JOC Note

Facile Multistep Synthesis of Isotruxene and Isotruxenone†

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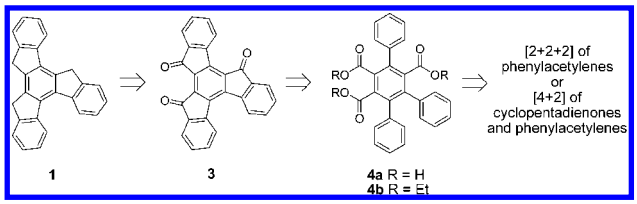
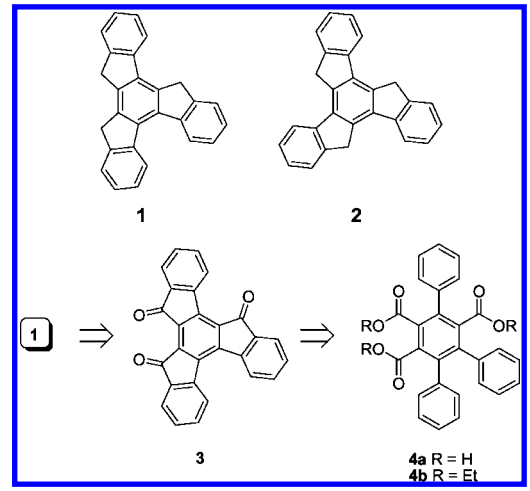


Three multistep approaches toward facile syntheses of isotruxene (**1**) and isotruxenone (**3**) are reported. The ortho−para conjugated backbone in the precursor **4** was constructed by either Co-catalyzed [2 + 2 + 2] cyclotrimerization or the [4 + 2] Diels−Alder reactions. The regioselectivity of the triple intramolecular Friedel−Crafts acylation of **4** plays the key role in determining the overall yield. Compared to the previous one-step method, the current approaches are more efficient in terms of product yield (27−36% vs 4−18%) and purification (i.e., free of column chromatography).

Isotruxene (**1**) is an isomer of truxene (**2**), and they differ in the arrangement, and thus the conjugation interactions, of the phenylene groups: namely, the peripheral phenylenes are ortho−para conjugated with respect to the central ring in **1**, it is meta−meta conjugated in **2**. Since the ortho and para conjugation interactions are inherently stronger than the meta one, the planar isotruxene scaffold is a potential phenylene-based branching unit for the development of new hyperbranched,[1] star-shaped,[2−5] and dendritic[6,7] π-conjugated systems of strong interbranch electronic couplings. For example, we recently revealed that the star-shaped isotruxene−oligofluorene hybrids demand a lower oxidation potential for generating the hole carrier and shorter π-conjugated backbone for achieving blue emission than the truxene−oligofluorene counterparts.[4] However, unlike the well-documented truxene derivatives,[5,7−9] the corresponding isotruxene chemistry is much less explored.[3,4] One of the most important origins could be ascribed to the poorly developed synthesis of isotruxene building blocks, including the parent isotruxene **1** and the isotruxenone **3**. Both of the two currently known methods for the preparation of **1** are the cyclotrimerization of indene.[3,10] The reactions suffer from either the requirement of a harsh condition (20 atm and 350 °C)[10] or the limitation of a small reaction scale (∼10 mmol).[3] Even worse are the low yields (∼18%) and the difficulties of product purification (i.e., by column chromatography with extreme care or small quantity). The subsequent synthesis of **3** from the oxidation of **1** by CrO_3 was also reported to be of low yield (21%).[10] To circumvent these problems, we have devised new methodologies toward facile synthesis of **1** and **3**, i.e., through the precursors **4a** or **4b** (Scheme 1). Our results reported herein significantly improve the yields and reduce the efforts in product purification.

SCHEME 1



To construct the ortho−para π-conjugated backbone with the desired carboxylic acid or ester substituents shown in **4**, our

† This paper is dedicated to Prof. Kwang-Ting Liu on the occasion of his 70th birthday.

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SCHEME 2

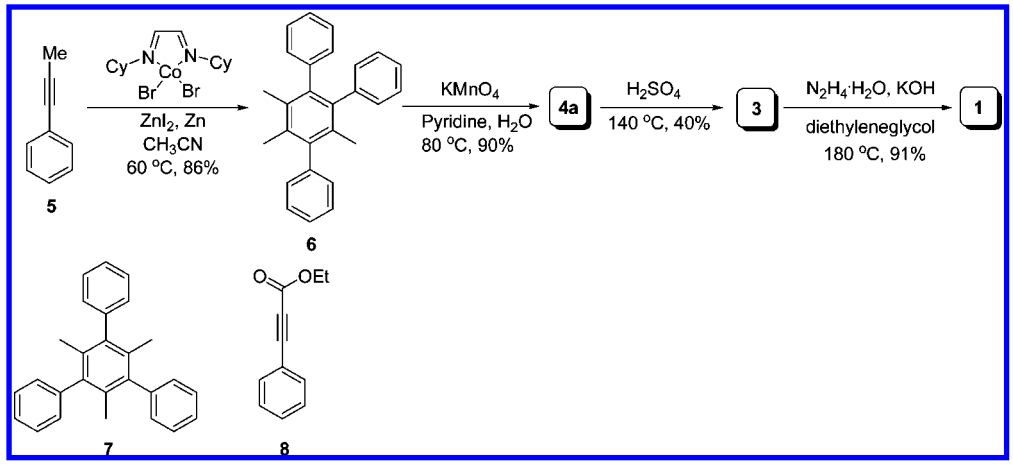
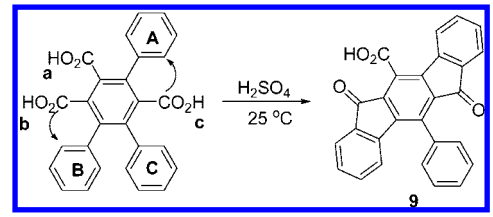


TABLE 1. Temperature Effect on the Yield of 3 and the Reaction Time for the Triple Intramolecular Friedel−Crafts Acylation of 4a

entry	temperature (°C)	time (min)	yield (%)
1	25	180	0
2	60	120	20
3	80	120	27
4	140	5	40
5	160	5	40

first approach is to adopt the protocol of Co-catalyzed [2 + 2 + 2]-cyclotrimerization of alkynes.[11] As shown in Scheme 2, we used the commercially available 1-phenylpropyne (**5**) for this purpose. The regioselective cyclotrimerization of **5** has been previously reported,[11] namely, the desired ortho−para system **6** is the major product (86%), and the meta−meta derivative **7** is a minor one (not isolated). Oxidation of the methyl groups of **6** with potassium permanganate in aqueous pyridine afforded **4a** with a high yield (90%). It should be noted that an attempt to construct the scaffold of **4b** in one step through the same [2 + 2 + 2]-cyclotrimerization method directly with ethyl phenylpropiolate (**8**) was unsuccessful. For the subsequent conversion of **4a** → **3**,[12] the yield is strongly temperature-dependent. As shown in Table 1, the yield increases and the reaction time decreases with raising the reaction temperature from 25 to 140 °C. No further increase of the yield was found at 160 °C. This can be rationalized by the competing side reaction shown in Scheme 3. As compared to phenyl ring A, phenyl rings B and C are expected to be less coplanar with the central ring due to larger steric hindrance. Consequently, the electrophilic addition of carboxylic acid group c to phenyl ring A should be more favorable than to ring C and thus lead to the formation of **9** (25 °C, 65% yield). However, such a preference is reduced upon raising the temperature, presumably due to the

SCHEME 3



increased torsional fluxions of phenyl ring A. The observed 40% yield for **3** from **4a** is close to the theoretical 50% yield for a nonselective attack of carboxylic acid group c toward phenyl ring C vs A. The isotruxene scaffold **1** was then accomplished by the Wolf−Kishner reduction of **3** in a yield of 91%. The overall yield of **1** with the four-step method shown in Scheme 2 is 28%, which is increased by more than 50% as compared to the previous one-step method (18%). More importantly, there is no need of column chromatography in product purification for all the steps, which is a merit for large-scale practice (e.g., 20 g).

Despite the significant improvement of the synthesis of **1** and **3** outlined in Scheme 2, one potential problem emerges in their subsequent derivatization. We have sometimes found contamination of a trace amount of truxene-based isomers that is undetectable with NMR but detectable with fluorescence spectroscopies in the final isotruxene-based π-conjugated materials. The contamination, albeit in a trace amount, is hardly removed and could cause severe interference in the photophysical studies. This phenomenon suggests that the precursor **6** is already contaminated with the isomer **7**, which might not be readily recognized based on ^{1}H and ^{13}C NMR spectroscopies. More specifically, the three chemically nonequivalent methyl groups in **6** display only two proton resonance peaks at 2.06 and 1.73 ppm with a 2:1 ratio. The signal of the methyl groups in **7** happens to overlap with the peak of **6** at 1.73 ppm. Thus, within the experimental error of peak integration, the presence of a small quantity of **7** in **6** would be hardly ascertained. Figure 1a shows one such example. The intensity ratio of the 2.06 to 1.73 ppm signal in this sample is very close to 2 (1.91), and it was later shown to be contaminated. For comparison, Figure 1b shows the corresponding region of ^{1}H NMR spectrum for another sample prepared using a less-selective palladium catalyst.[13] According to the integration, the ratio of **6/7** is ca.

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(12) Although **3** is a known compound, its NMR spectra are unknown. The ^{1}H NMR spectrum of **3** is provided in the Supporting Information, but due to its poor solubility, the corresponding ^{13}C NMR spectrum is not determined.

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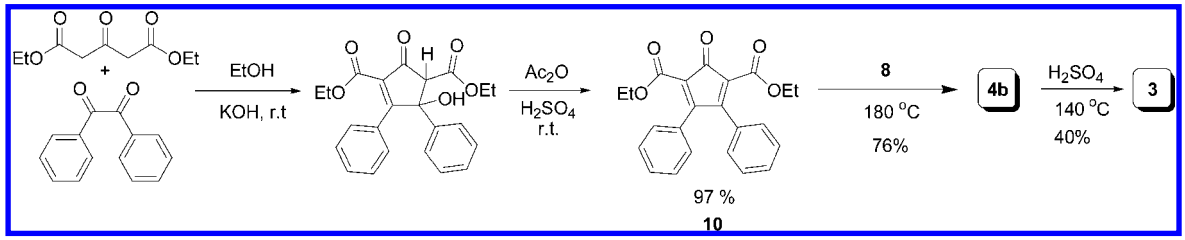
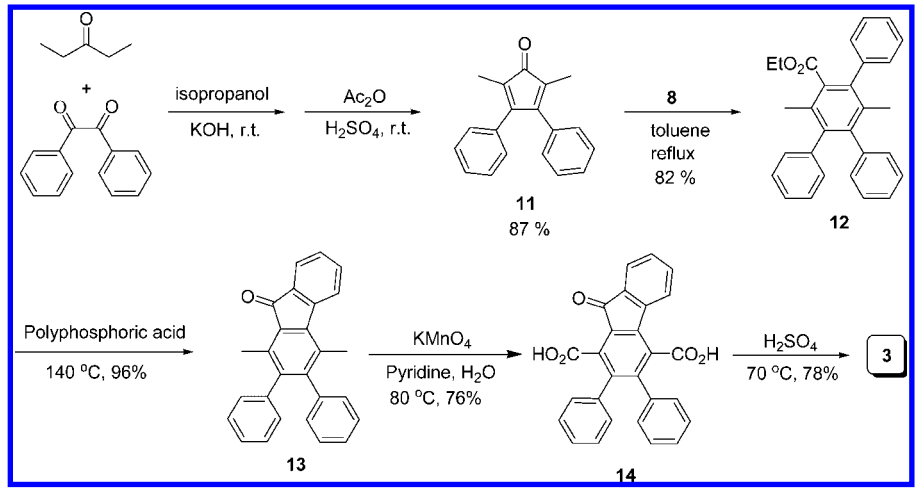
SCHEME 4



SCHEME 5



3:1. As shown in Figure 1c and d, similar situation is also present in their ^{13}C NMR spectra: namely, the signal of the methyl groups in **7** (19.6 ppm) overlaps with one of the three methyl signals of **6** (19.6, 18.4, and 18.2 ppm). While this problem could be resolved by integration with careful baseline correction along with multiple recrystallization of the product **6**, we decided to explore alternative synthetic strategies that provide only the desired π-conjugated pattern.

As shown in Scheme 4, the scaffold of **4b** can be constructed through the Diels−Alder reaction of the diethoxycarbonyldiphenylcyclopentadienone **10** and ethyl 3-phenylpropiolate (**8**). The starting material **10** was in turn prepared according to the literature procedures from diethyl 1,3-acetonedicarboxylate and benzil.[14] As is the condition for the transformation of **4a** → **3**, compound **4b** could be directly converted to **3** with the same yield (40%). Compared to the first approach (Scheme 2), this one adds one more step toward the isotruxenone **3** (4 steps) and isotruxene **1** (5 steps). Nonetheless, the overall yield is essentially the same (31% vs 30% and 28% vs 27%, respectively). Like the first approach, there is no need of column chromatography for product purification in all these steps. More importantly, the purification of the products is rather straightforward and it is free of contamination of hardly recognized side products toward **1** and **3**.

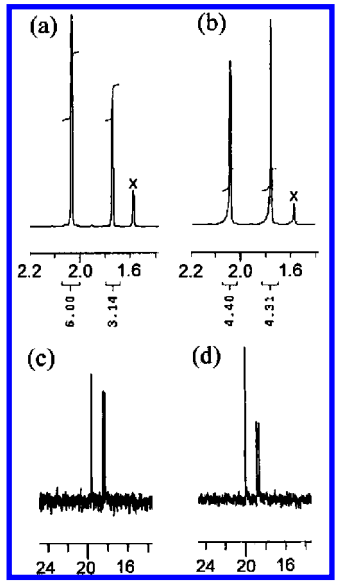


FIGURE 1. Comparison of the ^1H (a and b) and ^{13}C (c and d) NMR spectra ($CDCl_3$) of two samples of **6** containing a small (a and c) and significant amount (b and d) of **7**.The mark × denotes the signal of H_2O.

The intramolecular Friedel−Crafts acylation of **4** → **3** is a common step for both the first (Scheme 2) and the second (Scheme 4) approaches toward the synthesis of **1** and **3**. Because of the unfavorable regiochemistry, this step is also responsible for the low yield of the final products.

To circumvent the undesired side reaction shown in Scheme 3, we have carried out the third approach by modifying the second one. As shown in Scheme 5, a replacement of diethyl 1,3-acetonedicarboxylate with 3-pentanone for the condensation reaction with benzil leads to the dimethyldiphenylcyclopentadienone **11**, which exists as a dimer at room temperature.[15] The subsequent Diels−Alder reaction with **8** provides the monoester **12**, which undergoes single Friedel−Crafts acylation to form **13** in hot polyphosphoric acid. The two methyl groups were then oxidized to provide **14** in a way similar to that for **6** → **4a** (Scheme 2). The subsequent double Friedel−Crafts acylation will lead to the desired product **3** without the complication of

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regiochemistry. Although this "regio-controlled" approach lengthens the synthetic route by two more steps (i.e., 6 steps to **3**), the overall yield of **3** is higher than that of the previous two approaches (40% vs 30%).

In summary, we have developed three different facile synthetic approaches toward isotruxene (**1**) and isotruxenone (**3**). Although the synthesis of **1** requires 4−7 steps, none of the steps requires the use of column chromatography for product purification and the overall yields are all higher than the previous one-step methods. Our results should facilitate the development of isotruxene-based materials.

Experimental Section

Three key synthetic steps, which for the preparation of compounds **1**, **3**, and **4b** are described in the following text, and the synthesis and characterization data of **4a**, **6**, **9**, and **12**−**14** are presented in the Supporting Information.

Synthesis of Isotruxene (1) from Isotruxenone (3). The isotruxenone **3** (9.00 g, 23.4 mmol) was suspended in diethylene glycol (450 mL) containing KOH (45.0 g, 802 mmol). Hydrazine monohydrate (25.0 g, 1.32 mol) was added. The mixture was heated at 180 °C for 24 h and then cooled to ca. 60 °C. The warm solution was poured into ice containing HCl. The precipitate was filtered, washed with H_2O, and dried. The precipitate was then dissolved in CH_2Cl_2 and passed through a thin layer of silica gel. The CH_2Cl_2 solvent was then removed under reduced pressure and the crude product was recrystallized from $CHCl_3$/MeOH to afford the white solid of isotruxene with a yield of 91%. mp = 218−220 °C (lit.[3] 218−220 °C); ^{1}H NMR (400 MHz, $CDCl_3$): 3.99 (s, 4H), 4.25 (s, 2H), 7.31−7.39 (m, 3H), 7.43−7.50 (m, 3H), 7.59−7.63 (m, 2H), 7.67 (d, J = 7.2 Hz, 1H), 7.91 (d, J = 7.2 Hz, 1H), 8.58 (t, J = 8.4 Hz, 2H) ppm.

Synthesis of Isotruxenone (3). (a) From Compounds **4a** or **4b**: In a 250 mL round-bottom flask was added 100 mL of concd H_2SO_4 (17.7 M) and heated to 140 °C under stirring. A batch of 10.0 g of a powder of compound **4a** (22.8 mmol) or **4b** (19.1 mmol) was then added, and the mixture was kept at 140 °C for 5 min. After being cooled to room temperature, the solution was poured into ice. The mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine, and the CH_2Cl_2 solvent was removed under reduced pressure. The crude product was recrystallized from $CHCl_3$/MeOH to afford the orange solid of isotruxenone with a yield of 40%. (b) From Compound **14**: In a 250 mL round-bottom flask was added 100 mL of concd H_2SO_4 (17.7 M) and heated to 70 °C under stirring. A batch of 10.0 g of a powder of compound **14** (23.7 mmol) was then added and the mixture was kept at 70 °C for 3 h. After cooling to room temperature, the solution was poured into ice. The mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine, and the CH_2Cl_2 solvent was removed under reduced pressure. The crude product was recrystallized from $CHCl_3$/MeOH to afford the orange solid of isotruxenone with a yield of 78%. mp = 318−320 °C (lit.[10] 317−318 °C); ^{1}H NMR (400 MHz, $CDCl_3$) 7.40−7.48 (m, 3H), 7.59−7.65 (m, 3H), 7.72−7.80 (m, 3H), 8.08 (d, J = 7.6 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 9.03 (d, J = 7.6 Hz, 1H) ppm.

Synthesis of Compound 4b. A mixture of **10** (10.0 g, 26.5 mmol) and **8** (5.00 g, 28.7 mmol) in a 50 mL tube was sealed and then heated to 180 °C for 24 h. After being cooled to room temperature, the crude product was recrystallized from ether to afford the white solid of **4b** with a yield of 76%. mp = 154−156 °C (lit.[16] 157−158 °C); ^{1}H NMR (400 MHz, $CDCl_3$) 0.67 (t, J = 7.6 Hz, 3H), 0.84−0.91 (m, 6H), 3.64 (q, J = 7.6 Hz, 2H), 3.91−3.98 (m, 4H), 6.97−7.20 (m, 4H), 7.09−7.12 (m, 6H), 7.32−7.33 (m, 5H) ppm.

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Supporting Information Available: Experimental procedures and characterization data for compounds **4a**, **6**, and **9**−**14**, ^{1}H spectrum of **3** and ^{1}H and ^{13}C NMR spectra for new compounds **9** and **12**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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