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The application of vinamidinium salts to the synthesis of 2,4-disubstituted thiophenes

Ryan T. Clemens and Stanton Q. Smith*

Department of Chemistry, Virginia Military Institute, Lexington, VA 24450, USA

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Abstract—The synthesis of 2,4-disubstituted thiophenes by the condensation of symmetrical vinamidinium salts with methyl thioglycolate has been accomplished for the first time. Simple experimental conditions were used to prepare seven different methyl 4-aryl-2-thiophenecarboxylates, three of which are new compounds.

1. Introduction

Symmetrical vinamidinium salts undergo condensation reactions, similar to malonaldehyde derivatives, with bifunctional nucleophiles to form heterocycles. While these organic salts have been used to prepare many different monocyclic heterocycles including isoxazoles,[1] pyrazoles,[1] pyrimidines,[1] and pyrroles,[2] they have not yet been used to prepare thiophenes. 3-Substituted thiophenes, especially 3-alkyl or 3-arylthiophenes, find interesting uses such as monomers to prepare conducting poly(thiophenes).[3] Recent synthetic strategies that have been developed to prepare thiophenes include the condensation of methyl thioglycolate with malonaldehyde derivatives[4] forming 2,4-disubstituted thiophenes, the preparation of 2,3-disubstituted thiophenes using 2-chlorovinyl carbonyl compounds[5] and the preparation of 2,5-disubstituted thiophenes using chloropropenimium salts.[6] Additionally, there has been at least one report of an attempt to use vinamidinium salts and methyl thioglycolate to synthesize thiophenes, but those reaction conditions, involving strong base, led to pyrroles instead of thiophenes.[7]

2. Results and discussion

The vinamidinium salts (**1a**–**g**) used in this study were prepared by the standard Vilsmeier–Haack reaction of the appropriate aryl acetic acid.[1] As shown in Scheme 1, the vinamidinium salts **1a**–**g** were allowed to react with methyl thioglycolate (**2**) in refluxing DMF overnight to give the 2,4-disubstituted thiophenes **3a**–**g** (table of results is in Scheme 1).[8] After workup the crude reaction mixture was analyzed by TLC, GC/MS, and ^{1}H NMR. For the most part the reactions were rather clean and proceeded in good yield. The main contaminant was formation of the disulfide of methyl thioglycolate (not pictured). Using the hexafluorophosphate counter-ion instead of the perchlorate counter-ion produced essentially the same results with the disulfide still forming. The thiophenes **3a**,[4] **3e**,[4] **3b**,[9] **3g**[10] are known compounds and the synthesized thiophenes were in good agreement with the reported spectroscopic data for **3a**, **3b**, and **3e.** Analytical samples of the thiophenes could be obtained by column chromatography. Thiophenes **3c**, **3d**, and **3f** are new compounds and were characterized by NMR, GC/MS, and HRMS. The geometry of the thiophene ring was established by the C-3 and C-5 proton NMR signal $\delta = 8.03$ and 7.64 ($J = 1.6$ Hz) respectively for compound **3c**. Similar resonances (within 0.1 ppm) were also observed for the C-3 and C-5 hydrogens of thiophenes **3d** and **3f**. The experimental HRMS data of **3c**, **3d**, and **3f** matched the calculated data.[11]

3. Conclusion

In summary, we have demonstrated that vinamidinium salts can be effectively used for the regioselective preparation of 2-carbomethoxy-4-phenyl thiophenes using simple experimental conditions.

Keywords: Vinamidinium salts; Thiophenes; Methyl thioglycolate.
* Corresponding author. Tel.: +1 540 464 7426; fax: +1 540 464 7261; e-mail: smithsq@vmi.edu

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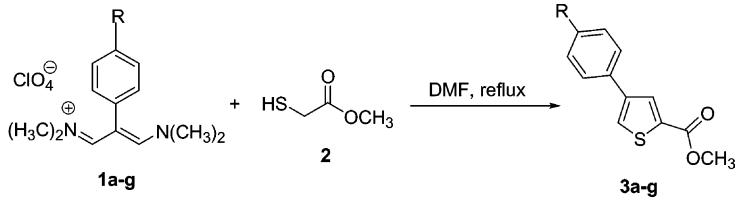

R	%CrudeYield	%Purity by GC/MS
H, **3a**	87	91
Br, **3b**	56	>95
Cl, **3c**	61	>95
F, **3d**	53	>95
OCH_3, **3e**	62	41
CH_3, **3f**	76	>95
NO_2, **3g**	67	89

Scheme 1. Preparation of 2,4-disubstituted thiophenes.

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8. *General procedure*: All reagents and solvents were obtained from Aldrich and ACROS and used without further purification. To a flame dried one-neck round-bottom flask equipped with magnetic stirring, reflux condenser, and nitrogen atmosphere was added the vinamidinium salt (0.300 g). Anhydrous DMF (2–3 mL) was added via syringe. Methyl thioglycolate (1.1–1.4 equiv) was added via microliter syringe. **CAUTION**: Handle methyl thioglycolate only in a good fume hood. The mixture was allowed to reflux overnight (15–18 h) under a nitrogen atmosphere. The flask was cooled to room temperature and the mixture was partitioned between ethyl acetate and saturated ammonium chloride (2×). The combined aqueous layers were extracted with fresh ethyl acetate, the combined ethyl acetate layers were then dried over sodium sulfate. The drying agent was filtered and the solvents removed in vacuo to give the crude material.
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11. Methyl 4-(4-chlorophenyl)-2-thiophenecarboxylate (**3c**): ^{1}H NMR 400 MHz ($CDCl_3$) δ 8.04 (d, 1H, J = 1.6 Hz), 7.64 (d, 1H, J = 1.6 Hz), 7.52 (d, 2H, J = 8.4 Hz), 7.39 (d, 2H, J = 8.4 Hz), 3.92 (s, 3H); HRMS calcd for $C_{12}H_9ClO_2S$ 252.0012, obsd 252.0018.
Methyl 4-(4-fluorophenyl)-2-thiophenecarboxylate (**3d**): ^{1}H NMR 400 MHz ($CDCl_3$) δ 8.03 (d, 1H, J = 1.6Hz), 7.59 (d, 1H, J = 2.0Hz), 7.54 (m, 2H), 7.11 (t, 2H, J = 8.8 Hz), 3.92 (s, 3H); HRMS calcd for $C_{12}H_9FO_2S$, 237.0386, obsd 237.0385.
Methyl 4-(4-methylphenyl)-2-thiophenecarboxylate (**3f**): ^{1}H NMR 400 MHz ($CDCl_3$) δ 8.06 (d, 1H, J = 1.2 Hz), 7.61 (d, 1H, J = 1.6 Hz), 7.48 (d, 2H, J = 8.0 Hz), 7.22 (d, 2H, J = 7.6 Hz), 3.91 (s, 3H), 2.38 (s, 3H); HRMS calcd for $C_{13}H_{12}O_2S$, 232.0558, obsd 232.0555.