An expedient synthesis of thienylacetic acids using the Willgerodt-Kindler reaction under PTC conditions

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Abstract
Novel (5-aryl-2-methylthiophen-3-yl)acetic acids were synthesized starting from 3-aryl-3-chloroacrylaldehydes via corresponding thienylcarbaldehydes and thienylethanones using Willgerodt-Kindler reaction under phase-transfer conditions. Their structures were established based on the data of ^{1}H, ^{13}C NMR, IR spectroscopy and mass-spectrometry.

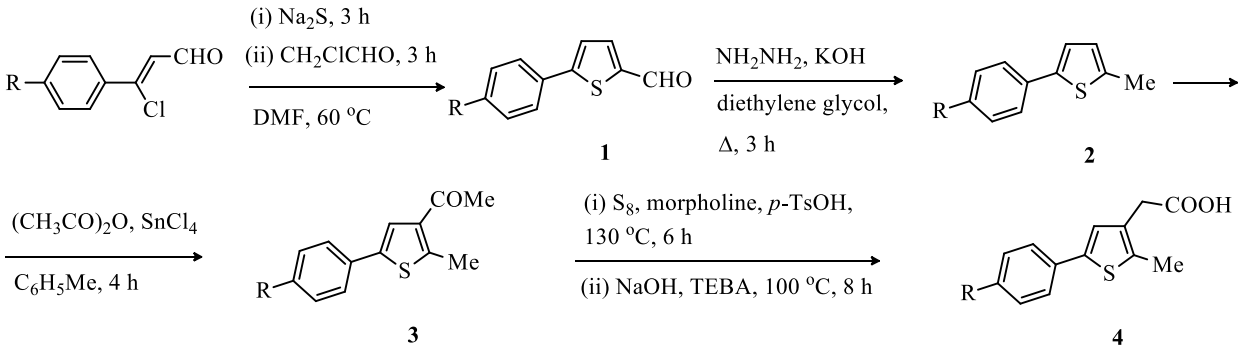
Keywords: 3-Thienylacetic acids, Willgerodt–Kindler reaction, phase-transfer catalysis

Introduction

Derivatives of 3-thienylacetic acids are important intermediates in the synthesis of drugs,[1] pesticides[2] and multifunctional photochromic molecular systems possessing fluorescent,[3-5] magnetic[6] and complexing properties.[7] The basic methods used for the synthesis of these compounds are based on hydrolysis of the corresponding nitriles,[8] the reduction of ketoacids,[9] Arndt-Eistert[10] and Willgerodt–Kindler[11] reactions. The Willgerodt–Kindler reaction is usually applied for the preparation of (thio)amides, carboxylic acids, and heterocycles.[12] At the same time because of the low yields of the targeted compounds and formation of complex reaction mixtures[13] this reaction has not been more widely employed in organic synthesis. Only a few papers have been published on application of this method for the synthesis of arylacetic acids performed under conditions of the phase-transfer catalysts (PTC).[14] Herein we report an expedient procedure for the synthesis of 5-arylsubstituted 3-thienylacetic acids starting from 3-aryl-3-chloroacrylaldehydes via corresponding thienylcarbaldehydes and thienylethanones based on the Willgerodt-Kindler reaction under PTC conditions.

Results and Discussion

No convenient and unequivocally characterized method for the preparation of 5-arylthiophene-2-carbaldehydes has yet been developed.[15-19] Aldehyde **1a** was previously synthesized by the Vilsmeier formylation of 5-(4-chlorophenyl)thiophene,[16] but no spectral data on the prepared compound were presented. The usually used Suzuki cross-coupling reaction of thienylboronic acids with bromothienyl compounds requires an inert gas atmosphere, palladium catalyst $Pd(PPh_3)_4$ and takes a long reaction time.[20] Thus, this reaction for the synthesis of aldehyde **1b** proceeds in 47 h (yield 31%). Our approach to the synthesis of 5-arylthiophene-2-carbaldehydes involves interaction of 3-chloro-3-arylacrylaldehydes with sodium sulfide and chloroacetaldehyde in DMF to give the compounds **1a,b** in 44-59% yields (Scheme 1). The reaction time of the general procedure for preparation of **1a,b** has been shortened to 6.5 hours.



Scheme 1. Synthesis of 3-thienylacetic acids **4a,b**.

2-Methyl-5-(4-chlorophenyl)thiophene **2a** was previously obtained by the treatment of 2-methyl-5-(4-chlorophenyl)furan with hydrogen sulfide under conditions of acid catalysis.[21] The reaction time was 48.5 h and the yield 54%. A significant drawback of this reaction is the presence in the reaction mixture of products of hydrolytic cleavage of the furans. We reduced aldehydes **1a,b** by hydrazine hydrate via Kishner-Wolff reaction which led to 2-methyl-5-arylthiophenes **2a,b** in 30-40% yields after 3h reflux of diethylene glycol solution. Acylation of **2a,b** with acetic anhydride in toluene in the presence of $SnCl_4$ gave rise to 1-(2-methyl-5-(arylthiophen-3-yl)ethanones **3a,b** in 41-84% yields. Then these compounds were exposed to the Willgerodt-Kindler reaction with sulfur and morpholine followed by the treatment of aqueous sodium hydroxide in the presence of a phase-transfer catalyst (benzyltriethylammonium chloride, TEBA) which produced 2-(2-methyl-5-(4-chlorophenyl)thiophen-3-yl)acetic acids **4a,b** in moderate 53-64% yields. The described synthetic protocol (Scheme 1) allows preparation of various functionalized 5-aryl substituted thienylacetic acids starting from the corresponding 3-aryl-3-chloroacrylaldehydes.

To evaluate the effectiveness of the Willgerodt-Kindler reaction under PTC conditions, we synthesized the known 2-(2,5-dimethylthiophen-3-yl)acetic acid (**4c)** and 2-(5-(4-bromophenyl)-2-methylthiophen-3-yl)acetic acid (**4d**). These compounds were previously obtained from 1-(2,5-dimethylthiophen-3-yl)ethanone[22] and 1-(5-(4-chlorophenyl)-2-methylthiophen-3-yl)ethanone,[13] correspondingly, in two steps including isolation of 2-(2,5-dimethylthiophen-3-yl)-1-morpholinoethanethione and 2-(5-(4-bromophenyl)-2-methylthiophen-3-yl)-1-morpholino-ethanethione and there subsequent hydrolysis. The above-described one-pot synthetic procedure led to acids **4c** and **4d** in good yields. The structures of the synthesized compounds **1-4** were confirmed by the data of ^{1}H, ^{13}C NMR and IR spectra**.**

Conclusions

We report on the expedient synthetic protocol which allows to prepare various novel 5-arylsubstituted 3-thienylacetic acids starting from 3-aryl-3-chloroacrylaldehydes via corresponding thienylcarbaldehydes and thienylethanones under phase-transfer conditions.

Experimental Section

General. The ^{1}H and ^{13}C NMR spectra in $CDCl_3$ were recorded on a Bruker DPX-250 (250 MHz for ^{1}H, 62.9 MHz for 13C) spectrometer, the signals were referred with respect to the signals of residual protons of deutero-solvent (7.24 ppm), δ values were measured with precision 0.01 ppm. The IR spectra were recorded on a Varian Excalibur 3100 FT-IR instrument using the attenuated total internal reflection technique (ZnSe crystal). Mass spectra were recorded on a Shimadzu GCMS-QP2010SE instrument with direct sample entry into the ion source (EI, 70 eV). Elemental analysis was performed on a KOVO CHN-analyzer. Melting points were determined on a PTP (M) instrument.

General procedure for the synthesis of 1a,b. A solution of 3-chloro-3-(4-chlorophenyl)acrylaldehyde (32 mmol, 6.5 g) or 3-([1,1'-biphenyl]-4-yl)-3-chloroacrylaldehyde (32 mmol, 7.8 g) in 100 mL of dry DMF was added dropwise with stirring to a suspension of $Na_2S{\cdot}9H_2O$ (33 mmol, 7.9 g) in 40 mL of dry DMF at 60 ºC within 1 h. The reaction mixture was stirred for 2 h at 60 ºC. 50% aqueous chloroacetaldehyde (36 mmol, 6 mL) was added dropwise and the reaction mixture was stirred for 3 h at 60 ºC. A solution of K_2CO_3 (60 mmol, 8.3 g) in 10 mL of water was added and the stirring at the same temperature was continued for 0.5 h. The reaction mixture was then poured into 1000 mL of water. The precipitate was filtered, washed with water, dried and recrystallized from ethanol with the charcoal.

5-(4-Chlorophenyl)thiophene-2-carbaldehyde (1a). Yield 4.2 g (59%), light yellow solid, mp 88-89 °C [lit.[16] mp 87 °C]. IR (ν_{max}, cm^{-1}): 1655 (C=O), 1599 (C=C), 1491, 1431. ^{1}H NMR (250

MHz, $CDCl_3$): δ 7.36-7.40 (m, 3H), 7.59 (d, *J* 8.40 Hz, 2H), 7.73 (d, *J* 3.80 Hz, 1H), 9.88 (s, 1H, CHO). EIMS, 70 eV, *m*/*z*: 222 $[M]^+$. Anal. Calcd. for $C_{11}H_7ClOS$: C, 59.33; H, 3.17. Found: C, 59.23; H, 3.15 %.

5-([1,1'-Biphenyl]-4-yl)thiophene-2-carbaldehyde (1b). Yield 3.7 g (44%), light yellow solid, mp 194-195 °C [lit.[19] mp 193-194 °C]. IR (ν_{max}, cm^{-1}): 1664 (C=O), 1608(C=C). ^1H NMR (250 MHz, $CDCl_3$): δ 7.32–7.85 (m, 11H, arom. H, thioph. H), 9.92 (s, 1H, CHO). MS (EI, 70 eV), *m/z*: 264 $[M]^+$. Anal. Calcd. for $C_{17}H_{12}OS$: C, 77.24; H, 4.58. Found: C, 77.41; H, 4.35 %.

General procedure for the synthesis of 2a,b. A mixture of **1a** (10 mmol, 2.2 g) or **1b** (10 mmol, 2.6 g), 85% hydrazine hydrate (135 mmol, 6.75 g) and KOH (75 mmol, 4.2 g) in 50 mL of diethylene glycol was stirred at reflux for 3 h. The solution was then diluted with water (150 mL). The crude product was filtered, dried and recrystallized from ethanol.

2-(4-Chlorophenyl)-5-methylthiophene (2a). Yield 0.84 g (40%), light yellow solid, mp 107-109 °C [lit.[20] mp 108-109 °C]. IR (ν_{max}, cm^{-1}): 1599, 1491, 1431. ^1H NMR (250 MHz, $CDCl_3$): δ 2.54 (s, 3H, Me), 6.68-7.50 (m, 6H, arom. H, thioph. H). MS (EI, 70 eV), *m/z*: 208 $[M]^+$. Anal. Calcd. for $C_{11}H_9ClS$: C, 63.30; H, 4.35. Found: C, 63.43; H, 4.45 %.

2-([1,1'-Biphenyl]-4-yl)-5-methylthiophene (2b). Yield 0.75 g (30%), light yellow solid, mp 144-145 °C. IR (ν_{max}, cm^{-1}): 3058, 1598, 1497. ^1H NMR (250 MHz, $CDCl_3$): δ 2.54 (s, 3H, Me), 6.84-6.86 (m, 1H, thioph. H), 7.32-7.74 (m, 10H, arom. H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 17.15; 124.95; 127.58; 127.59; 128.30; 128.67; 128.68; 128.99; 129.30; 129.31; 130.75; 130.76; 135.62; 141.51; 141.76; 142.34; 143.31. MS (EI, 70 eV), *m/z*: 250 $[M]^+$. Anal. Calcd. for $C_{17}H_{14}S$: C, 81.56; H, 5.64. Found: C, 81.43; H, 5.49 %.

General procedure for the synthesis of 3a,b. A solution of **2a** (10 mmol, 2.1 g) or **2b** (10 mmol, 2.5 g) in 75 mL of dry toluene was cooled to 0-5 °C. Acetic anhydride (20 mmol, 2.0 g) and then $SnCl_4$ (20 mmol, 5.2 g) were added under stirring at this temperature. The reaction mixture was heated to 20°C, stirred for 4 h and then acidified with 10% aqueous HCl (100 mL). The organic layer was separated and dried (Na_2SO_4). The solvent was removed using a rotary evaporator to give a crude residue which was recrystallized from ethanol.

1-(5-(4-Chlorophenyl)-2-methylthiophen-3-yl)ethanone (3a). Yield 1.0 g (41%), light yellow solid, mp 114-115 °C. IR (ν_{max}, cm^{-1}): 1800 (C=O), 1750 (C=C), 1431. ^1H NMR (250 MHz, $CDCl_3$): δ 2.51 (s, 3H, Me), 2.73 (s, 3H, Me), 7.24 (s, 1H, thioph. H), 7.31-7.34 (d, 2H, arom. H), 7.44-7.47 (d, 2H, arom. H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 16.30; 29.82; 124.60; 124.61; 126.78; 126.79; 129.15; 129.16; 133.56; 137.04; 138.15; 148.73; 193.88. MS (EI, 70 eV), *m/z*: 250 $[M]^+$. Anal. Calcd. for $C_{13}H_{11}ClOS$: C, 62.27; H, 4.42. Found: C, 62.34; H, 4.45 %.

1-(5-(1,1'-Biphenyl-4-yl)-2-methylthiophen-3-yl)ethanone (3b). Yield 2.45 g (84%), light yellow solid, mp 153-154 °C. IR (ν_{max}, cm^{-1}): 1801 (C=O), 1747 (C=C), 1428. ^1H NMR (250 MHz, $CDCl_3$): δ 2.53 (s, 3H, Me), 2.75 (s, 3H, Me), 7.37-7.65 (m, 10H, arom. H, thioph. H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 16.03; 29.68; 41.41; 124.37; 125.84; 125.85; 126.79; 126.80; 127.52;

127.54; 128.87; 128.88; 132.53; 137.19; 138.92; 140.19; 140.33; 148.14; 193.75. MS (EI, 70 eV), *m/z*: 292 $[M]^+$. Anal. Calcd. for $C_{19}H_{16}OS$: C, 78.05; H, 5.52. Found: C, 78.13; H, 5.45 %.

General procedure for the synthesis of 4a,b. A mixture of **3a** (0.4 mmol, 0.1 g) or **3b** (0.68 mmol, 0.20 g), sulfur (0.8 mmol, 0.026 g), *p*-toluenesulfonic acid (0.14 mmol, 0.024 g) and morpholine (1.2 mmol, 0.11 g) was heated while stirring in an oil bath at 130 ºC for 6 h. The reaction mixture was cooled to ambient temperature and then 5 mL of 20% aqueous NaOH and benzyltriethylammonium chloride (TEBA) (0.02 mmol, 0.005 g,) were added. The reaction mixture was heated at reflux while stirring for 8 h, diluted with 5 mL of water and cooled to ambient temperature. The solution was filtered and acidified with 10% aqueous HCl up to pH = 6. The precipitate was filtered. The filtrate was further acidified with 10% aqueous HCl up to pH = 2 and the new portion of precipitate was filtered. The combined precipitate was washed with water, dried and recrystallized from CCl_4.

2-(5-(4-Chlorophenyl)-2-methylthiophen-3-yl)acetic acid (4a). Yield 0.68 g (64%), light yellow solid, mp 134-135 °C. IR (ν_{max}, cm^{-1}): 3061, 2559, 1705. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.39 (s, 3H, Me), 3.55 (s, 2H, CH_2), 7.18 (s, 1H, thioph. H), 7.31-7.39 (d, 2H, arom. H), 7.50-7.54 (d, 2H, arom. H), 10.50-11.60 (br. s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 11.74; 33.20; 125.69; 126.13; 126.14; 128.57; 128.58; 131.40; 132.28; 133.12; 133.50; 138.03; 173.52. MS (EI, 70 eV), *m/z*: 266 $[M]^+$. Anal. Calcd. for $C_{13}H_{11}ClO_2S$: C, 58.54; H, 4.16. Found: C, 58.43; H, 4.25 %.

2-(5-([1,1'-Biphenyl-4-yl)-2-methylthiophen-3-yl)acetic acid (4b). Yield 0.11 g (53%), light yellow solid, mp 105-106 °C. IR (ν_{max}, cm^{-1}): 3058, 2555, 1700. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.46 (s, 3H, Me), 3.60 (s, 2H, CH_2), 7.33-7.36 (m, 1H, thioph. H), 7.39-7.71 (m, 9H, arom. H), 10.50-11.50 (br. s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.13; 31.75; 33.94; 125.43; 125.44; 125.69; 126.57; 126.65; 127.34; 127.38; 127.48; 128.88; 128.92; 131.69; 133.44; 135.11; 139.56; 140.23; 169.83. MS (EI, 70 eV), *m/z*: 308 $[M]^+$. Anal. Calcd. for $C_{19}H_{16}O_2S$: C, 74.00; H, 5.23. Found: C, 74.13; H, 5.35 %.

(2,5-Dimethylthiophen-3-yl)acetic acid (4c). The general procedure above described was applied using 1-(2,5-dimethylthiophen-3-yl)ethanone (10 mmol, 1.54 g). Yield 0.92 g (54%), light yellow solid, mp 68-69 °C [lit.[22] mp 69-70 °C]. IR (ν_{max}, cm^{-1}): 3068, 2565, 1705. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 2.26 (s, 3H, Me), 2.34 (s, 3H, Me), 3.39 (s, 2H, CH_2), 6.56 (s, 1H, thioph. H), 10.30-11.20 (br. s, 1H, OH). MS (EI, 70 eV), *m/z*: 170 $[M]^+$. Anal. Calcd. for $C_8H_{10}O_2S$: C, 56.44; H, 5.92. Found: C, 56.43; H, 5.85 %.

2-(5-(4-Bromophenyl)-2-methylthiophen-3-yl)acetic acid (4d). The general procedure above described was applied using 2-(5-(4-bromophenyl)-2-methylthiophen-3-yl)-1-morpholinoethanethione (10 mmol, 2.95 g). Yield 2.15 g (69%), light brown solid, mp 162-163 °C [lit.[13] mp 161-162 °C]. IR (ν_{max}, cm^{-1}): 3062, 2558, 1704. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.41 (s, 3H, Me), 3.56 (s, 2H, CH_2), 7.12 (s, 1H, thioph. H), 7.21-7.48 (m, 4H, arom. H), 10.60-11.50 (br. s, 1H, OH). MS (EI, 70 eV), *m/z*: 311 $[M]^+$. Anal. Calcd. for $C_{13}H_{11}BrO_2S$: C, 50.17; H, 3.56. Found: C, 50.08; H, 3.66 %.

Supplementary Material

^{1}H and ^{13}C spectra for all novel obtained compounds.

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