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Efficient route for the synthesis of 3,4-cycloalkoxy-2,5-diethoxycarbonyl-thiophenes obtained with bulky alkyl dibromides using trialkylamines as base–solvent

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Abstract—New reaction conditions were investigated for dialkylizing diethyl 3,4-dihydroxy-2,5-thiophenedicarboxylate with sterically hindered alkyl-dibromides, using as reaction system DMF–trialkylamine or only the trialkylamine as base–solvent. This methodology produced the corresponding 3,4-cycloalkoxy-2,5-diethoxycarbonyl-thiophene derivatives faster and with better yields than those reported previously for K_2CO_3–DMF. Experiments were performed with triethylamine, tripropylamine, and tributylamine. Tributylamine produced the best results in a general reaction with alkyl-bromides. Aromatic amines like *N*,*N*-dimethylaniline, *N*-methyldiphenylamine, and triphenylamine failed to react at all. Reactions using only the tributylamine as base–solvent demonstrated that DMF is not necessary as a solvent to obtain good yields.

1. Introduction

Alkoxy-thiophenes are starting products to generate interesting new materials.[1] They are used as monomers for the synthesis of organic conducting polymers[2] (**7**) with technological applications.[3] Due to their high electrical conductivity, and chemical and mechanical stability, the polymers obtained with 4,4′-dimethoxybithiophene,[4] 3,4-ethylendioxythiophene[2c,5] (**6** R = –CH_2–CH_2– EDOT), and derivatives, are the most promising monomers known up to now for industrial use. Hence, the synthesis of 3,4-dialkoxy-thiophenes is a subject of considerable significance[6] and the access to optimized synthesis of new 3,4-dialkoxy-thiophenes is always desirable. The classic synthesis of the 3,4-dialkoxy-thiophenes monomers **6** includes as key reaction, a double Williamson etherification using ethyl or methyl 3,4-dihydroxy-2,5-thiophene-dicarboxylate (**1** or **2**),[3h,7] K_2CO_3 as base, DMF, and a dihalide-compound **4** (Scheme 1). This reaction generates the intermediates **5**, which after saponification and decarboxylation, generate the monomers **6**.[3h,5b,6d,h,11,14] It has been demonstrated that the yield of 3,4-alkoxy-2,5-diethoxycarbonyl-thiophene intermediates (**5**) using these reaction conditions, is very sensitive to the alkyl halide used. Thus, when a primary alkyl dihalide is used, a yield of 70–75% is obtained, but with sterically hindered alkylhalides, the reaction needs at least 48 h to produce moderate yields (30% or less).[8] The use of secondary alkylhalide compounds, or, the use of a *gem*-dihalide derivative, severely complicates the reaction, due to the sterical demand for the two consecutive substitution reactions.[5b] Several variations of this reaction have been proposed by other research groups to overcome this problem,[6e,9,10] but because of the availability and cost of the starting materials used in the classic approach depicted in Scheme 1, this reaction is preferred for the production of large quantities of derivatives (**5**).[5b]

Our research group is interested in the electrochemical polymerization of new 3,4-dialkoxy-thiophene derivatives (**6**), where R is an alkyl group with large substituents. Hence, the classical K_2CO_3 approach is unlikely to provide good yields of the intermediates **5**. New reaction conditions are required to prevent the double Williamson etherification reaction of **1** from becoming the limiting step during the synthesis of monomers **6** using

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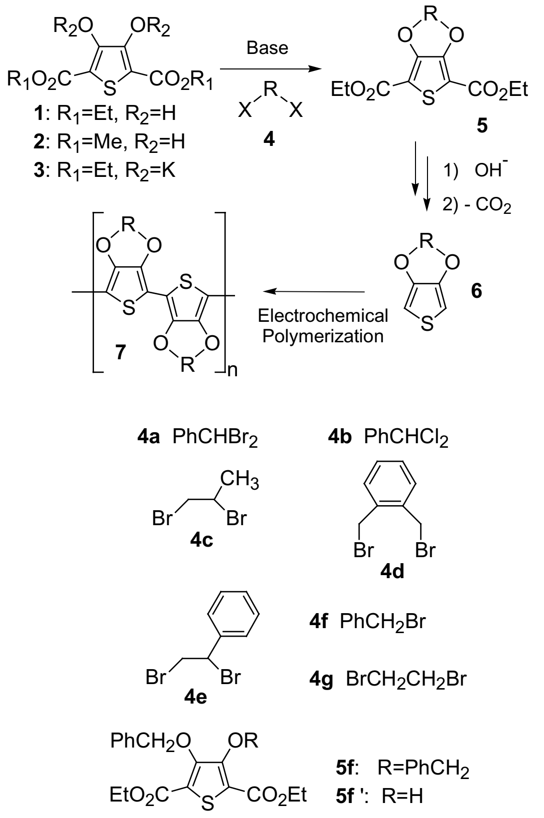

Scheme 1. Classic reaction pathway for the synthesis of 3,4-dialkoxy or 3,4-cycloalkoxythiophenes **6** and alkyl-halides (**4**) used in this work.

sterically hindered substituents, as described previously.[6d,f,3h] In this letter, we present the results of our attempts to increase the low yields so far reported for the Williamson reaction using these thiophene derivatives.

2. Results and discussion

Commercially available α,α-dibromo and dichloro-toluene **4a** or **4b** were chosen as starting materials. Due to the high sterical demands on the benzylic carbon owing to the *gem*-dihalide substitution, this substitution reaction presented a good challenge (Table 1). Moreover, following the sequence of reactions depicted in Scheme 1, we would be in a position to synthesize benzyl-acetal-3,4-dioxythiophene (**6** R = PhCH), an interesting monomer for electrochemical studies; these results will be published on due course. First, we verified the reactivity of **4a** and **4b** with **1** for the synthesis of **5a** (R = PhCH) under the typical conditions reported in the literature, that is, dry DMF as solvent and K_2CO_3 as base.[6,11] The low efficiency of this method was confirmed using both dihalides. Using dibromide **4a**, derivative **5a** was produced only after a reaction time of 3 days with a poor 5% yield (Table 1, entry 2). Increasing the reaction time to 5 days and using dichloro compound **4b** produced a still low 9% yield (Table 1, entry 4). The recovery during the reaction workup of a high quantity of the di-potassium salt of **1** (**3**), and the dihalide compound during the chromatography column separation, suggests a very slow substitution reaction, as expected for the reaction of hindered dihalide compound with K_2CO_3. Our search for other conditions[12] to produce **5a** using α,α-dihalide-toluenes **4a**–**b** demonstrated that biphasic reactions using $CH_2Cl_2/H_2O/$TBApTs with K_2CO_3 satd or NaOH 10% as base were not useful (Table 1, entries 5 and 7). Contrary to the expectations, the addition of $AgNO_3$ to the biphasic systems complicated the reaction because of the reduction of Ag(I) ion to Ag° in the reaction conditions (Table 1, entries 6 and 8).[13]

Merz[14] proposes that in order to enhance the bis-O-alkylation when using dianion **3** and following the principles of the HSAB theory, the solvent of choice should be a dipolar. They used this method to successfully dimethylate **3** in toluene with a crown ether as catalyst. Following these concepts instead of the classic K_2CO_3, we tried to synthesize **5a** by decreasing the polarity of the media with an organic base with a high hydrocarbon substitution. Triethylamine (TEA) was our first choice and 3 equiv were used in the following experiments. This base is cheap, easy to remove, and strongly decreases the polarity media when mixed with DMF;[15] furthermore, it allowed the acid–base reaction to be carried out in a totally homogeneous system. The first reaction carried out with TEA, **1** and α,α-dichloro-toluene produced **5a** in 15% yield in a reaction of only 12 h (Table 1, entry 9), which represents a considerable improvement compared with that obtained using K_2CO_3. This result encouraged us to look for the best experimental conditions to obtain **5a** using TEA and the dihalide compounds **4a**–**b** (Table 1, entries 9–18). Using α,α-dichloro-toluene (**4b**), the best yield was 45% in a 72-h reaction; however, 2 equiv of dihalide compound were required. The change to dibromide **4a** increased the yield of the product obtained to 60% using 1 equiv and only 12 h (Table 1, entry 13). This result can be rationalized if one considers that the limiting step of the reaction is the first substitution and that, as bromide is a better leaving group than chloride, the reaction with α,α-dibromo-toluene is faster. When the reaction time was increased to 20 h, the yield increased to 71%; longer periods did not work better. The best reaction conditions for obtaining **5a** (83% yield, Table 1, entry 18) required a slight excess of dibromide **4a** (1.3 equiv), 3 equiv of TEA and a reaction time of 20-h, using dry DMF at 90 °C. Two scale-up reactions using these experimental conditions with 10 g and 30 g of **1** demonstrated the synthetic utility of this reaction without loss of yield (Table 1, entries 19–20).

The general applicability of these reaction conditions for the double Williamson etherification of **1** was verified with other bulky dibromo compounds (**4c**–**e**), the middle hindered benzylbromide (**4f**) and the primary dibromide 1,2-dibromoethane (**4g**) (Table 2). Compared with the reported method using K_2CO_3 and 48 h of reaction, compounds **5c** (Table 2, entry 1) and **5d** (Table 2, entry 2) were produced, increasing its yield by more than 20% in only 20 h of reaction versus the 48 h required using the inorganic base. Once again the applicability of these conditions for large-scale production was checked using

Table 1. Synthesis of **5a** (R = PhCH) under basic conditions[a]

Rn	Base and quantity	Dihalide **4** (equiv)	Time (h)	**5a** (R = PhCH)%[b]
1	K_2CO_3 3 equiv	**4a** (1)	24	No reaction[e]
2	K_2CO_3 3 equiv	**4a** (1)	72	5[e,f]
3	K_2CO_3 3 equiv	**4b** (1)	72	7[e,f]
4	K_2CO_3 3 equiv	**4b** (1)	120	9[e,f]
5	$K_2CO_{3\ \text{satd}}$[c]	**4b** (1)	24	No reaction[e]
6	$K_2CO_{3\ \text{satd}}$ + Ag(I)[c,d]	**4b** (1)	24	Ag(I) → Ag°
7	NaOH 10%[c]	**4b** (1)	24	No reaction[e]
8	NaOH 10% + Ag(I)[c,d]	**4b** (1)	24	Ag(I) → Ag°
9	Triethylamine 3 equiv	**4b** (1)	12	15[e]
10	Triethylamine 3 equiv	**4b** (1)	20	20[e]
11	Triethylamine 3 equiv	**4b** (1)	72	25[e]
12	Triethylamine 3 equiv	**4b** (2)	72	45
13	Triethylamine 3 equiv	**4a** (1)	12	60
14	Triethylamine 3 equiv	**4a** (1)	20	71
15	Triethylamine 3 equiv	**4a** (l)	72	57
17	Triethylamine 3 equiv	**4a** (l.3)	12	80
18	Triethylamine 3 equiv	**4a** (1.3)	20	83
19	Triethylamine 3 equiv	**4a** (1.3)	24	85[g]
20	Triethylamine 3 equiv	**4a** (1.3)	24	80[h]

[a] With exception of entries 5–8, the reactions were carried out in 2 g scale (7.7 mmol) of **1**, using dry DMF as solvent at 90 °C in an oil bath under Ar and magnetically stirred.

[b] Yield after column chromatography, except for entries 19 and 20.

[c] Biphasic conditions using CH_2Cl_2/H_2O and TBApTs under strong magnetic stirring at rt.

[d] $AgNO_3$ 1 equiv.

[e] Recovery of a high quantity of the starting materials.

[f] By-products observed in TLC controls.

[g] 10 g scale reaction of **1** (38.4 mmol).

[h] 30 g scale reaction of **1** (107 mmol).

Table 2. Yield for the syntheses of **5** with TEA–DMF and K_2CO_3–DMF catalyzed reactions using **1** and the bromo-compounds **4**

Rn	Alkyl bromide	TEA–DMF[a] 20 h	K_2CO_3–DMF 48 h	Mp (reported) °C
1	**4c** 1.3 equiv	**5c** 45%	**5c** 21% Ref. 6d	143–144 (144–145)
2	**4d** 1.3 equiv	**5d** 63%	**5d** 40% Ref. 6d	145–146 (147–148)
3[c]	**4d** 1.3 equiv	**5d** 60%	**5d** 40% Ref. 6d	145–146 (147–148)
4	**4e** 1.3 equiv	**5e** 27%	**5e** 30% Ref. 6d	115–116 (116–117)
5[b]	**4e** 1.3 equiv	**5e** 10%	**5e** 30% Ref. 6d	115–116 (116–117)
6	$PhCH_2Br$	**5f** 25%	**5f** 71% Ref. 6h	69–70 (69–70)
	4f 2 equiv	**5f′** 40%	**5f′** non reported	107–109
7	$PhCH_2Br$	**5f** 30%	**5f** 71% Ref. 6h	69–70 (69–70)
	4f 3 equiv	**5f′** 37%	**5f′** non reported	107–109
8[b]	$PhCH_2Br$	**5f** 69%	**5f** 71% Ref. 6h	69–70 (69–70)
	4f 3 equiv	**5f′** 20%	**5f′** non reported	107–109
9[d]	$Br(CH_2)_2Br$	**5g** 73%	**5g** 70% Ref. 3h	145–146 (146–147)
	4g 1.3 equiv			Ref. 6h

[a] Reactions were carried out in 2 g scale of **1** (7.7 mmol) using dry DMF as solvent, 3 equiv of triethylamine (TEA) at 90 °C in an oil bath under Ar and magnetically stirred. Yields after flash column chromatography.

[b] Yield obtained after 48 h of reaction.

[c] 10 g scale reaction of **1** (38.4 mmol), same experimental protocol as for **5a** synthesis but 10% CH_2Cl_2 was added to the ether to facilitate the extraction.

[d] 24 h of reaction.

dibromo compound **4d** and 10 g of **1** (Table 2, entry 3); no erosion of the yield was observed with the scale-up. Using dibromo alkyl **4e**, the obtained yield of **5e** was almost the same as previously reported, but it must be noted that this quantity was obtained in that half of the time. Thus, as observed in the synthesis of **5a**, this reaction was faster with triethylamine than with K_2CO_3. Just like the reaction with **4a**, longer reaction periods did not work better; under these conditions for **4e**, large quantities of α and β-bromo-styrene[16] were obtained as by-products. Comparing reactions using dibromides **4c** and **4e**, it is clear that the phenyl group favors the elimination reactions via the activation of the benzylic carbon. Despite the presence of these side reactions, and taking into account the time of reaction, the yield obtained in **5e** is among the highest reported when using dibromide **4e** as starting material. The reaction of 2 equiv of benzylbromide (**4f**) with **1** (Table 2, entry 6), produced a mixture of the dibenzylated **5f** and, as the major compound, the unreported monobenzyl derivative **5f′**. With 1 equiv excess of **4f**, the reaction produced a 30% yield for **5f**; only after 48 h reaction, a

Table 3. Effect of trialkylamine in the reaction of **1** with benzylbromide

Rn	$PhCH_2Br$ (equiv)	Alkylamine (pK_a[b]) 3 equiv[a]	Product and yield of reaction after 20 h
1	3	Triethylamine (11.1)[17]	**5f**: 30% **5f′**: 37%
2	3	Tripropylamine (10.7)[17]	**5f**: 51% **5f′**: 32%
3	3	Tributylamine (10.9)[17]	**5f**: 63% **5f′**: 25%
4	3	$PhNMe_2$ (5.16)[18]	No reaction
5	3	Ph_2NMe (0.86)[18]	No reaction
6	3	Triphenylamine (−3.9)[18]	No reaction

[a] Reactions were carried out in 2 g scale of **1** (7.7 mmol) using dry DMF as solvent at 90 °C in an oil bath under Ar and magnetically stirred. The reported yields are after flash column chromatography separation.

[b] Dissociation reaction of the protonated amines in water.

reasonable 69% yield was obtained (Table 2, entry 8). 1,2-dibromoethane **4g** (Table 2, entry 9) successfully produced a 73% yield of 2,5-diethoxycarbonyl-3,4-ethylendioxy-thiophene **5g** in 20 h. These reactions confirm the general applicability of the method to several types of bromo-compounds. Monobromo derivatives react slower than dibromo because in the case of the latter the second alkylation reaction involves a faster intramolecular reaction instead of the two inter-molecular required for the former.

In order to speed up the reaction, the effect of using other trialkylamines with a longer alkyl-chain (Table 3) was tested. Benzylbromide was used as test compound, because, as mentioned, it reacts slowly and requires higher temperatures to complete the reaction faster.[6h]

Fortunately, as expected, the reaction was faster and the yield of dibenzylated compound increased from 30% using triethylamine to 63% using tributylamine in a reaction time of 20 h. This increase in the yield of the dibenzylated derivative **5f** with a trialkylamine of longer alkyl chain cannot be explained by a change in the basicity of the media. All the trialkylamines have almost the same pK_a value (see Table 3). As proposed by Merz,[14] a decrease in the dielectric constant of the media speeds up the substitution reaction of dianion **3** with the bromo derivatives. This fact is in agreement with a poor stabilized dianion in the less polar media; as a result, its reactivity increases. Aromatic amines failed in this reaction and the typical yellow color of dianion **3** was not observed. A minimum pK_a of 10 (the pK_a of CO_3^{2-} ion is 10.2) is required for a successful reaction with an organic base.

Finally, we tried the trialkylamine as sole base–solvent system for the double Williamson substitution reaction of **1** with bromo-derivatives (Table 4). The behavior using benzylbromide was similar to that for the reactions with DMF. The yield of the dibenzylated compound **5f** correlated with the trialkylamine alkyl chain length (Table 4, entries 1–3). The highest yield (65%) was obtained using tributylamine as base–solvent. Our last experiment with benzylbromide and tributylamine demonstrated that the reaction rate is enhanced dramatically without DMF, and a 61% yield of **5f** was obtained for only 12 h of reaction time (Table 4, entry 4). When triethylamine was used, a large quantity of solids was observed in the reaction flask, which hindered the magnetic stirring. By contrast, with tributylamine the reaction occurred in a biphasic system that allowed a nice stirring of the reaction, which probably contributed to the reaction performance.

This situation also occurred with α,α-dibromo-*o*-xylene **4d**, which also reacted better using tributylamine, producing a very acceptable 67% yield (Table 4, entries 7–8). The comparison between α,α-dibromo and dichloro-toluenes **4a** or **4b** using only tributylamine produced the same behavior observed when triethylamine–DMF was employed as the reaction system. Thus, dibromide **4a** reacted faster than dichloride **4b** (Table 4, entries 5–6), producing **5a** in 66% yield. These results demonstrate that if tributylamine is used as sole base–solvent system, DMF is not required as solvent. This is important for large-scale reactions that require huge quantities of water during purification to eliminate DMF; omitting DMF also decreases the time and cost associated with the use of this dry solvent.

Table 4. Reaction of **1** with bromo compounds **4** in 20 h of reaction using as base–solvent only the trialkylamine

Rn	Alkyl halide (equiv)	Trialkylamine	Product and yield
1	$PhCH_2Br$ (3)	Triethylamine	**5f**: 30% **5f′**: 37%
2	$PhCH_2Br$ (3)	Tripropylamine	**5f**: 51% **5f′**: 32%
3	$PhCH_2Br$ (3)	Tributylamine	**5f**: 65% **5f′**: 25%
4	$PhCH_2Br$ (3)	Tributylamine, 12 h	**5f**: 61% **5f′**: 16%
5	**4a** (1.3)	Tributylamine	**5a**: 66%
6	**4b** (1.3)	Tributylamine	**5a**: 12%
7	**4d** (1.3)	Triethylamine[a]	**5d**: 39%
8	**4d** (1.3)	Tributylamine[a]	**5d**: 67%

Reactions were carried out in 2 g scale of **1a** (7.7 mmol) using 20 mL of trialkylamine as base–solvent at 90 °C in an oil bath under Ar and magnetically stirred. Yields obtained after flash column chromatography.

[a] 10% CH_2Cl_2 was added to the ether for facilitate extraction.

3. Experimental

3.1. General

Overnight oven or flame-dried material was used for all the reactions. All the halide-compounds, and other solvents and reactives were used as received unless specified. Anhydrous DMF (Aldrich), KOH distilled trialkylamines, and oven dried K_2CO_3 were used.

3.2. Diethyl 2-phenylthieno[3,4-*d*][1,3]-dioxole-4,6-dicarboxylate (5a)

Optimization reactions procedure. Compound **1** (2 g, 7.7 mmol), DMF (30 mL), α,α-dibromo-toluene (1.3 equiv) and triethylamine (3 equiv) were placed in a 100 mL two neck round bottom reaction flask fitted with, a reflux condenser with argon balloon and a septa. The mixture was heated to 90–95 °C in an oil bath and magnetically stirred. After 20 h the reaction was cooled at room temperature and poured into 75 mL of ether. Triethylamine hydrobromide salt, white needles mp 255–258 °C, precipitates when reaction yield is high. The organic salt was filtrated and rinsed with 50 mL ether. The ethereal mixture was extracted from H_2O–brine solution (100 and 30 mL) with ether (3×100 mL). The organic extracts were collected and washed twice with the same ratio of H_2O–brine solution. The ethereal extract was $MgSO_4$ dried, filtered and concentrated in a rotary vacuum evaporator. The reaction products were separated by flash chromatography on silica gel using mixtures of EtOAc/petroleum ether (40–60 °C) as eluent. Product **5a** showed almost the same polarity of **1**, but did not show tailing on the SiO_2-TLC control. After solvent evaporation, a slightly yellow oil was obtained. A few mL of ether were added and the product was allowed to cool and crystallize (2.16 g, 83%). The recrystallization of this product yielded cream crystals mp 109–110 °C (ether/pentane). IR (KBr) ν cm^{-1}: 1707, 1625, 1597, 1429, 1377, 1309, 1264, 1084, 1028, 760. ^1H NMR ($CDCl_3$), δ ppm J = Hz: 7.57 (dd, 2H, $J = 7.6$, 1.5; *o*-HPh) 7.48 (s, 1H; CH), 7.47–7.40 (m, 3H; *m,p*-HPh), 4.32 (qd, 4H, $J = 7.1$, 1.1; CH_2CO), 1.33 (t, 6H, $J = 7.1$; CH_3). ^{13}C NMR ($CDCl_3$), δ ppm: 160.3, 150.5, 133.9, 131.1, 128.8, 126.6, 121.7, 105.4, 61.6, 14.2. MS (EI 70 eV) *m*/*z* (rel. int. %) $C_{17}H_{16}O_6S$ requires $[M^+]$ at 348.3713: $[M+1]^+$ 349 (9), M^+ 348 (60), 303 (11), 136 (10), 135 (100), 106 (39), 104 (7), 78 (12). HRMS FAB^+ *m*/*z*: $C_{17}H_{16}O_6S$ $[M+1]^{1+}$ calcd 349.3793, observed 349.3796. EA: $C_{17}H_{16}O_6S$ calcd C 58.61%, H 4.63%, S 9.39%; found C 58.54%, H 4.58%, S 9.39%.

For the macroscale synthesis of **5a** (**1** 30 g, 107 mmol), all the quantities of chemicals were linearly scaled-up using the same temperature and 24 h of reaction time. For the workup reaction the following volumes of solvents were used with a 2 L extraction funnel: reaction poured into 400 mL ether, crystals rinsed with 350 mL ether, ethereal mixture extracted with a H_2O–brine solution (700 mL and 200 mL), three times extraction with 400 mL ether, wash of organic phase with 500 mL H_2O–brine (4:1). After drying with $MgSO_4$, the solution was filtrated and concentrated in rotary vacuum evaporator until the precipitation of a small quantity of product on the flask walls (ca. 300 mL). Compound **5a** crystallized slowly from the concentrated ethereal solution in the fridge overnight. Next day the product was filtrated and washed with cold pentane to give 55–60% yield of a 98% purity product determined by NMR (cream crystals, mp 108–109 °C). Additional product (20–25%) can be recovered from the mother liquors by column chromatography on SiO_2 using mixtures of EtOAc/petroleum ether (40–60 °C) as eluent.

The reactions of **1** with alkyl dibromides **4c–e**, benzyl bromide, and 1,2-dibromoethane were carried out following the procedure described for **5a** optimization reactions. In these reactions, the sole experimental variation was whether the trialkylamine was used with or without DMF. For reactions using trialkylamine other than triethylamine, during the workup of reaction, the organic salt was not filtrated because it did not precipitate. Reactions without DMF were also extracted without filtration of the salt. The whole reaction mixture was dissolved in a small quantity of ether/water mixture and extracted using ether or ether with 10% CH_2Cl_2 (see table footnotes). The excess of trialkylamine was eliminated with two acid washes (25 mL of 20% HCl dissolved in 100 mL H_2O–brine 8:2) during extraction, followed by two rinses with H_2O–brine (100 mL 8:2). The ethereal fraction was treated as previously described for compound **5a**. All the products were separated by flash chromatography on silica gel using EtOAc/petroleum ether (40–60 °C) as eluent. The sole exception was product **5d**, which was separated using CH_2Cl_2/petroleum ether (40–60 °C) as eluent.

3.3. Diethyl 3-benzyl,4-hydroxy-2,5-thiophene-dicarboxylate (5f′)

This product was obtained from the reaction between **1** and benzyl bromide under the reaction conditions described for **5a** (Table 2, entry 6). No product crystallized from the ethereal concentrated mixture, but the change to diisopropyl ether and overnight cooling yielded 40% of product **5f′**. The recrystallization of an analytical sample of **5f′** yielded transparent needle crystals, mp 107–109 °C (CH_2Cl_2/diispropyl ether). IR (KBr) ν cm^{-1}: 3308, 1716, 1682, 1503, 1370, 1294, 1204, 1171, 1047, 1019. ^1H NMR ($CDCl_3$) δ ppm J = Hz: 9.5 (br-s, 1H, OH), 7.5 (d, 2H, $J = 7.6$, *o*-Ph), 7.35–7.25 (m, 3H, *m,p*-Ph), 5.33 (s, 2H, $PhCH_2$), 4.352, (q, 2H, $J = 7.1$ CH_2), 4.350, (q, 2H, $J = 7.1$, CH_2), 1.371 (t, 3H, $J = 7.1$, CH_3), 1.370 (t, 3H, $J = 7.1$, CH_3). ^{13}C NMR ($CDCl_3$) δ ppm: 165.8, 160.9, 155.8, 148.0, 136.6, 128.38, 128.30, 128.26, 120.5, 106.5, 75.0, 61.7, 61.4, 14.2, 14.18. MS (EI 70 eV) *m*/*z* (rel. int. %) $C_{17}H_{18}O_6S$ requires $[M^+]$ at 350.3872: M^+ 350 (31), 288 (5.5), 214 (19.6), 168 (10.1), 167 (17.6), 91 (100), 65 (10), 45 (11). HRMS FAB^+ *m*/*z*: $C_{17}H_{18}O_6S$ $[M+1]^{1+}$ calculated 351.3952, observed 351.3956. EA: $C_{17}H_{18}O_6S$ calcd C 58.27%, H 5.18%, S 9.15%; found C 58.35%, H 5.23%, S 9.18%. After flash chromatography (SiO_2) of the mother liquors of **5′** and using EtOAc/petroleum ether (40–60 °C) as eluent, a 25%

yield of dibenzylated compound **5f** was obtained. Due to the hard chromatographic separation of these two compounds, all the other ratios between **5f** and **5f′** were determined by the ^{1}H NMR signal of their benzylic protons (**5f** $\delta = 5.19$ ppm and **5f′** $\delta = 5.33$ ppm) in the crude mixture obtained passing it trough a short SiO_2 column (eluted with EtOAc/petroleum ether 40–60 °C).

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References and notes

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8. As example of this behavior, the synthesis of 2,5-diethoxycarbonyl-3,4-ethylendioxythiophene (**5** R = $-(CH_2)_2-$) in 24 h reaction time has a 70% yield, the synthesis of 2,5-diethoxycarbonyl-5-octyldioxeno[2,3-c]thiophene (**5** R = $-(CH_2CH(C_8H_{17})-)$ in 48 h reaction time has a 52% yield and the synthesis of 2,5-diethoxycarbonyl-5-tetradecyldioxeno[2,3-c]thiophene (**5** R = $-(CH_2CH(C_{14}H_{29})-)$ in 48 h reaction time has 24% yield. See Ref. [3h] for details.
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12. For this compound the typical acid-catalyzed acetal formation reactions using benzaldehyde, benzaldehyde dimethyl acetal or *p*-anisaldehyde dimethyl acetal and **1** in DMF or dry benzene or toluene also failed to produce compound **5a**. The acid catalysis must decrease the nucleophilicity of **1**, which by its nature is a poor nucleophile, due to the stability of its conjugated base (**1** is deprotonated with CO_3^{2-} ion). This explains why the syntheses of the **5** by the route depicted in Scheme 1 are carried out in basic media or by the use of the corresponding di-potassium salt **3**.
13. It was confirmed that the dipotassium salt (**3**) of **1** reduces rapidly the Ag(I) ion to Ag° in the basic conditions. This dialcoholate behaves as a reducing agent, common property of the alcohols in basic media. For examples see (a) Prato, M.; Quintily, U.; Scorrano, G. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1419–1424; (b) Shirra, A. *J. Chem. Soc., Perkin Trans. 2* **1977**, 759–765; (c) Muth, C. W.; Darlak, R. S.; Patton, J. C. *J. Heterocycl. Chem.* **1972**, *9*, 1003–1007.
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