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ORIGINAL PAPER

A new procedure for the synthesis of 2-[(4-dodecyloxyphenyl)sulfonyl]butanoic acid

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A new, practical and cost-effective route for scalable synthesis of 2-[(4-dodecyloxyphenyl)sulfonyl] butanoic acid, a key intermediate of a new cyan dye-forming coupler containing a sulfone group, was developed by adopting phenol as the starting material. The synthesis was accomplished in five steps with etherification, chlorosulfonation, reduction, nucleophilic reaction by C–S coupling and hydrolyzation. An important objective of the new synthetic route was the synthesis of 2-[4-(dodecyloxyphenyl)sulfonyl]butanoate. Overall yield obtained at optimized conditions increased to 66 %. The synthetic strategy was proven to be a process enabling rapid delivery of the target product with high purity.

Keywords: cyan dye-forming coupler, 2-[(4-dodecyloxyphenyl)sulfonyl]butanoic acid, phenol, C–S coupling.

Introduction

Cyan dye-forming coupler *I* (Fig. 1), a typical class of dye-forming couplers for silver halide photosensitive materials in terms of improved color reproducibility and image dye stability, has been extensively used in color photographic film and paper products (Begley et al., 2001). 2-[(4-Dodecyloxyphenyl)sulfonyl]butanoic acid (*II*) (Fig. 1) is the key building block of *I*. Compound *II* has been successfully substituted for other intermediates because of its better stability.

An important method (Fig. 2) for the preparation of *II* (Han et al., 2011) involved the reaction of 4-mercaptophenol and 2-bromobutyric methyl ester. Subsequent oxidation, etherification and hydrolization provided *II* in a 57.4 % yield. However, the critical factor which has prevented this strategy from becoming the preferential synthesis route was the high cost of 4-mercaptophenol (*III*), and the development of the process was limited by non-availability of the starting materials. Furthermore, this method is impractical for large-scale preparation of *II* because of the high ignitability and instability of hydrogen peroxide as the oxidant and lower overall yield of the final product. Thus, a reinvestigation of possible synthesis routes providing *II* was necessary to accelerate the scale-up development and quick delivery of the product with high purity.

Considering the drawbacks of the previous method, an inexpensive and efficient process for the key intermediate *II* was attempted (Fig. 3). The new procedure substituting phenol for 4-mercaptophenol is more economical and superior to those presented in literature (Han et al., 2011). To accomplish high-quality synthesis of *II*, some published procedures (Murár et al., 2013) were applied to the synthesis of *II* to reduce the safety issues and to improve the overall yield of the method. Etherification of phenol and 1-bromododecane was first studied. 2-[4-(Dodecyloxyphenyl)sulfonyl]butanoate (*VI*) was introduced as an intermediate by way of chlorosulfonation, reduction and a nucleophilic reaction. Sub-

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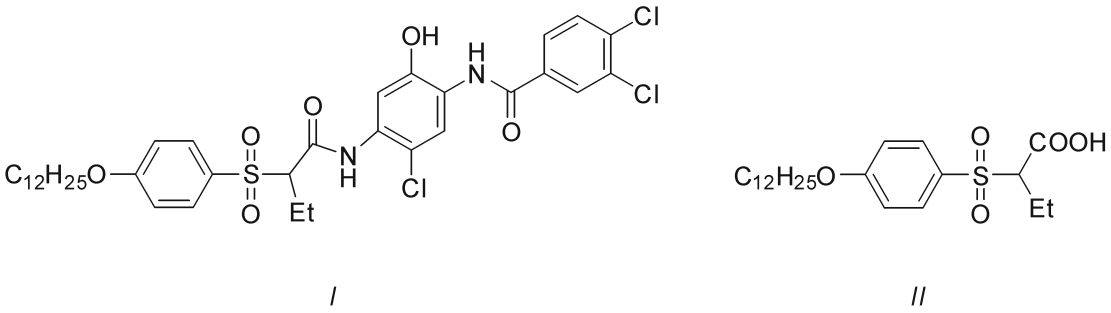
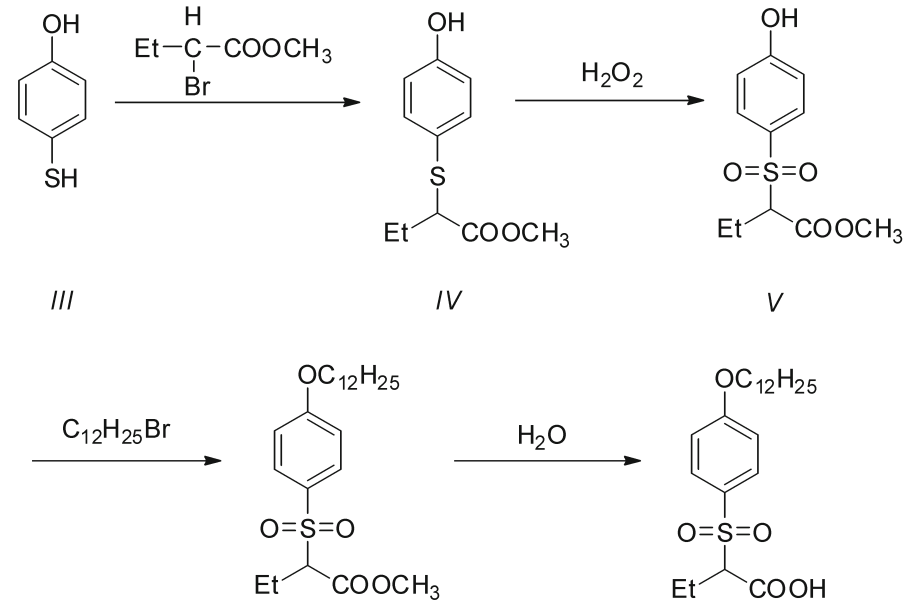


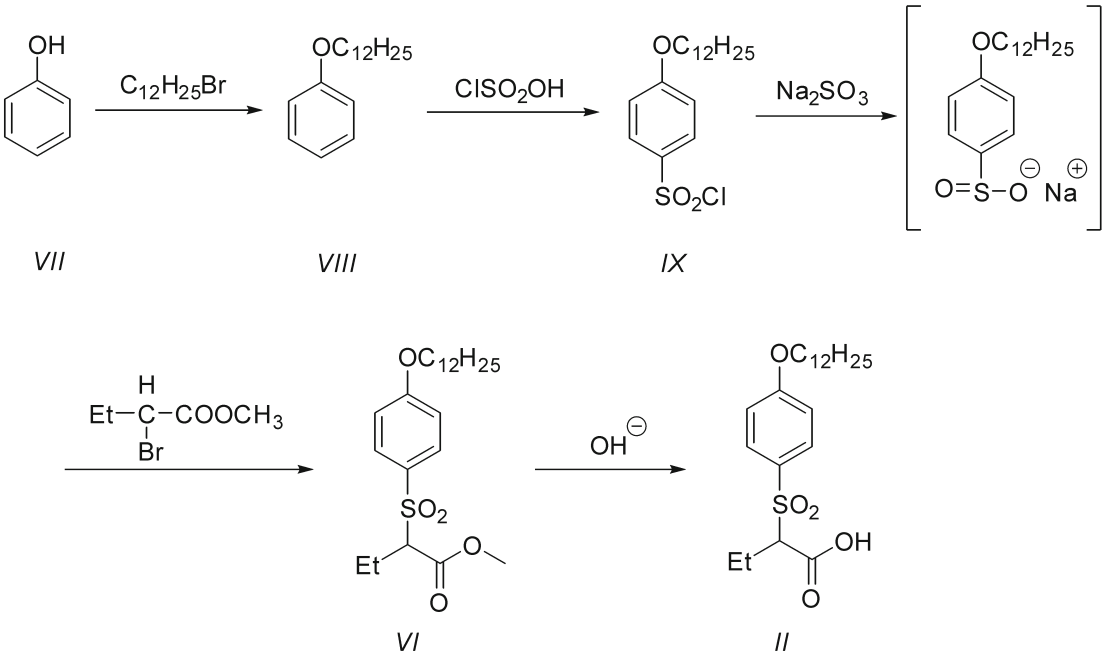
I *II*

Fig. 1. Structure of cyan dye-forming coupler (*I*) and 2-[(4-dodecyloxyphenyl)sulfonyl]butanoic acid (*II*).



III *IV* *V*

Fig. 2. Previous method for the synthesis of *II* (Han et al., 2011).



VII *VIII* *IX*

VI *II*

Fig. 3. Summary route to the key intermediate *II*.

Table 1. Spectral data of the corresponding compounds

Compound	Spectral data
VIII	^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.26–7.13 (m, 2H), 6.91–6.74 (m, 3H), 3.87 (t, J = 6.6 Hz, 2H), 1.70 (dt, J = 13.5 Hz, J = 6.7 Hz, 2H), 1.37 (dd, J = 13.7 Hz, J = 6.3 Hz, 2H), 1.19 (s, 16H), 0.81 (t, J = 6.5 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$), δ: 158.13, 128.36, 119.41, 113.49, 66.87, 30.91, 28.65, 28.63, 28.59, 28.57, 28.40, 28.34, 28.30, 25.06, 21.68, 13.10
IX	^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.88 (d, J = 9.0 Hz, 2H), 6.95 (d, J = 9.0 Hz, 2H), 3.98 (t, J = 6.5 Hz, 2H), 1.83–1.66 (m, 2H), 1.38 (dd, J = 13.8 Hz, J = 6.3 Hz, 2H), 1.19 (s, 16H), 0.81 (t, J = 6.5 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$), δ: 163.53, 134.78, 128.52, 114.07, 67.94, 30.90, 28.62, 28.61, 28.55, 28.50, 28.32, 28.27, 27.88, 24.87, 21.67, 13.10
VI	^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.69 (d, J = 8.9 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 3.95 (t, J = 6.5 Hz, 2H), 3.78 (dd, J = 11.2 Hz, J = 3.9 Hz, 1H), 3.64 (s, 3H), 1.99 (dqd, J = 15.0 Hz, J = 7.5 Hz, J = 4.0 Hz, 1H), 1.85 (ddd, J = 13.5 Hz, J = 11.3 Hz, J = 7.2 Hz, 1H), 1.79–1.65 (m, 2H), 1.47–1.34 (m, 2H), 1.20 (s, 16H), 0.88 (t, J = 7.4 Hz, 3H), 0.81 (t, J = 6.7 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$), δ: 165.66, 162.84, 130.52, 127.05, 113.60, 71.47, 67.60, 51.83, 30.90, 28.63, 28.61, 28.56, 28.52, 28.32, 27.98, 24.93, 21.67, 19.86, 13.09, 10.42
II	^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.73 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 6.74 (s, 1H), 3.95 (t, J = 6.5 Hz, 2H), 3.80 (dd, J = 11.1 Hz, J = 3.9 Hz, 1H), 2.08–1.93 (m, 1H), 1.92–1.79 (m, 1H), 1.80–1.66 (m, 2H), 1.48–1.33 (m, 2H), 1.19 (s, 15H), 0.94 (t, J = 7.4 Hz, 3H), 0.81 (t, J = 6.6 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$), δ: 169.12, 163.01, 130.58, 126.70, 113.77, 71.36, 67.66, 30.90, 28.64, 28.61, 28.57, 28.53, 28.33, 27.98, 24.93, 21.67, 19.87, 13.10, 10.38

sequently, *VI* was directly converted to *II* via a modified hydrolization process. In this paper, this route was subjected to further studies and an optimized process with the yield of 65.8 % is described.

Experimental

The reactants were supplied by Jiangxi Renming Pharmaceutical Chemicals (China) and all solvents were purchased from Sinopharm Chemical Reagent (China). TLC analyses were performed on a glass plate (30 mm × 100 mm). GC analyses were performed on a GC Agilent 1790F series. HPLC analyses were done on an HPLC Agilent 1100 series. Melting points were determined using a melting point apparatus (INESA, WRS-2). ^{1}H NMR and ^{13}C NMR spectrums were recorded in $CDCl_3$ on a NMR spectrometer (Bruker, AV 400) using 400 MHz and 100 MHz. Spectral data of prepared compounds are in Table 1. and in supplementary data.

(Dodecyloxy)benzene (VIII)

Phenol (18.95 g, 0.2 mol), K_2CO_3 (55.66 g, 0.4 mol) and butan-2-one (80 g) were heated to reflux under stirring for 0.5 h. Then, 1-bromododecane (50.18 g, 0.2 mol) was added dropwise to the solution. A Dean–Stark apparatus was used to remove water from the reaction by azeotropic distillation. After a further 4 h, butan-2-one was distilled and then the reaction mixture was slowly cooled to 25 ℃, followed by dilution with water (100 mL) and extraction with ethyl acetate (2 × 75 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The result was a white solid (*VIII*). Yield: 48.67 g (92.1 %). Melting point: 24.7–25.6 ℃.

p-Dodecyloxybenzenesulfonyl chloride (IX)

Chlorosulfonic acid (26.64 g, 0.23 mol) was added dropwise to a stirred mixture of NaCl (3 g, 0.05 mol) and *VIII* (20.00 g, 0.076 mol) in CH_2Cl_2 (120 mL) at 15 ℃. The mixture was kept at this temperature for 3 h; then, the mixture was slowly poured into an ice-water mixture (300 g). The organic layer was partitioned and the water layer was extracted with CH_2Cl_2 (50 mL). The combined organic phase was washed with a saline solution, dried over Na_2SO_4 and condensed under reduced pressure. The product (*IX*) was purified by recrystallization from ethanol. Yield: 24.18 g (87.9 %). Melting point: 35.0–37.0 ℃.

2-[4-(Dodecyloxyphenyl)sulfonyl]butanoate (VI)

Sodium sulfite (12.61 g, 0.1 mol) and sodium bicarbonate (8.40 g, 0.105 mol) were added to 100 mL of water and 10 mL of tetrahydrofuran and then stirred. When the salts dissolved completely, *IX* (18.05 g, 0.05 mol) was added and the temperature of 15 ℃ was maintained for 12 h, while stirring. Upon the reaction completion, the precipitated solid was obtained by filtration and the filter cake was directly added to a stirred mixture of 2-bromobutyric acid methyl ester (9.05 g, 0.05 mol) and methanol (200 mL), which was then heated to 60 ℃. The progress of the reaction was monitored by GC up to complete disappearance of 2-bromobutyric acid methyl ester. The resulting mixture was then cooled to room temperature and the first precipitated solid was removed by filtration. *VI* was further crystallized from the filtrate. Yield: 18.27 g (85.6 %). Melting point: 47.9–48.9 ℃.

2-[(4-dodecyloxyphenyl)sulfonyl]butanoic acid (II)

To a solution of NaOH (3.2 g, 0.08 mol) dissolved in 80 mL of water 2-[[4-(dodecyloxyphenyl]sulfonyl]butanoate (*VI*) (17.1 g, 0.04 mol) was added. The mixture was stirred at 75 °C for 2 h. The reaction mixture was then cooled to room temperature acidified with 1 M HCl (80 mL) to precipitate a solid mass (*II*), which was purified by filtration. Yield: 15.71 g (95.0 %). Melting point: 81.3–82.6 °C.

Results and discussion

Preparation of (dodecyloxy)benzene (VIII)

In order to find a convenient method for the synthesis of (dodecyloxy)benzene (*VIII*), the method reported by Haap (2006) was applied with some modifications. In this method, phenol is used as the raw material reacting with an equivalent amount of 1-bromododecane in *N*, *N*-dimethylformamide under moderate temperature. In preliminary experiments, the high hydroscopicity of the solvent resulted in a byproduct which was formed by hydrolyzation of 1-bromododecane. Thus, the conversion of phenol at a high rate could not be achieved and a low yield was obtained. Considering this issue, a series of solvents were screened in order to find an optimal solvent. The results showed that no conventional solvent provides the desired product *VIII* except for butanone (Table 2). Compared with other solvents, butanone has the advantage of forming a low boiling point azeotrope. Water was eliminated from the process by a Dean–Stark apparatus. At the end of the reaction, the solvent, butanone, was evaporated under reduced pressure for recycling and *VIII* was collected by extraction with ethyl acetate. The salts were filtered on a Buchner funnel under vacuum and the filtered liquor was distilled under vacuum to provide the desired product as a white solid.

Table 2. Screening of solvents for the synthesis of *VIII*[a]

Solvent	Temperature/ °C	Time/h	Yield[b]/%
N,*N*-Dimethylformamide	80	4	87.3
Cyclohexanone	80	4	83.3
Butan-2-one	80	4	92.1
Toluene	80	4	78.5
Tetrahydrofuran	80	4	75.4
Cyclohexane	80	4	80.4

a) All reactions were charged with phenol : 1-bromododecane : K_2CO_3 = 1 : 1 : 2 (molar ratio); *b*) yields were determined by GC with butanoic acid ethyl ester as the internal standard.

Preparation of p-dodecyloxybenzenesulfonyl chloride (IX)

A variety of methods for the preparation of sulfonyl chlorides are available, including the Reed reaction (Reed, 1933, 1934, 1938), chlorosulfonation with chlorosulfonic acid (Alam et al., 2007), chlorination of sulfonic acid (Greig et al., 2006), etc. Chlorosulfonic acid is an easy to use eco-friendly reagent efficiently converting reactants to the corresponding sulfonyl chlorides. In our improved process, sodium chloride was an additional reagent reacting with the redundant sulfuric acid providing sodium hydrogen sulfate and HCl; experimental data showed that it can accelerate the reaction process (Table 3). In addition, the molar ratio of *VIII* and chlorosulfonic acid played an important role in the yields. However, an increase in the chlorosulfonic acid concentration does not correspond to the increase in the reaction yield. In literature (Feng et al., 2011), the yield of *IX* was lower than 80 %. Decreasing the amount of chlorosulfonic acid seemed to be favorable (Table 3) as under the same conditions, the participation of sodium chloride resulted in an increased yield of *IX* (Table 3, entries 2, 4, 6).

Preparation of 2-[4-(dodecyloxyphenyl) sulfonyl]butanoate (VI)

Sulfinates were prepared by two approaches: reduction with zinc or sodium sulfite (Field & Clark, 1963). The first approach reported by Frank C. Whitmore and Hamilton (1922) involves the application of metal zinc. However, the catalyst resulted in a large amount of metal residue causing serious negative environmental problems. Therefore, the second approach, where

Table 3. Different equivalents of acids and NaCl screening for the preparation of *IX*[a]

Entry	Molar ratio of *VIII* : $ClSO_3H$	Mass of NaCl/g	Time/h	Yield/%
1	1 : 2	–	4	75.3
2	1 : 2	3	3	81.1
3	1 : 3	–	4	79.7
4	1 : 3	3	3	87.9
5	1 : 4	–	4	75.4
6	1 : 4	3	3	82.0

a) Solvent used in all reactions was CH_2Cl_2 and the reaction temperature was 15 °C.

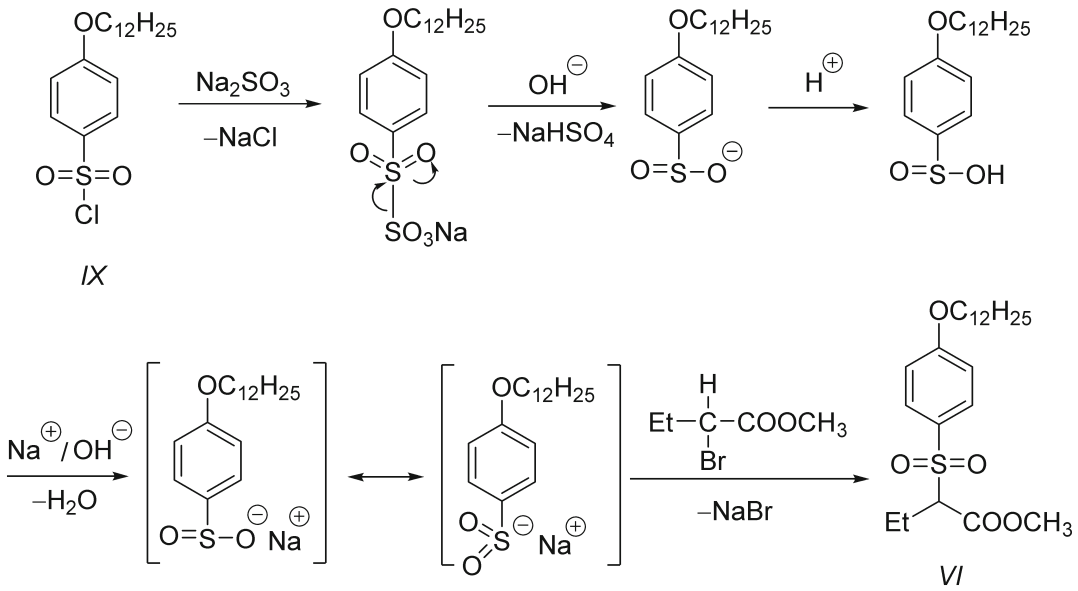


Fig. 4. Mechanism of the synthesis of *VI*.

Table 4. Effects of bases on the yield (*VI*)[a]

Entry	Base	Yield/%
1	–	70.3
2	NaOH	74.8
3	Na_2CO_3	77.1
4	Na_2HPO_4	80.2
5	$NaHCO_3$	85.6

a) Reduction condition: mole ratio of *IX* : Na_2SO_3 : base of 1 : 2 : 2.1, reaction temperature of 15 °C, solvent = a mixture of 100 mL of water and 10 mL of tetrahydrofuran. Nucleophilic reaction condition: mole ratio of *IX* : 2-bromobutyric acid methyl ester of 1 : 1, reaction temperature of 60 °C, solvent = methanol.

sulfonic chloride is reduced by sodium sulfite (Krishna & Singh, 1928) is investigated in this study. The assertion that the alkali metal salts of sulfinic acids give only sulfones on alkylation with alkyl halides has been confirmed repeatedly (Wildeman & Van Leusen, 1979). In the present study, reduction was combined with nucleophilic reaction so that the process of purification was greatly simplified. Based on the analysis of Smiles and Bere (1941) and to our further study, the possible mechanism of synthesis of *VI* presented in Fig. 4. can be assumed. Alkalinity of the solution played a major role in the formation of the intermediate. Under this hypothesis, reactions of *IX* and sodium sulfite were carried out under diverse alkaline conditions (Table 4).

Experimental data in Table 4 indicate that the increase in the basicity of the base resulted in lower yield of *VI* and that sodium bicarbonate as the reductant (Table 4, entry 5) is more favorable than other bases. Sulfonylchloride is easily hydrolyzed under higher temperatures, but the hydrolyzation process is inhibited at lower temperatures. Thus, it is unreasonable to increase the temperature of the reduction reaction. The reaction time was determined by the conversion of *IX* which was monitored by TLC. Upon completion of the reduction, the mixture was filtered and then the filter cake was directly added to a stirred mixture of 2-bromobutyric acid methyl ester and different solvents. As shown in Table 5, methanol resulted in the best yield of this reaction compared with other solvents. Using solvents like ethanol, isopropanol, dichloroethane and DMF, the yield and purity of the products were lower. DMF is usually the best solvent for nucleophilic reactions. Nevertheless, the use of DMF in this reaction gave an unexpectedly low yield probably due to the hydrolysis of 2-bromobutyric acid methyl ester. Therefore, to minimize the moisture content, water-carrying agents were added to DMF (Table 5, entries 6, 7) to form azeotropes with water so that it could be removed from the reaction by azeotropic distillation. Similarly, the Dean-Stark apparatus was used to remove water produced in the reaction.

To our delight, the decreasing temperature led to direct *VI* crystallization in methanol. Moreover, the solubility of sodium bromide in methanol was lower than that of *VI*. After the reaction completion, the reaction mixture was cooled to room temperature and the precipitated sodium bromide was removed by filtration. Then, the filtrate was cooled to lower temperature and the product was obtained. Hence, methanol was chosen as the best solvent for the reaction and crystallization process. Under optimal condition, the yield of *VI* was 85.6 % and the purity of *VI* reached as high as 99.5 %. The chemical structure of *VI* was confirmed by ^{1}H NMR and ^{13}C NMR spectra and its purity was determined by HPLC.

Table 5. Screening of solvents for the synthesis of *VI*[a]

Entry	Solvent	Temperature/℃	Yield/%	Purity/%[b]
1	Methanol	60	85.6	99.5
2	Ethanol	60	75.7	99.0
3	Isopropanol	60	72.1	98.9
4	Dichloroethane	60	70.1	97.3
5	DMF	60	65.7	95.0
6	DMF + toluene	60	85.8	96.2
7	DMF + cyclohexane	60	82.3	95.6

a) Reduction condition: mole ratio of *IX* : Na_2SO_3 : $NaHCO_3$ of 1 : 2 : 2.1, reaction temperature of 15 ℃, solvent = a mixture of 100 mL of water and 10 mL of tetrahydrofuran. Nucleophilic reaction condition: mole ratio of *IX* : 2-bromobutyric acid methyl ester of 1 : 1; *b*) Separations were performed using a reverse-phase C18 column. HPLC analysis conditions included the mobile phase (acetonitrile : methanol = 60 : 40 (vol.) at 1.0 mL min^{-1}), detection wavelength (254 nm) and retention time (15.3 min).

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The hydrolysis reaction was used to convert an ester into the corresponding carboxylic acid (Aranapakam et al., 2003). The reaction of *VI* was performed in the presence of NaOH in water employing the modified method to get *II* as a solid mass. Eventually, *II* was obtained by filtration after the reaction mixture acidification with 1 M HCl. The yield of the final hydrolysis product was 95 % and its purity was over 95.0 % after its recrystallization from 1,2-dichloroethane.

Conclusions

The key intermediate *II* was successfully prepared using a new and efficient method. This synthetic sequence is more suitable for further optimization and scale-up because it benefits from the use of inexpensive starting materials, the synthesis of *VI* and acceptable yields. This paper presents a significant improvement with respect to the usual methods and the total yield of up to 65.8 %.

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Supplementary data

Supplementary data (spectral data of prepared compounds) associated with this article (A new procedure for the synthesis of 2-[(4-dodecyloxyphenyl)sulfonyl]butanoic acid) can be found in the online version of this paper (DOI: 10.1515/chempap-2015-0125).

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