Troublesome Alkoxythiophenes. A Highly Efficient Synthesis via Cyclization of γ-Keto Esters

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A variety of alkoxythiophenes have been synthesized that represent ideal subunits for the synthesis of a new class of thermotropic liquid crystals via palladium-catalyzed cross-coupling reactions and organometallic derivatization. The methodology used represents the first highly efficient synthesis of alkoxythiophenes unlike previous pathways that have presented serious synthetic difficulties when the alkoxy chain consisted of more than four carbon atoms. The scope of the new procedure (relative to liquid crystalline intermediates) is presented and is compared and contrasted with the current literature.

Introduction

In designing new liquid crystals for ferroelectric and nematic display applications, we have identified alkoxythiophenes as being suitable units for incorporation at the terminus of the mesogen. The new materials have been carefully designed with structures that should provide physical properties that are desirable for ferroelectric applications in particular.[1−3] Such properties include (but are not limited to) low viscosity, high dielectric biaxiality[4] (directly related to the magnitude of the transverse dipole moment), low melting point, and a wide smectic C (S_C) mesophase.[5,6] The heterocycle is particularly advantageous as this is a low viscosity unit and thus promotes fast reorientational response times of the liquid crystal in the presence of an electric field.[7] In addition, the lateral dipole provided by the heterocycle increases dielectric biaxiality, which allows for AC field stabilization in a ferroelectric device.[4,8−10]

Recently, our work has included the synthesis of brominated derivatives of alkoxythiophenes for use as precursors in the synthesis of liquid crystal materials such as **A** (see Figure 1).

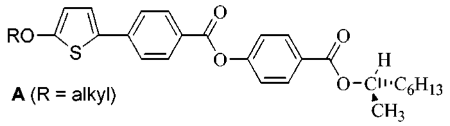

Figure 1. Targeted ferroelectric alkoxythiophene-containing liquid crystals.

These mesogens have been shown to possess broad smectic C phase range[11] and exhibit a variety of chiral subphases including the ferri- and antiferroelectric variants. The new subunit thus appears to have excellent potential for device use, and we are currently exploring new alkoxythiophene-based systems for nematic, ferroelectric, and antiferroelectric device use.

Previous synthesis of alkoxythiophenes has proven to be surprisingly problematic and current methodology gives very low yields in unattractive reactions. The cyclization methodology we have used in constructing the heterocycle represents a significant addition to the current literature methodology and provides a general entry into a variety of alkoxythiophene-containing systems. This work also enables the synthesis of materials that will have additional use in medical applications.[12] Such materials have previously been produced in only low-yielding reactions; this chemistry is exemplified by, for example, the work of Parker et al.[13]

It might at first appear that the synthesis of suitable subunits used in the construction of compounds **A** can be accomplished using a Williamson's ether synthesis. However, the well-known Williamson's ether synthesis of alkoxyphenyl systems has little counterpart when compared with 2-thienyl systems such as 2-hydroxythiophene.[14−21]

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Nucleophilic aromatic substitution has been reported as a method used for the synthesis of alkoxythiophenes from both iodo- and bromothiophenes. Both catalyzed (cupric sulfate)[22] and noncatalyzed[13] reactions have been reported. Yields of methoxy and ethoxy derivatives are acceptable, although longer chains are produced in yields under 40% at best.

Brunet et al. have described the cyclization reactions of both alkyl- and aryl-substituted γ-ketoesters with a mixture of hydrogen sulfide and hydrogen chloride gases.[23] Yields of the aryl-substituted materials were very low (10−20%), and the alkyl-substituted materials proved to be even worse as the major products were mixtures of 4-thiolen-2-ones, 3-thiolene-2-ones, and thiolactams (alkoxythiophene formation was not observed). Remarkably, there is very little literature on classical cyclizations of γ-ketoesters using phosphorus pentasulfide, and there is no literature whatsoever on the use of Lawesson's reagent[24−27] in such cyclization reactions. A paper by Sagitdinov et al.[28] describes the high-yielding cyclization of four different *n*-alkyl 3-(4′-*n*-alkylbiphenyl-4-ylcarbonyl)propanoates using phosphorus pentasulfide. This is the only time that this reaction has reported to be successful in the literature. Despite seven attempts at this reaction under varying reaction times and conditions, we were unable to repeat the results obtained by Sagitdinov. Instead, we obtained black tarry products in all cases, which were accompanied by a very small amount of the desired product (GLC analysis confirmed approximately 9% maximum yield of the desired products which proved to be inseparable). Later work by Sedavkina et al.[29] has in fact shown that 5-alkyl-4-thiolen-2-ones and 5-alkyl-3-thiolen-2-ones are the major products of cyclization of the ethyl esters of the related γ-keto carboxylic acids.

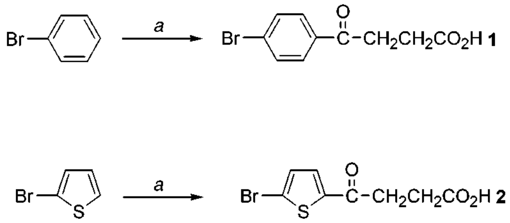
In this paper, we describe the synthesis of a number of γ-keto esters and highlight the reproducible ease and efficiency of their conversion into alkoxythiophene-containing materials using Lawesson's reagent-based cyclization methodology.

Results and Discussion

Scheme 1 depicts the syntheses of **1** and **2** that involve the Friedel−Crafts acylation of bromobenzene and bromothiophene, respectively.

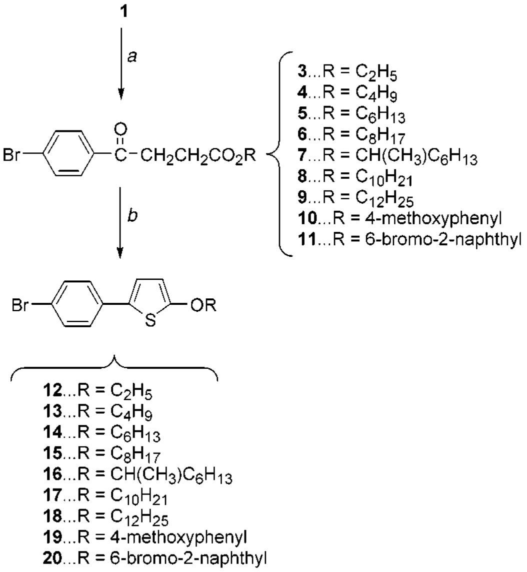
The acylation of bromobenzene with succinic anhydride is a well-documented procedure;[30−33] however, most of the literature dates back to an original procedure by Fieser[30] that provides modest yields and regioselectivity of just over 90%. In addition, dehalogenation has been observed to be a serious side-reaction.[34] Our modified method (longer reaction time and low temperature) gives complete regioselectivity and very high, consistently reproducible yields. This method has been tried on a variety of other substrates including toluene, anisole, and iodobenzene, each time giving excellent results.[35]

Scheme 1[a]



[a] Key: (a) (i) succinic anhydride, $AlCl_3$; (ii) 18% aqueous HCl.

Scheme 2[a]



[a] Key: (a) alkyl or aryl alcohol, *N*,*N*′-dicyclohexylcarbodiimide, 4-(*N*,*N*-dimethylamino)pyridine; (b) Lawesson's reagent, dry toluene.

Esterification of the carboxylic acids **1** and **2** (Schemes 2 and 3) used the method of Hassner and Alexanian[36] and gave the γ-keto esters (**3**−**11** and **21**) in excellent yields. In the subsequent step, we used our new procedure to cyclize the above γ-keto esters in good to excellent yields after purification (Table 1). Our studies clearly showed that the reaction time is crucial in obtaining optimum yields of the desired alkoxythiophenes. Extension of the reaction times beyond those stated in the experimental procedures resulted in the accumulation of unidentified volatile products (observed by GC analysis). A large number of impurities were observed by GC, and isolation/identification of the byproducts was not attempted as there were often more than 10 impurities

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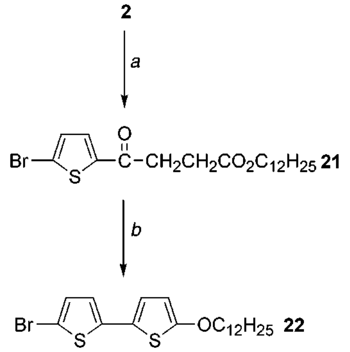
Scheme 3[a]



[a] Key: (a) dodecan-1-ol, *N*,*N*′-dicyclohexylcarbodiimide, 4-(*N*,*N*-dimethylamino)pyridine; (b) Lawesson's reagent, dry toluene.

Table 1. Synthesis of Alkoxy- and Aryloxythiophenes via Cyclization of γ-Keto Esters

γ-keto ester	reaction time (h)	product (yield,[a] %)
3	11.3	**12** (47)
4	16	**13** (52)
5	20	**14** (86)
6	22	**15** (62)
7	24	**16** (83)
8	25	**17** (94)
9	48	**18** (94)
10	22	**19** (75)
11	29	**20** (74)
21	1.5	**22** (35)

[a] Yields refer to isolated purified products.

produced in each reaction. Initially, we thought that the product alkoxythiophenes might be reacting with Lawesson's reagent, and this was disproved by heating **18** under reflux with Lawesson's reagent for 10 days without any significant reaction being observed. Clearly, the oxidized form of Lawesson's reagent (produced during the cyclization) must be responsible for the side reactions observed; all of the reactions were stopped once byproduct formation was observed (even if cyclization was not complete, as was the case for alkoxythiophenes **3**−**6**). Analysis of the results shows that there is a clear trend in the reaction time required to effect optimum cyclization. The shorter is the alkyl chain on the γ-keto esters (**3**−**9**), the shorter is the time required for observation of the unwanted byproducts.

Derivatives having chain lengths in excess of 12 carbon atoms were not evaluated as the use of such long chains in thermotropic liquid crystals results in increases in viscosity that are not compatible with fast responding electrooptic materials.

Conclusions

We have demonstrated the first reliable and highly efficient synthesis of alkoxythiophenes from γ-keto ester precursors. The described procedure represents the first synthetic methodology that provides a general entry into functional alkoxythiophene derivatives that may, for example, be used in the synthesis of thermotropic liquid crystals. The methodology is a significant addition to the currently available literature and may also be used in the synthesis of precursors for materials used in medical applications.

Experimental Section

4-(4-Bromophenyl)-4-oxobutanoic Acid (1). Anhydrous aluminum chloride (26.67 g, 0.2000 mol) was added in one portion to a mechanically stirred mixture of powdered succinic anhydride (10.01 g, 0.1000 mol) in bromobenzene (96.87 g, 0.6170 mol) at −5 °C, under dry argon. The reaction temperature was maintained at −5 °C for 4 h and was then allowed to warm to room temperature. The reaction mixture was stirred at room temperature for 96 h (ceasing of HCl gas evolution indicated a complete reaction). The reaction mixture was poured onto a mechanically stirred solution of dilute hydrochloric acid (250 mL, 18%) at 0 °C, and the mixture was stirred for a further 30 min while the solution was allowed to warm to room temperature. The yellowish white solid was filtered off, washed with water, and dried in vacuo ($CaCl_2$, P_2O_5, 20 h). The crude product was purified by crystallization from toluene to afford a white crystalline solid, which was dried in vacuo ($CaCl_2$, P_2O_5, 24 h): yield 24.23 g (94%); mp 147−148 °C (lit.[34] mp 149.5−150.2 °C); ^{1}HNMR (500 MHz, DMSO-d_6) δ 2.59 (2H, t, 6.35 Hz), 3.21 (2H, t, 6.35 Hz), 7.88 (2H, d, J = 8.79 Hz), 7.96 (2H, d, J = 8.79 Hz), 12.19 (1H, s); IR (KBr) ν_{max} 2600−3400, 1730, 1670, 1585, 1479, 1447, 1410, 1105, 1074, 840 cm^{-1}; MS m/z 256.2 (M$^+$), 185.1, 183.1 (100), 157.1, 155.1, 76.1, 75.1. Anal. Calcd for $C_{10}H_9BrO_3$: C, 46.72; H, 3.53. Found: C, 46.69; H, 3.49.

4-(5-Bromothien-2-yl)-4-oxobutanoic Acid (2). γ-keto acid **2** was prepared as described for the preparation of compound **1** except that nitrobenzene was used as solvent, and the reaction mixture was stirred at −5 to −10 °C for 5 h before workup, using the quantities stated: anhydrous aluminum chloride (1.32 g, 9.90 mmol), succinic anhydride (0.45 g, 4.5 mmol), and 2-bromothiophene (0.733 g, 4.50 mmol). After treatment with hydrochloric acid, a semisolid was observed to settle at the bottom of the flask. The top layer was discarded, and water was added before the mixture was extracted with diethyl ether. The organic layer was washed with potassium hydroxide (5% aqueous), and the aqueous layer was separated and brought to pH 2−3 by the addition of hydrochloric acid (10%). A cream-orange solid was filtered off, washed with water, and dried ($CaCl_2$, P_2O_5, 20 h). The crude product was purified by crystallization from water to afford a white crystalline solid, which was dried in vacuo ($CaCl_2$, P_2O_5, 24 h): yield 1.12 g (95%); mp 141−142 °C (lit.[37] mp 141 °C); ^{1}H NMR ($CDCl_3$) δ 2.80 (2H, t, J = 6.56 Hz), 3.20 (2H, t, J = 6.56 Hz), 7.20 (1H, d, J = 3.9 Hz), 7.50 (1H, d, J = 3.9 Hz), the carboxylic acid proton was not detected; IR (KBr) ν_{max} 3079, 2761, 1703, 1651, 1526, 1413, 1332, 1278, 1247, 979 cm^{-1}.

General Procedure for the Synthesis of γ-Keto Esters 3−11 and 21. *N*,*N*′-Dicyclohexylcarbodiimide (8.53 g, 41.3 mmol) was added in one portion to a stirred solution of the appropriate alcohol (1.588 g, 34.47 mmol), γ-keto acid (7.38 g, 28.7 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (1.68 g, 13.8 mmol) in dry dichloromethane (250 mL) under dry argon at room temperature. The reaction mixture was stirred at room temperature overnight (TLC analysis revealed a complete reaction), and the *N*,*N*′-dicyclohexylurea was filtered off. The filtrate was washed successively with potassium hydroxide (5% aqueous), water, acetic acid (5% aqueous), and water and dried ($MgSO_4$). The drying agent was filtered off, and the solvent was removed in vacuo before being purified as described.

General Procedure for the Synthesis of Thiophenes 12−20 and 22. The method described by Shridar et al.[25] was employed with minor modifications to the reaction time. Lawesson's reagent (5.11 g, 12.6 mmol) was added in one portion to a stirred solution of the appropriate γ-keto ester (3.00 g, 10.5 mmol) in dry toluene (100 mL) under dry argon. The reaction mixture was heated under reflux (see Table 1 for the appropriate reaction times) before the reaction mixture was cooled to room temperature and the solvent was removed in vacuo. The crude products were purified as described.

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Supporting Information Available: Purification procedures and spectroscopic and elemental analysis details for compounds **3**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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