PrMgCl.

(20) Yield and equivalents are based on the limiting reagent phthalic anhydride.

Scheme 4. **Intermediate scale-up of thiophene-phthalazinone 6**

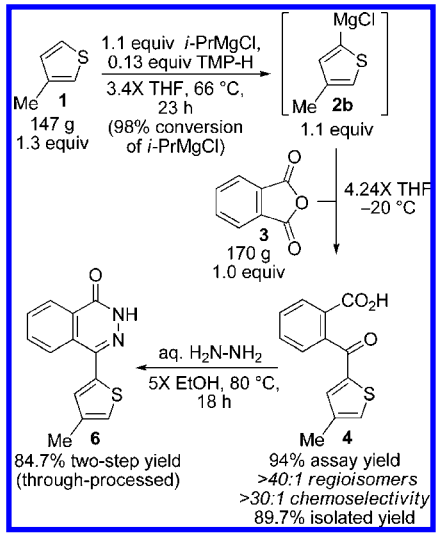
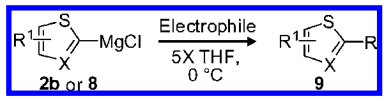


Table 3. **Magnesiation with Mg-TMP and reaction with electrophiles**



entry	magnesium reagent[a]	electrophile	product (R)	yield[b]
1	**2b**	$(HCHO)_n$	**9a** (CH_2OH)	57
2	**2b**	DMF	**9b** (CHO)	60
3	**2b**	TMSCl	**9c** (TMS)	60
4	**2b**	PhCHO	**9d** (CH(OH)Ph)	61
5	**2b**	MeCON(OMe)Me	**9e** (COMe)	69
7	**8a**	DMF	**9f** (CHO)	54
8	**8b**	DMF	**9g** (CHO)	53
9	**8c**	PhCHO	**9h** (CH_2Ph)	64
10	**8d**	$(HCHO)_n$	**9i** (CH_2OH)	57

[a] Formation: 1.4 equiv heterocycle, 1.0 equiv of *i*-PrMgCl, 0.1 equiv of TMP-H, THF, 66 °C, 18 h. [b] Isolated yield after chromatography (not optimized). [c] Assay yield after workup.

To examine the reactivity of this metalated heterocycle, preformed Mg-thiophene **2b** was subjected to a number of electrophiles at 0 °C. As shown in Table 3, this reagent provided moderate yield of the resulting bifunctional thiophenes **9a**−**e**, indicating compatibility with a range of electrophiles. In all cases, the products were formed with excellent (>40:1) regioselectivity, favoring the 2,4-disubstituted thiophene product. Similarly, the one-pot catalytic TMP-H/*i*-PrMgCl mediated deprotonation is amenable to heterocycles bearing appropriately acidic protons. Several heterocyclic thiophene and benzothiazole magnesium reagents **8a**−**d** were generated via this protocol and shown to possess similar reactivity to **2b**. On the basis of this preliminary survey, the most appropriate heterocycles possess acidic protons in the approximate pK_a range of 27−33. It is important to note that the one-pot Mg-TMP formation/deprotonation sequence is not compatible with substrates that undergo nucleophilic attack by *i*-PrMgCl under these conditions (i.e., quinoline, isoquinoline, thiazole) or substrates susceptible to metal−halogen exchange (i.e., 2-chloropyridine, 2-chloropyrimidine). Nevertheless, this method provides a means for rapid installation of select heterocycles into more complex chemical frameworks via the metalated heterocycle, utilizing bench-stable commercial reagents and scalable conditions.

Conclusion

In summary, a commercially viable regioselective deprotonation of 3-substituted thiophenes based on the inexpensive base *i*-PrMgCl and substoichiometric TMP-H has been developed. This protocol replaces lithium-based methods using stoichiometric amine additives and cryogenic conditions. This study revealed the divergent reactivity of lithio- and magnesiothiophene reagents toward cyclic anhydrides, and identified a dynamic solvation effect that influences $MgCl_2$/THF-promoted transmetalations. Importantly, this magnesiation process displays excellent compatibility with cyclic anhydrides, unlike similar Li or Li/Mg systems. Mechanistic studies have also established the reversibility of the Mg-TMP promoted deprotonation of 3-methylthiophene. Together, these findings have enabled a practical, regioselective, and chemoselective synthesis of a target thiophene-phthalazinone **6** in 84.7% yield (two steps, one isolation) from inexpensive commercially available materials.

Experimental Section

General. *i*-PrMgCl quality was monitored by titration versus menthol, using 1,10-phenanthroline as indicator.[21] Reactions were conducted under an atmosphere of nitrogen with a suitable outlet to accommodate modest pressure changes. Reaction temperatures were monitored by an internal thermocouple. Reaction progress and compound purity were determined by HPLC analysis, using an Eclipse XDB C8, 4.6 mm × 150 mm, 5 μm column, with a gradient method using 0.1% (v/v) 70% $HClO_4$/water and acetonitrile as mobile phase. Purity was assessed using high-purity reference standards and confirmed by quantitative ^{1}H NMR. HRMS (ESI-TOF) spectra were obtained using Agilent 1100 systems.

2-(4-Methylthiophene-2-carbonyl)benzoic Acid (4). 2,2,6,6-Tetramethylpiperidine (25.2 mL, 150 mmol) was charged in one portion to 3-methylthiophene **1** (147 g, 144 mL, 1500 mmol) in THF (576 mL). *iso*-Propylmagnesium chloride (2.00 M solution in THF, 633 mL, 1270 mmol) was added over 10 min at <30 °C. The resulting solution was heated to reflux at 66 °C. After 23 h, ^{1}H NMR analysis of a reaction aliquot quenched with CD_3OD indicated 98%[19] conversion to the Mg-thiophene **2b** (96.8% 2-D-4-methylthiophene, 1.2% 2-D-3-methylthiophene of theoretical 0.85 equiv). The Mg-thiophene solution was cooled to 20 °C. Phthalic anhydride **3** (170 g, 1150 mmol) in THF (720 mL) was charged to a separate flask, and the resulting slurry was cooled to −20 °C. The Mg-thiophene

(21) Lin, H.-S.; Paquette, L. A. *Synth. Commun.* **1994**, *24*, 2503–2506. See Supporting Information for a detailed procedure.

solution (at 20 °C) was added to the phthalic anhydride slurry over 45 min, at −25 to −20 °C. After 20 min, the reaction was quenched with H_2O (510 mL) added over 10 min between −20 and 10 °C,[22] followed by 6 N HCl (289 mL) to pH 2. The reaction mixture was warmed to 20 °C, and MTBE (289 mL) was added. After 10 min, the layers were separated; the upper organic layer was assayed to 267 g keto acid **4** (94.1%[20]).

The crude keto acid **4** was concentrated by distillation (60 °C, 350 mbar) to 530−545 mL, and the resulting pot was maintained at 60 °C. Ethanol (1070 mL) was added, and the solution was distilled again to 530−545 mL total volume. HPLC analysis of the distillate revealed 3-methylthiophene as the only UV-active component. After breaking vacuum, ethanol (800 mL) was charged and the flask was cooled to 20 °C over 3 h. Water (1330 mL) was added over 2 h, and then aged for 10 h. The slurry was filtered, and the cake was displacement-washed with 25% EtOH/H_2O (535 mL). The collected mother liquors and wash contained 11.6 g (4.1%) product **4**. The solid was dried on the frit at 20 °C for >24 h, under a nitrogen stream, to provide keto acid **4** as an off-white solid (261 g, 97.3 wt %, 89.7% adjusted yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.16 (br s, 1H), 7.96 (ddd, J = 0.5, 1.5, 7.5 Hz, 1H), 7.64−7.72 (m, 3H), 7.49 (ddq, J = 0.6, 1.5, 7.5 Hz, 1H), 7.09 (dq, J = 0.4, 1.5 Hz, 1H), 2.18 (dd, J = 0.4, 0.6 Hz, 3H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 188.5, 166.9, 143.6, 140.7, 138.6, 136.1, 132.1, 130.7, 129.9, 129.9, 129.8, 127.4, 15.0; HRMS calculated for $C_{13}H_9O_2S_1$ $[M + H - H_2O]^+$ 229.0318, found 229.0316; IR (neat): 3050, 2970, 2920, 1690 cm^{-1}; mp: 191 °C.

4-(4-Methylthiophene-2-yl)phthalazine-1(2*H*)-one (6). Crude keto acid **4** (91.9 g) was synthesized as described above. The crude MTBE/THF layer was concentrated by distillation (60 °C, 300 mbar) to 180−190 mL, and the resulting pot was maintained at 60 °C. Ethanol (367 mL) was added, and the solution was distilled again to 180−190 mL total volume. After breaking vacuum, ethanol (367 mL) was charged to the reaction and the flask was cooled to 20−30 °C. To the resulting solution was added hydrazine (35 wt % solution in H_2O, 169 mL, 1870 mmol) over 10 min, at 35 °C. The reaction was heated to 80 °C for 18 h, until HPLC assay of the resulting slurry indicated >95% conversion to product.[23]

The reaction was cooled to 20 °C over 2 h and then aged at 20 °C for 1 h. The resulting slurry was filtered, and the cake was displacement-washed with 50% EtOH/H_2O (180 mL). The cake was dried under N_2 stream at 20 °C to give 82.7 g thiophene-phthalazinone **6** as a pale-yellow solid (98.6 wt %, 84.7% adjusted yield over two steps). The collected mother liquors and wash contained 1.78 g of product **6** (1.9%) and 5.70 g of keto acid **7** (6.1%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.38 (d, J = 0.8, 3H), 7.09 (dq, J = 0.8, 1.1, 1H), 7.28 (d, J = 1.1, 1H), 7.86 (m, 2H), 8.17 (m, 1H), 8.53 (m, 1H), 10.31 (bs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.83, 122.91, 126.63, 127.08, 128.22, 129.38, 130.88, 131.71, 133.70, 136.33, 138.14, 142.43, 159.72; mp: 232 °C.

(22) In a power compensation calorimetry experiment conducted at 10 °C isothermal, quenching the reaction with water (4 volumes over 1 h, 60.6 mmol scale) resulted in a 74 kJ/mol exotherm, uncorrected for heat of mixing.

(23) This reaction proceeds below the flash point of 35% hydrazine/water (112.7 °C) and below the boiling point of a hydrazine/water azeotrope (120.3 °C). DSC and ARC scanning of the reaction components at 300 and 250 °C, respectively, showed no unsafe thermodynamic events.

Acknowledgment

We thank Kelly Nadeau and Karl Hansen for helpful discussions.

Supporting Information Available

Procedures and representative NMR spectra for compounds **4**, **6**, and **9**. This material is available free of charge *via* the Internet at http://pubs.acs.org.

Received for review August 13, 2010.

OP100226K