STUDIES TOWARD ALKYLTHIOPHENE-2-CARBOXALDEHYDES. REDUCTION OF 3-ALKENYLTHIOPHENES WITH TRIETHYLSILANE/ TRIFLUOROACETIC ACID. REGIOSELECTIVITY IN FORMYLATION REACTIONS OF 3-ALKYLTHIOPHENES

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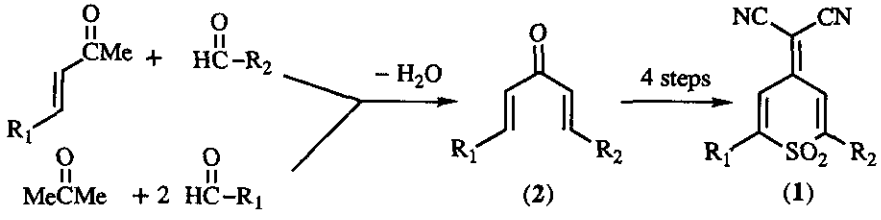
Abstract- Reduction of 2- or 3-alkenylthiophenes with Et_3SiH/CF_3CO_2H in CH_2Cl_2 gives the corresponding 2- or 3-alkylthiophene in >90% isolated yield. The regioselectivity of various Vilsmeier formylations of 3-alkylthiophenes was found to be a function of increasing steric bulk in the 3-alkyl substituent and in the Vilsmeier reagent . The regioselectivity of formylations of 3-alkylthiophenes by initial lithiation with butyllithium in ether followed by quenching with DMF is independent of the presence or absence of TMEDA.

INTRODUCTION

1,1-Dioxo-4-dicyanomethylene-2,6-disubstituted 4*H*-thiopyrans (**1**), which have been described as analogues of tetracyanoquinodimethane (TCNQ)[1] and have been utilized as electron-transport materials in electrophotographic applications,[2,3] display increased planarity in the neutral molecule and increased electron delocalization in the corresponding anion radicals when R_1 and/or R_2 are 2-thienyl substituents. We were interested in derivatives of (**1**) with alkyl-substituted 2-thienyl groups (branched alkyl substituents in particular), which might show improved solubility in various polymeric binders. In order to prepare such

compounds as shown in Scheme I, we sought highly regioselective routes to various 3-, 4-, and 5-alkylthiophene-2-carboxaldehyde derivatives.

Scheme I



The most direct approaches to such molecules are formylation reactions of alkylthiophenes.[4-6] One formylation procedure is the Vilsmeier reaction on 3-alkylthiophenes (**3**) to give **4** and **5** and on 2-alkylthiophenes (**6**) to give **7**.[4,6] Another formylation procedure is lithiation of the thiophene rings followed by quenching with an appropriate electrophile such as dimethylformamide (DMF).[5]

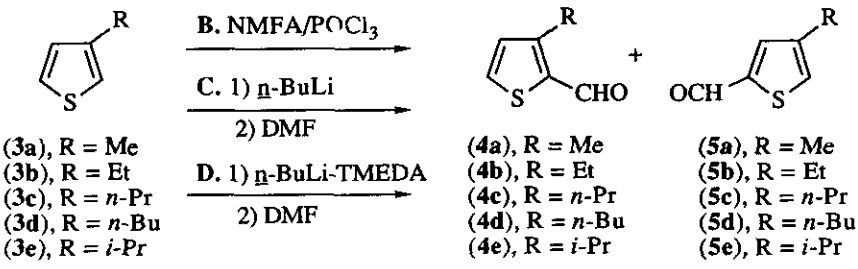
The claims of regioselectivity in these reactions have varied significantly. The 5-alkylthiophene-2-carboxaldehydes (**7**) have been prepared with greater than 95% regioselectivity under Vilsmeier conditions.[4,6] The syntheses of the methyl derivatives (**4a**) and (**5a**) have been the subject of many investigations with greatly varying claims of regioselectivity.[4,5] A Vilsmeier approach gives regiochemical preference to isomer (**4a**),[4,5a,b,d] while lithiation of **3a** followed by treatment with dimethylformamide (DMF) gives the 2,4-isomer (**5a**) as the regiochemically preferred isomer.[4,5g] Vilsmeier approaches to the isopropyl derivatives (**4e**) and (**5e**) have also been described.[7] A regioselective preparation of isopropyl derivative (**5e**) (95% selectivity) has been described, which involves bromination of **3e** followed by lithium-bromine exchange and reaction of the resulting thienyl lithium species with DMF.[7,8]

A second problem associated with the synthesis of alkyl-substituted thiophene-2-carboxaldehydes is the preparation of branched-alkyl substituents from alkenyl precursors. In our experience, heterogeneous hydrogenation catalysts are readily poisoned by the thiophene nucleus.

We have examined two aspects of the chemistry associated with alkylthiophene precursors to thiophene-2-carboxaldehydes. The regiochemical selectivities of four approaches to the formylation of 3-alkylthiophenes(**3**) shown in Scheme II have been calculated from integral ratios of the two isomers (**4**) and (**5**) as determined by 200 MHz ^{1}H nmr spectra. Two different Vilsmeier reagents with different steric bulk were examined

(Procedures A and B). Two different thiophene lithiation procedures with different butyllithium reagents followed by treatment with DMF were also examined (Procedures C and D). The reduction of alkenyl-substituted thiophene derivatives with triethylsilane and trifluoroacetic acid in dichloromethane was found to give excellent yields of 3-alkyl- (**3**) and 2-alkylthiophenes (**6**) with branched alkyl substituents as shown in Scheme III.

Scheme II.

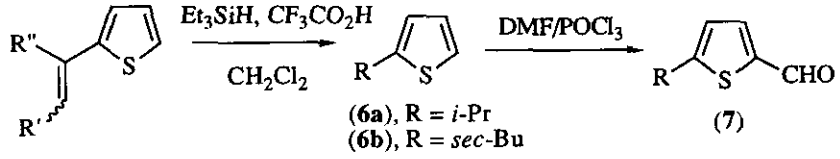


(**3a**), R = Me
(**3b**), R = Et
(**3c**), R = *n*-Pr
(**3d**), R = *n*-Bu
(**3e**), R = *i*-Pr

(**4a**), R = Me
(**4b**), R = Et
(**4c**), R = *n*-Pr
(**4d**), R = *n*-Bu
(**4e**), R = *i*-Pr

(**5a**), R = Me
(**5b**), R = Et
(**5c**), R = *n*-Pr
(**5d**), R = *n*-Bu
(**5e**), R = *i*-Pr

Scheme III.



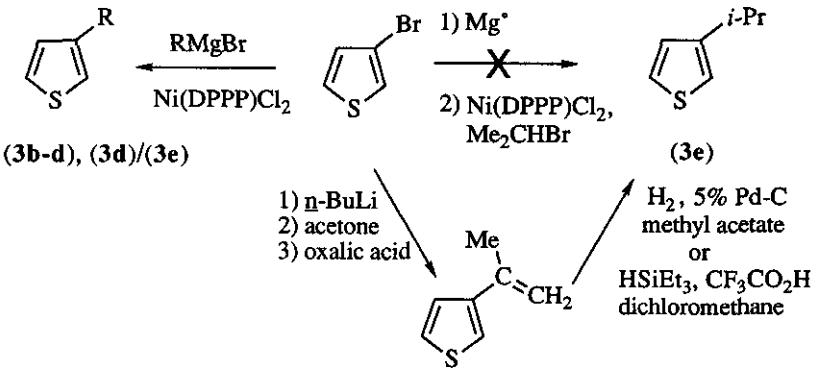
(**6a**), R = *i*-Pr
(**6b**), R = *sec*-Bu

(**7**)

RESULTS AND DISCUSSION

Preparation of 3-Alkylthiophenes (**3**). 3-Methylthiophene (**3a**) is commercially available (Aldrich). 3-Alkylthiophenes (**3b-d**) were prepared according to the procedure of Van Pham, Mark, and Zimmer as shown in Scheme IV.[9] The appropriate alkyl Grignard reagent was coupled to 3-bromothiophene with a catalytic quantity of [1,3-bis(diphenylposphino)propane]nickel(II) chloride [Ni(DPPP)Cl_2] in ether. The products were isolated as distilled, colorless oils in 58-75% isolated yield. Attempts to prepare 3-isopropylthiophene (**3e**) *via* this procedure gave 1:1 mixtures of 3-n-propyl- (**3c**) and 3-isopropylthiophene (**3e**). Preparation of the Grignard reagent of 3-bromothiophene and attempted coupling with 2-bromopropane in the presence of catalytic Ni(DPPP)Cl_2 gave thiophene and none of the desired product.

Scheme IV.



3-Isopropylthiophene (**3e**) was successfully prepared in several steps as shown in Scheme IV. Lithiation of 3-bromothiophene according to the procedure of Gronowitz, Cederlund, and Hörnfeldt[8] followed by addition of acetone and dehydration with oxalic acid gives 3-(2-propenyl)thiophene in 37% overall yield. Hydrogenation with 5% palladium on carbon in methyl acetate gave **3e** in 85% isolated yield, but additional catalyst needed to be added at frequent intervals during the hydrogenation, which suggests some poisoning by the thiophene. As an alternative procedure, we investigated the reduction of 3-(2-propenyl)thiophene with triethylsilane/ trifluoroacetic acid in dichloromethane. Reduction was nearly instantaneous and was mildly exothermic. The reagents and by-products of the reaction are volatile leaving 3-isopropylthiophene (**3e**) as the residue in essentially quantitative yield. Distillation gave **3e** in 92% isolated yield. This procedure was found to be equally successful for the reduction of 2-(2-propenyl)thiophene to give 2-isopropylthiophene (**6a**) in 90% isolated yield and for the reduction of 2-butenylthiophenes (a mixture of isomers) to give 2-sec-butylthiophene (**6b**) in 93% isolated yield.

Formylation Reactions of 3-Alkylthiophenes. Vilsmeier Reactions. The two Vilsmeier approaches compare the standard DMF-$POCl_3$ reagent system with the bulkier *N*-methylformanilide (NMFA)-$POCl_3$ reagent system.[5e] With 3-alkylthiophenes (**3**), the preferential site of electrophilic attack by the electrophilic species is the 2-position leading predominantly to 2,3-disubstituted products (**4**) (Table I). As the steric bulk of the 3-substituent increases, more of the 2,4-disubstituted products (**5**) are formed and the **4** : **5** ratio decreases. As shown in Table I, the bulkier NMFA-$POCl_3$ system provides slightly more of the 2,4-products (**5**) than does the DMF-$POCl_3$ system, which suggests that steric interactions are important. Formation of the 2,4-iosmers (**5**) should be sterically less demanding than formation of the 1,2-isomers (**4**). Attempts to use even sterically

more demanding reagents such as *N,N*-diphenylformamide or *N,N*-diisopropylformamide with $POCl_3$ were fruitless, as no product formation was observed, even after extended periods of heating. The 3-alkylthiophene-2-carboxaldehydes (**4**) were separated from the 4-alkyl isomer via careful chromatography on activated silica gel eluted with 10% ethyl acetate in hexanes and were isolated in greater than 60% isolated yield. The (**4e**)/(**5e**) mixtures were not efficiently separated by chromatography on silica gel.

Table I. Regiochemical selectivity for the formylation of 3-alkylthiophene (**3**) as determined by 200 MHz ^1H nmr. Isolated yields of the mixture are given in parentheses. Numbers are the average of two or more runs.

Reagents	(4a):(5a)	(4b):(5b)	(4c):(5c)	(4d):(5d)	(4e):(5e)
DMF/$POCl_3$	86 : 14	74 : 26	78 : 22	73 : 27	52 : 48
	(99)	(94)	(80)	(87)	(93)
NMFA/$POCl_3$	75 : 25	67 : 33	64 : 36	64 : 36	42 : 58
	(98)	(95)	(78)	(97)	(97)
n-BuLi, DMF	18 : 82	11 : 89	11 : 89	9 : 91	4 : 96
	(97)	(85)	(85)	(85)	(82)
n-BuLi/TMEDA,	11 : 89	14 : 86	10 : 90	10 : 90	5 : 95
DMF	(84)	(80)	(84)	(85)	(84)

Lithiation Reactions. Regioselectivity opposite to that observed in the Vilsmeier reactions is obtained upon lithiation of 3-alkylthiophenes (**3**) in ether at ambient temperature followed by the addition of DMF as shown in Table I. Surprisingly, the use of tetramethylethylenediamine with n-butyllithium (BuLi/TMEDA) had little if any effect on the regioselectivity of reaction (Table I). Increased steric bulk at the 3-position gives increased regioselectivity for the 2,4-product, which suggests that kinetic acidity is product determining. The 4-alkylthiophene-2-carboxaldehydes (**5**) were separated from the 3-alkyl isomer *via* chromatography on activated silica gel eluted with 10% ethyl acetate in hexanes and were isolated in greater than 70% isolated yield.

The absence of any significant effect from the addition of TMEDA is somewhat surprising. It is well-recognized that aggregation of organolithium reagents occurs in organic solvents (as tetrameric units for alkyllithiums in ethereal solvents) and that the aggregation affects both steric bulk and reactivity.[10] The addition of coordinating species such as TMEDA or hexamethylphosphoramide (HMPA) can convert tetrameric or higher aggregates to dimers and even monomers and can dramatically affect product ratios.[10-12]

Although one might expect lihiation products from butyllithium and thiophenes to reflect kinetic control, the

absence of any effect from added TMEDA suggests that thermodynamic control may be operative. However, exchange rates of H1 and H5 for 3-isopropylthiophene (**3e**) for deuterium were not a factor of 20 different but were nearly identical in NaOMe/MeOD, which suggests that thermodynamic acidity is not product-ratio determining in the lithiation procedures. If the thiophene sulfur atom were to break up higher aggregates by coordination to the organolithium reagent, then the addition of TMEDA might have little effect on the observed regioselectivity and reactivity.

EXPERIMENTAL

General Experimental. ^{1}H Nmr spectra were recorded on a Varian Gemini-200 (200 MHz) instrument in deuteriochloroform ($CDCl_3$) with chloroform (7.26 ppm) as an internal reference. Chemical shifts are in ppm (δ); multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), sext (sextet), hept (heptet), m (multiplet); coupling constants, *J*, are reported (Hz); proton count is based on integration. Product ratios were determined by integration of the 200 MHz ^{1}H nmr spectra. Elemental analyses are reported only for previously unknown compounds. However, nmr, infrared, and mass spectral characterization is provided for all molecules for which such data has not been previously described. Infrared spectra were recorded on a Perkin-Elmer 298 Infrared Spectrophotometer. Peak positions are reported (cm^{-1}). Mass spectra were obtained by the Eastman Chemical Analytical Technology Division. Column chromatography was performed by the method of Still[13] with 32-63 μm silica gel (ICN Biomedicals). Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Bulb-to-bulb distillations were done in a coffee pot Kugelrohr, and boiling points correspond to uncorrected, air bath temperatures. All reactions were performed under a dry, argon atmosphere in oven-dried glassware.

N-Methylformanilide (NMFA), anhydrous ether 99+%, anhydrous dichloromethane 99+%, butyllithium (2.5 M in hexanes), [1,3-bis(diphenylphosphino)propane]nickel(II) chloride ($Ni(DPPP)Cl_2$), triethylsilane, and 3-methylthiophene were obtained from the Aldrich Chemical company and were used without further purification. 3-Bromothiophene was obtained from the Aldrich Chemical Company and was distilled prior to use. Phosphorous oxychloride, magnesium turnings, 2,4-dinitrophenylhydrazine, methyl acetate, 5 % palladium on carbon (Pd/C), bromoethane, 1-bromopropane, and 1-bromobutane were obtained from the Eastman Chemical Company and were used without further purification. *N,N*-Dimethylformamide was obtained from the Eastman Chemical Company and was dried over 3Å molecular sieves prior to use. Tetramethylethylenediamine

(TMEDA) was distilled from CaH_2 and stored over 3Å molecular sieves prior to use. Solvents used for extractions and chromatography were reagent grade and were used without purification. "Brine" refers to a saturated aqueous solution of NaCl. 2,4-Dinitrophenylhydrazones (2,4-DNP) were prepared from the thiophene aldehydes according to the method given in Fieser and Fieser[14] and were recrystallized from ethyl acetate.

Preparation of 3-alkylthiophenes (**3b-d**). Compounds (**3b-d**) were prepared according to the method of Van Pham, Mark, and Zimmer.[9] Magnesium turnings (1.34 g, 55.2 mmol) were dried and activated by heating and stirring under a stream of argon for 1 h. Ether (100 ml) was added, and the alkyl Grignard reagent was prepared from the corresponding 1-bromoalkane (60.7 mmol). When most or all of the magnesium had disappeared, $Ni(DPPP)Cl_2$ (33 mg) was added, and then the 3-bromothiophene (8.15 g, 50.0 mmol) was added dropwise. The reaction was refluxed for 15 hours and then quenched by pouring into a 2 N HCl/ice mixture (50 ml). After workup with diethyl ether, the solvent was removed by distillation under argon. The residues were distilled at 20 torr to afford the 3-alkylthiophene as a colorless oil (58-75%).

For (**3b**): 74%, bp 87-92 °C at 20 torr.[15]

For (**3c**): 75%, bp 98-100 °C at 20 torr.[15]

For (**3d**): 58%, bp 127-133 °C at 20 torr.[16]

The use of 2-bromopropane in the procedure above gave a 1:1 mixture of 3-*n*-propylthiophene (**3c**) and 3-isopropylthiophene (**3e**). Preparation of the Grignard reagent from 3-bromothiophene coupled with 2-bromopropane under the conditions described above gave none of the desired product (**3e**) and significant quantities of thiophene.

3-Isopropylthiophene (**3e**) A. Hydrogenation with Palladium on Carbon. 3-(2-Propenyl)thiophene (16.0 g, 129 mmol), prepared according to the method of Gronowitz, Cederlund, and Hörnfeldt,[8] was placed in a Parr shaker bottle along with 5 % Pd/C (4.0 g) and methyl acetate (150 ml). The reaction was allowed to proceed under an atmosphere of hydrogen (56 psi) for 4 h, at which time an additional 2.0 g of 5% Pd/C was added. The reaction was allowed to proceed under an atmosphere of hydrogen (56 psi) for an additional 4 h, at which time the suspension was filtered through a pad of Celite. After removal of the solvent by distillation under an atmosphere of argon, the residue distilled from 95-97 °C at 20 torr to afford 13.8 g of **3e** as a colorless oil (85%). ^1H Nmr data agree with the published results.[8]

B. Hydrogenation with Triethylsilane/Trifluoroacetic Acid. 3-(2-Propenyl)thiophene (12.4 g, 100 mmol) and triethylsilane (17.5 g, 150 mmol) were dissolved in 100 ml of dichloromethane. Trifluoroacetic acid (18.5 g, 150 mmol) and a catalytic amount of trifluoroacetic anhydride (0.25 g, 1.0 mmol) in 25 ml of dichloromethane were added dropwise. The reaction was mildly exothermic. After addition was complete, the reaction mixture was stirred 5 min at ambient temperature and was concentrated. Distillation of the residue gave 11.6 g (92%) of **3e** as a colorless oil, bp 95-100 °C at 20 torr.[8]

The procedure was repeated with 2-(2-propenyl)thiophene (12.4 g, 100 mmol) to give 11.4 g (90%) of **6a** as a colorless oil, bp 102-104 °C at 20 torr.[8]

The procedure was repeated with 2-(2-butenyl)thiophene (20.0 g, 145 mmol) to give 19.1 g (93%) of **6b** as a colorless oil, bp 38-42 °C at 1.0 torr: ^{1}H Nmr ($CDCl_3$) δ 7.11 (dxd, 1 H, J = 1, 5 Hz), 6.91 (dxd, 1 H, J = 3, 5 Hz), 6.78 (dxd, 1 H, J = 1, 3 Hz), 2.92 (sext, 1 H, J = 7 Hz), 1.64 (m, 2 H), 1.30 (d, 3 H, J = 7 Hz), 0.87 (t, 3H, J = 7 Hz); ir (neat, NaCl) 2963, 2928, 2875, 1454, 1441, 1378, 1234, 853, 821, 691 cm^{-1}; *m/z* 140 (M^+). Anal. Calcd for $C_8H_{12}S$: C, 68.51; H, 8.63; S, 22.87. Found: C, 68.66; H, 8.61; S, 22.46.

Preparation of 2-(2-Propenyl)thiophene. n-Butyllithium (240 ml of 2.5 M in hexanes, 600 mmol) was added dropwise to a stirred solution of thiophene (55.5 g, 660 mmol) in 1 l of THF cooled to -78 °C. The resulting solution was stirred for 1.5 h at -78 °C. Acetone (43.0 g, 740 mmol) in 100 ml of THF was added. The resulting solution was stirred for 1 h at -78 °C and was then warmed to ambient temperature over a 2-h period. The reaction mixture was quenched by the slow addition of 1 l of saturated ammonium chloride solution. The organic phase was separated and the products were extracted with ethyl acetate (3 x 500 ml). The combined organic extracts were washed with brine, dried over magnesium sulfate, and concentrated. The residue was purified by distillation to give 68.3 g (80.0%) of a colorless oil, bp 50-55 °C at 1 torr, which crystallized upon standing.

The alcohol was dissolved in 1 l of dry pyridine. Methanesulfonyl chloride (107.9 g, 942 mmol) was added dropwise over 20 min. The reaction was cooled in an ice bath. The cooling bath was removed and stirring was continued for 1 h. The reaction mixture was poured onto 1 l of ice water. The products were extracted with ether (3 x 400 ml). The combined organics were washed with 2 N HCl (3 x 300 ml) and saturated sodium bicarbonate (2 x 300 ml), were dried over magnesium sulfate, and concentrated. The residue was purified by distillation to give 47.7 g (82%) of 2-(2-propenyl)thiophene as a colorless oil, bp 30-33 °C at 1 torr.[8]

Preparation of 2-Butenylthiophenes. n-Butyllithium (40 ml of 2.5 M in hexanes, 100 mmol) was added dropwise to a stirred solution of thiophene (9.26 g, 110 mmol) in 150 ml of THF cooled to -78 °C. The resulting solution was stirred for 1.5 h at -78 °C. 2-Butanone (8.88 g, 123 mmol) in 20 ml of THF was added. The resulting solution was stirred for 1 h at -78 °C and was then warmed to ambient temperature over a 2 h period. The reaction mixture was quenched by the slow addition of 150 ml of saturated ammonium chloride solution. The organic phase was separated and the products were extracted with ethyl acetate (3 x 150 ml). The combined organic extracts were washed with brine, dried over magnesium sulfate, and concentrated. The residue was purified by distillation to give 14.1 g (90.0%) of a colorless oil, bp 49-54 °C at 0.2 torr, which crystallized upon standing.

The alcohol (12.0 g, 77.0 mmol) was dissolved in 150 ml of ether. The resulting solution was stirred for 1 h over 100 ml of 10% HCl. The organic phase was separated and the aqueous phase was extracted with 100 ml of ether. The combined ether extracts were washed with saturated sodium bicarbonate solution (3 x 100 ml) and brine, were dried over magnesium sulfate, and concentrated. The residue was purified by distillation to give 7.80 g (73%) of 2-butenylthiophenes as a colorless oil, bp 58-62 °C at 1 torr. By ^{1}H nmr, there is a 6:1 mixture cis and trans isomers of the 2-(2-butenyl)thiophenes and trace amounts of 2-(1-butenyl)thiophene. For the major component of the 6:1 mixture: ^{1}H Nmr ($CDCl_3$) δ 7.07 (m, 1 H), 6.95 (m, 2 H), 6.00 (q + other splittings, 1 H, J = 7 Hz), 2.02 (t, 3 H, J = 1 Hz), 1.77 (dxd, 3 H, J = 1, 7 Hz). For the minor component of the 6:1 mixture: ^{1}H Nmr ($CDCl_3$) δ 5.61 (q +, 1 H), 2.12 (t, 3 H), 1:88 (dxd, 3 H); ir (mixture, neat, NaCl) 3085, 2980, 2925, 2870, 1441, 1380, 1353, 1329, 849, 810, 690 cm^{-1}; *m/z* 138 (M^+). The mixture of isomers gave a satisfactory elemental analysis: Anal. Calcd for $C_8H_{10}S$: C, 69.21; H, 7.26; S, 23.53. Found: C, 68.96; H, 7.61; S, 23.46.

Formylation of 3-Alkylthiophenes Using POCl3/DMF. Procedure A. Standard Vilsmeier conditions were employed,[7] and a typical procedure follows. To the *N,N*-dimethylformamide (0.77 g, 10.5 mmol) was added phosphorous oxychloride (1.61 g, 10.5 mmol). The mixture was stirred at room temperature for one hour, at which time the 3-alkylthiophene (7.00 mmol) was introduced. The reaction was stirred at room temperature for one hour, then at 100 °C for 1 h. The reaction mixture was cooled to room temperature, diluted with 50 ml of CH_2Cl_2, and poured into 50 ml saturated $NaHCO_3$. The organic phase was drawn off, and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine (1x) and dried over $MgSO_4$. After concentration on a rotary evaporator, the residue was purified by flash column

chromatography (hexanes/EtOAc) to afford a mixture of 3- and 4-alkylthiophene-2-carboxaldehydes. Careful chromatography (10% EtOAc/hexanes) allowed the separation of the pure 3-alkylthiophene-2-carboxaldehyde (**4**).

Formylation of 3-alkylthiophenes using POCl3/NMFA. Procedure B. The general procedure of Weston and Michaels[5c] was followed. To the *N*-methylformanilide (0.82 g, 6.07 mmol) was added phosphorous oxychloride (0.93 g, 6.07 mmol). The yellow mixture was allowed to stand for 30 min, at which time the 3-alkylthiophene (6.68 mmol) was introduced. After stirring for 17 h, the reaction was diluted with 30 ml of CH_2Cl_2 and was poured into 30 ml of ice water. The organic layer was drawn off, and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organics were washed with 2 N HCl (2x), and the acidic layers were extracted with CH_2Cl_2 (2x). The organic layers were further washed with saturated $NaHCO_3$ (2x), and then with brine (1x). After drying ($MgSO_4$), the solvent was removed on a rotary evaporator, and the resulting residue was purified by flash column chromatography (hexanes/EtOAc) to afford a mixture of 3- and 4-alkylthiophene-2-carboxaldehydes.

Formylation of 3-alkylthiophenes using n-BuLi/DMF. Procedure C. The general lithiation prodedure of Gronowitz was followed.[8] To a solution of the 3-alkylthiophene (7.0 mmol) in ether (7 ml) was added the n-butyllithium (7.0 mmol) at such a rate that a slight reflux was maintained. The reaction was then heated to reflux for 15 minutes, the heat source was removed, and the *N,N*-dimethylformamide (0.70 ml, 9.1 mmol), was added in a solution of diethyl ether (3.5 ml). After stirring for 4 h, the reaction was quenched by the addition of 20 ml of saturated NH_4Cl. The organic layer was drawn off, and the aqueous layer was extracted with ether (3x). The combined organic extracts were washed with brine (1x), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc) to afford a mixture of 3- and 4-alkylthiophene-2-carboxaldehydes. Careful chromatography on freshly activated silica gel (10% EtOAc/hexanes) allowed the separation of the pure 4-alkylthiophene-2-carboxaldehyde (**5**).

Formylation of 3-alkylthiophenes using n-BuLi/TMEDA/DMF. Procedure D. The general lithiation prodedure of Gronowitz was followed.[8] To a solution of the 3-alkylthiophene (7.0 mmol) in ether (7 ml) was added a mixture of n-butyllithium (7.0 mmol) and TMEDA (0.90 g, 7.7 mmol) at such a rate that a slight reflux was maintained. The reaction was then heated to reflux for 15 minutes, the heat source was removed, and the *N,N*-dimethylformamide (0.70 ml, 9.1 mmol), was added in a solution of ether (3.5 ml). After stirring for 4 h, the reaction was quenched by the addition of 20 ml saturated NH_4Cl. The organic layer was drawn off, and the

aqueous layer was extracted with ether (3x). The combined organic extracts were washed with brine (1x), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc) to afford a mixture of 3- and 4-alkylthiophene-2-carboxaldehydes.

The spectral characterization of many of the thiophene carboxaldehydes is described below for the first time although many of these compounds have been known in the literature for some time.[15,16]

3-Methyl-2-thiophenecarboxaldehyde (**4a**). ^{1}H Nmr of the major product ($CDCl_3$) δ 10.05 (d, 1 H, J = 1.1 Hz), 7.63 (dxd, 1 H, J = 1.1, 4.9 Hz), 6.97 (d, 1 H, J = 4.9 Hz), 2.58 (s, 3 H); ir (neat, NaCl) 1660 cm^{-1}; *m/z* 126 (M^+); bp (air bath temperature)60-63°C at 0.3 torr; 2,4-DNP of **4a** : mp 211-213 °C; Anal. Calcd for $C_{12}H_{10}N_4O_4S$: C, 47.05; H, 3.29; N, 18.29. Found: C, 47.47; H, 3.32; N, 18.51.

3-Ethyl-2-thiophenecarboxaldehyde (**4b**). ^{1}H Nmr ($CDCl_3$) δ 10.04 (d, 1 H, J = 1.1 Hz), 7.65 (dxd, 1 H, J = 5.0 Hz, 1.1 Hz), 7.04 (d, 1 H, J = 5.0 Hz), 2.99 (q, 2 H, J = 7.6 Hz), 1.30 (t, 3 H, J = 7.6); ir (neat, NaCl) 1660 cm^{-1}; *m/z* 140 (M^+); bp (air bath temperature) 70-75 °C at 0.3 torr; 2,4-DNP of **4b** : mp 191-193 °C; Anal. Calcd for $C_{13}H_{12}N_4O_4S$: C, 48.75; H, 3.78; N, 17.49. Found: C, 48.49; H, 3.91; N, 17.39.

3-Propyl-2-thiophenecarboxaldehyde (**4c**). ^{1}H Nmr ($CDCl_3$) δ 10.04 (d, 1 H, J = 1.1 Hz), 7.64 (dxd, 1 H, J = 1.1, 5.0 Hz), 7.01 (d, 1 H, J = 5.0 Hz), 2.94 (t, 2 H, J = 7.6 Hz), 1.70 (m, 2 H), 0.97 (t, 3 H, J = 7.3 Hz); ir (neat, NaCl) 1660 cm^{-1}; *m/z* 154 (M^+); bp (air bath temperature) 80 °C at 0.3 torr; 2,4-DNP of **4c** : mp 173-175 °C; Anal. Calcd for $C_{14}H_{14}N_4O_4S$: C, 50.29; H, 4.22; N, 16.76. Found: C, 49.95; H, 4.12; N, 16.46.

3-Butyl-2-thiophenecarboxaldehyde (**4d**). ^{1}H Nmr ($CDCl_3$) δ 10.04 (d, 1 H, J = 1.2 Hz), 7.64 (dxd, 1 H, J = 1.1, 5.0 Hz), 7.01 (d, 1 H, J = 5.0 Hz), 2.97 (t, 2 H, J = 7.6 Hz), 1.64 (m, 2 H), 1.37 (m, 2 H), 0.93 (t, 3 H, J = 7.2 Hz); ir (neat) 1660 cm^{-1}; *m/z* 168 (M^+); bp 75-78 °C at 0.3 torr; 2,4-DNP of **4d** : mp 158-161 °C; Anal. Calcd for $C_{15}H_{16}N_4O_4S$: C, 51.71; H, 4.63; N, 16.08. Found: C, 51.75; H, 4.32; N, 16.27.

3-Isopropyl-2-thiophenecarboxaldehyde (**4e**). ^{1}H Nmr ($CDCl_3$) δ 10.10 (dxd, 1 H, J = 0.3, 1.1 Hz), 7.65 (dxdxd, 1 H, J = 0.5, 1.1, 5.1 Hz), 7.11 (dxd, 1 H, J = 0.4, 5.1 Hz, 1 H), 3.66 (hept, 1 H, J = 6.9 Hz), 1.32 (d, 6 H, J = 6.9 Hz); ir (neat, NaCl) 1660 cm^{-1}; *m/z* 154 (M^+); bp of mixture (air bath temperature) 75-80 °C at 0.3 torr.; 2,4-DNP of **4d** : mp 65-80 °C; Anal.(of mixture) Calcd for $C_{14}H_{14}N_4O_4S$: C, 50.29; H, 4.22; N, 16.76. Found: C, 50.75; H, 4.22; N, 16.27.

4-Methyl-2-thiophenecarboxaldehyde (**5a**). ^{1}H Nmr ($CDCl_3$) δ 9.87 (d, 1 H, J = 1.3 Hz), 7.36 (d, 1 H, J = 1.5 Hz), 7.36 (dxd, 1 H, J = 1.3, 1.5 Hz), 2.32 (s, 3 H); ir (neat, NaCl) 1660 cm^{-1}; *m/z* 126 (M^+); bp of

mixture (air bath temperature) 55-60 °C at 0.4 torr; 2,4-DNP of **5a** : mp 233-234 °C; Anal. Calcd for $C_{12}H_{10}N_4O_4S$: C, 47.05; H, 3.29; N, 18.29. Found: C, 47.32; H, 3.23; N, 18.41.

4-Ethyl-2-thiophenecarboxaldehyde (**5b**). ^{1}H Nmr ($CDCl_3$) δ 9.88 (d, 1 H, *J* = 1.3 Hz), 7.63 (d, 1 H, *J* = 1.5 Hz), 7.39 (m, 1 H), 2.68 (q, 2 H, *J* = 7.6 Hz), 1.27 (t, 3 H, *J* = 7.6); ir (neat, NaCl) 2980, 2940, 1670, 1470, 1390, 1240, 1190, 1130, 860, 670 cm^{-1}; *m/z* 140 (M^+); bp (air bath temperature) 70 °C at 0.5 torr; 2,4-DNP of **4b** : mp 185-186 °C; Anal. Calcd for $C_{13}H_{12}N_4O_4S$: C, 48.75; H, 3.78; N, 17.49. Found: C, 48.40; H, 4.01; N, 17.28.

4-Propyl-2-thiophenecarboxaldehyde (**5c**). ^{1}H Nmr ($CDCl_3$) δ 9.88 (d, 1 H, *J* = 1.3 Hz), 7.60 (d, 1 H, *J* = 1.5 Hz), 7.37 (m, 1 H), 2.62 (t, 2 H, *J* = 7.6 Hz), 1.66 (m, 2 H), 0.95 (t, 3 H, *J* = 7.3 Hz); ir (neat, NaCl) 2980, 2940, 2880, 1660, 1440, 1390, 1240, 1190, 1140, 670 cm^{-1}; *m/z* 154 (M^+); bp (air bath temperature) 70 °C at 0.5 torr; 2,4-DNP of **5c** : mp 186-187 °C; Anal. Calcd for $C_{14}H_{14}N_4O_4S$: C, 50.29; H, 4.22; N, 16.76. Found: C, 49.85; H, 4.18; N, 16.97.

4-Butyl-2-thiophenecarboxaldehyde (**5d**). ^{1}H Nmr ($CDCl_3$) δ 9.87 (d, 1 H, *J* = 1.3 Hz), 7.61 (d, 1 H, *J* = 1.5 Hz), 7.37 (m, 1 H), 2.65 (t, 2 H, *J* = 7.6 Hz), 1.64 (m, 2 H), 1.37 (m, 2 H), 0.93 (t, 3 H, *J* = 7.2); ir (neat, NaCl) 1660 cm^{-1}; *m/z* 168 (M^+); bp 75-78 °C at 0.3 torr; Anal. Calcd for $C_9H_{12}OS$: C, 64.24; H, 7.19; Found: C, 63.97; H, 7.51.

4-Isopropyl-2-thiophenecarboxaldehyde (**5e**). ^{1}H Nmr ($CDCl_3$) δ 9.88 (d, 1 H, *J* = 1.2 Hz), 7.67 (d, 1 H, *J* = 1.5 Hz), 7.40 (m, 1 H), 3.00 (hept, 1 H, *J* = 6.9 Hz), 1.27 (d, 6 H, *J* = 6.9 Hz); ir (neat, NaCl) 2980, 1660, 1470, 1430, 1390, 1240, 1200, 1170 cm^{-1}; *m/z* 154 (M^+); bp (air bath temperature) 70 °C at 0.3 torr; 2,4-DNP of **5e** : mp 201-202 °C; Anal. Calcd for $C_{14}H_{14}N_4O_4S$: C, 50.29; H, 4.22; N, 16.76. Found: C, 49.85; H, 4.18; N, 16.97.

REFERENCES

1. C. H. Chen, G. A. Reynolds, H. R. Luss, and J. H. Perlstein, *J. Org. Chem.*, **1986**, *51*, 3282.
2. M. Scozzafava, C. H. Chen, G. A. Reynolds, and J. H. Perlstein, *U. S. Patent*, 4,514, 481 (1985) (Chem. Abstr., 1985, 79452a).
3. M. R. Detty, J. A. Sinicropi, J. R. Cowdery, and R. H. Young *U. S. Patent*, 5,300,385 (1994) (Chem. Abstr., 1994, 46586r).

4. Y. Poirier, L. Legrand, and N. Lozac'h, *Bull. Soc. Chim. Fr.*, **1966**, *3*, 1054.

5. (a) W. J. King and F. F. Nord, *J. Org. Chem.*, **1948**, *13*, 635; (b) H. D. Hartough and J. J. Dickert, Jr., *J. Am. Chem. Soc.*, **1949**, *71*, 3922; (c) A. W. Weston and R. J. Michaels, Jr., *J. Am. Chem. Soc.*, **1950**, *72*, 1422; (d) E. Campaigne and W. L. Archer, *J. Am. Chem. Soc.*, **1953**, *75*, 989; (e) S. Gronowitz, P. Moses, A.-B. Hörnfeldt, and R. Hakansson, *Arkiv Kemi*, **1961**, *17*, 165; (f) L.-Y. Chia and W. R. McWhinnie, *J. Organomet. Chem.*, **1980**, *188*, 121; (g) J. Sicé, *J. Org. Chem.*, **1954**, *19*, 70; (h) Y. Tominaga, R. N. Castle, and M. L. Lee, *J. Heterocycl. Chem.*, **1982**, *19*, 1125-1130; (i) J. Lamy, D. Lavit, and Ng. Ph Buu-Hoï, *J. Chem. Soc.*, **1958**, 4202.

6. Reviews: (a) V. I. Minkin and G. N. Dorofeenko, *Russ. Chem. Rev.*, **1960**, *29*, 599; (b) M.-R. de Maheas, *Bull. Soc. Chim. Fr.*,**1962**, 1989.

7. R. M. Kellogg and J. Butler, J. *J. Org. Chem.*, **1971**, *36*, 2236.

8. S. Gronowitz, B. Cederlund, and A.-B. Hörnfeldt, *Chem. Script.*, **1974**, *5*, 217.

9. C. Van Pham, H. B Mark, and H. Zimmer, *Synth. Commun.*, **1986**, *16*, 689.

10. For organolithium structure: E. Weiss and G. Hencken, *J. Organomet. Chem.*, **1970**, *21*, 265; H. Dietrich, *Acta Cryst.*, **1963**, *16*, 681; H. Hope and P. P. Power, *J. Am. Chem. Soc.*, **1983**, *105*, 5320; G. Fraenkel, M. Henrichs, M. Hewitt, and B. M. Su, *J. Am. Chem. Soc.*, **1984**, *106*, 255; J. F. McGarrity and C. A. Ogle, *J. Am. Chem. Soc.*, **1984**, *106*, 1805; W. Bauer, W. R. Winchester, and P. v. R. Schleyer, *Organometallics*, **1987**, *6*, 2371.

11. With added TMEDA: J. Heinzer, J. F. M. Oth, and D. Seebach, *Helv. Chim. Acta*, **1985**, *68*, 1848; D. Seebach, R. Hässig, and J. Gabriel, *Helv. Chim. Acta*, **1983**, *66*, 308; M. Schlosser, 'Struktur und Reactivität polarer Organometalle,' Springer-Verlag, Berlin, 1973; A. J. Pearson and M. K. M. Babu, *Organometallics*, **1994**, *13*, 2539.

12. With added HMPA: H. J. Reich, J. P. Borst, R. R. Dykstra, and D. P. Green, *J. Am. Chem. Soc.*, **1993**, *115*, 8728.

13. W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **1978**, *43*, 2923.

14. L. F. Fieser and M. Fieser, 'Reagents for Organic Synthesis,' Vol. 1, Wiley, New York, 1967, p. 330.

15. H. Scheibler and M. Schmidt, *Chem. Ber.*, **1921**, 139.

16. H. Scheibler and F. Rettig, *Chem Ber.*, **1926**, 1194.

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