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An Efficient and Scalable Synthesis of Substituted Phenanthrenequinones by Intramolecular Friedel–Crafts Reaction of Imidazolides

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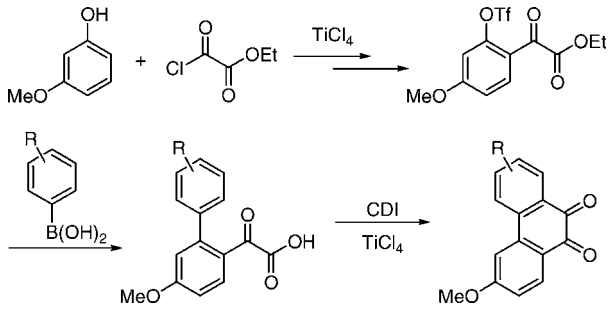
ABSTRACT



An efficient synthesis of 9,10-phenanthrenequinones is described. The two carbonyl groups were introduced by an orthoselective intermolecular Friedel–Crafts reaction of 3-methoxyphenol with ethyl chlorooxoacetate. The formation of a biaryl bond by Suzuki–Miyaura coupling reaction, followed by the hydrolysis of the ester, gave a biaryloxoacetic acid. Treatment of this acid with CDI gave the corresponding imidazolide. The ring closure to the desired phenanthrenequinone was accomplished by intramolecular Friedel–Crafts reaction of the imidazolide promoted by $TiCl_4$.

9,10-Phenanthrenequinones have been studied in many scientific fields, including photochemistry, analytical chemistry, physical chemistry, and bioorganic chemistry, due to their unique properties. The simple 9,10-phenanthrenequinone has been found by Smith et al. to act as a redox-dependent receptor for the selective recognition of urea and amide derivatives.[1] Urbanek et al. have recently identified that a number of substituted 9,10-phenanthrenequinones are highly potent inhibitors of the protein tyrosine phosphatase (PTP) CD45 and the selective inhibition was achieved by structural modification of the phenanthrenequinone.[2] CD45 is a family of transmembrane PTPs that are expressed exclusively by hematopoetic cells; therefore, the development of the inhibitors has received increased interest. The derivatives of phenanthrenequinone have also been studied for their interaction with DNA. Barton et al. have demonstrated that the metal complexes of 9,10-phenanthrenequinone diimine, which is readily prepared from 9,10-phenanthrenequinone, showed sequence-specific recognition of DNA[3] and have

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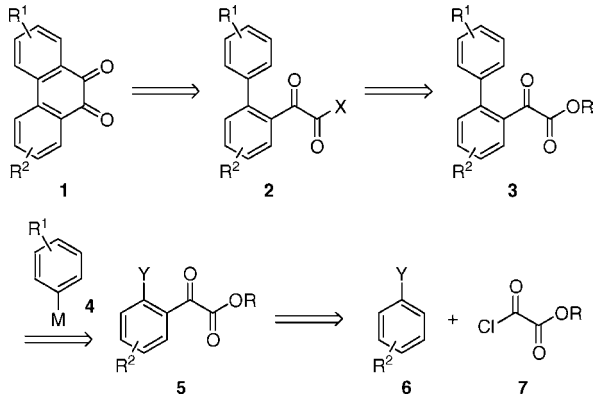
recently applied it to the development of artificial nucleases for shape-selective DNA photo cleavage.[4] The metal complexes of phenanthrenequinone thiosemicarbazone were studied as potential anticancer agents.[5]

Most of the syntheses of phenanthrenequinones have involved the oxidation of the corresponding phenanthrenes.[6] This oxidation is, however, often performed using toxic heavy metals such as chromium. The phenanthrenequinone core has also been constructed directly using various methods, i.e., the cyclization of benzil derivatives using potassium graphite[7] or transition metals[8] and the benzoin/acyloin type condensation of functionalized biphenyls.[9−11] Another approach is to prepare 9-phenanthrols and oxidize them to 9,10-phenanthrenequinones. 9-Phenanthrols have been prepared by the benzoin condensation of 2,2′-dialdehydobiphenyls,[12] the photocyclization of benzoin derivatives,[13] and the anionic cyclization of 2-amido-2′-methylbiphenyls.[14] Fuson and Talbott have described that 2-biphenylylglyoxal cyclized to 9,10-dihydroxyphenanthrene by treatment with aluminum chloride; however, the chemical yield was only 40%.[15]

Herein we report a novel strategy for the synthesis of phenanthrenequinones (**1**, Scheme 1) by the intramolecular

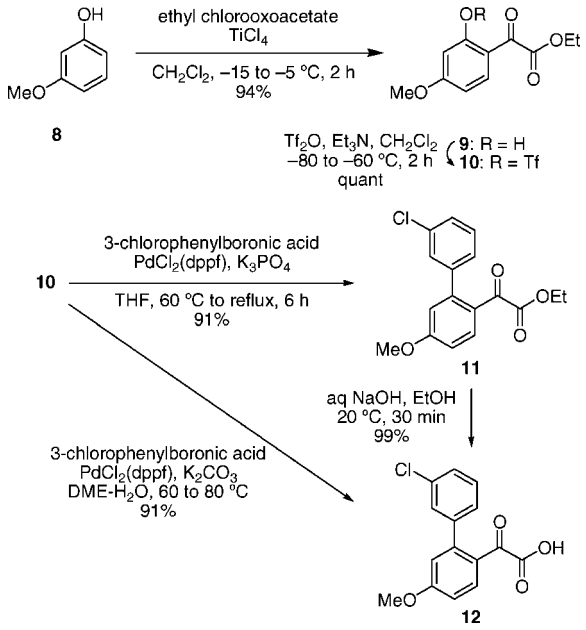
Scheme 1. Retrosynthetic Analysis



Friedel−Crafts type reaction of biaryloxoacetic acid derivatives (**2**). The biaryl bond was expected to be formed by a cross-coupling reaction of **4** and benzoylformic acid esters **5**. The benzoylformic acid derivatives **5** would be prepared by a Friedel−Crafts type acylation of aromatic compounds **6** with **7**. The development of a regio- and chemoselective method to install the oxalyl group to **6** seemed to be critical in order to attain an efficient overall process. First of all, the conventional Friedel−Crafts reaction of **6** with **7** promoted by $AlCl_3$ was examined; however, it gave **5** as a mixture of ortho- and parasubstituted regioisomers. To circumvent this problem, we were interested in the use of unprotected phenols for the regiospecific acylation with the aid of the strong coordinative capability of the free hydroxyl group. Piccolo et al. had reported the orthoselective acylation of phenols in the presence of Lewis acids.[16] Although most examples reported therein were the BCl_3-promoted acylation of regular acid chloride such as benzoyl chloride, they described one example of $TiCl_4$-mediated acylation using methyl chlorooxoacetate as the acylating reagent. Inspired by this report, we started to examine the orthoselective acylation of phenols.

We were pleased to find that the Friedel−Crafts reaction of 3-methoxyphenol (**8**, Scheme 2) with ethyl chlorooxoacetate proceeded smoothly even at −78 °C by using $TiCl_4$ as promoter. The ortho position of the phenol was selectively acylated to produce **9** in 94% yield. The para-acylated compound or the corresponding ester (oxygen acylation) was not obtained at all. The crude product after aqueous work up was pure enough and used for the subsequent step without

Scheme 2. Synthesis of Biaryloxalic Acid by Intermolecular Friedel−Crafts Reaction and Suzuki−Miyaura Coupling Reaction



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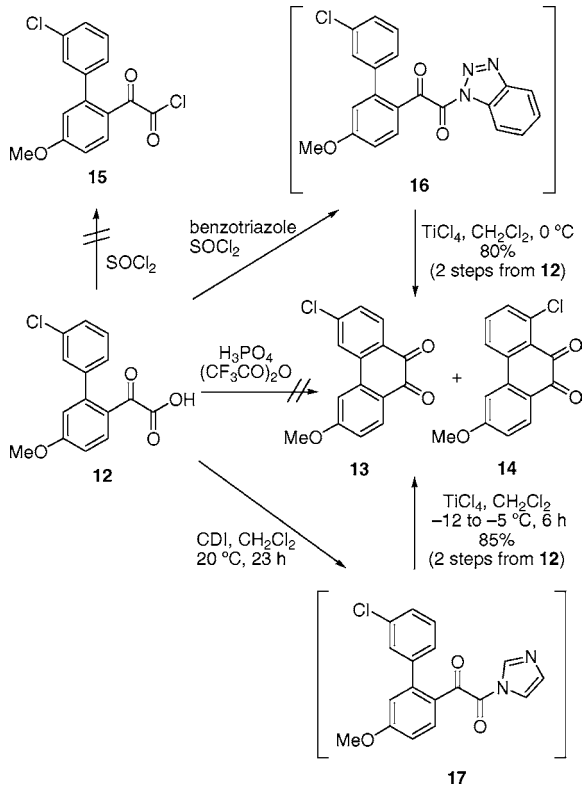
purification. The triflation of the hydroxyl group was performed by using Tf_2O and Et_3N in CH_2Cl_2 to afford the corresponding triflate (**10**) in quantitative yield. The biaryl bond was formed by Suzuki−Miyaura coupling reaction of **10** with 3-chlorophenylboronic acid catalyzed by $PdCl_2$(dppf) in the presence of K_3PO_4 in refluxing THF to afford biaryl **11** in 91% yield. The ester was readily hydrolyzed by aqueous NaOH to give benzoylformic acid **12** in 99% yield. Although these two steps once afforded an excellent yield, the process suffered from poor reproducibility, presumably due to varied particle sizes of K_3PO_4 and the presence of different amounts of boronic acid anhydrides. This issue was circumvented by employing an aqueous biphasic condition. The triflate was treated with the same boronic acid and the same catalyst in DME−H_2O in the presence of K_2CO_3 as base. The reaction was gradually heated to 60 °C to effect the coupling step and then to 80 °C for the ester hydrolysis to afford acid **12** in 91% yield with good reproducibility. The crude **12** was used for the subsequent cyclization step without further purification.

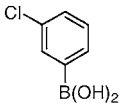
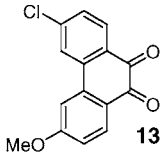
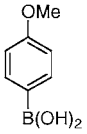
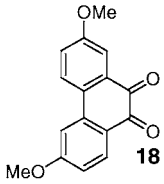
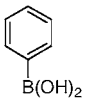
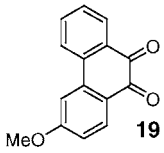
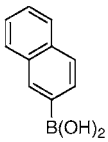
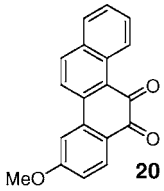
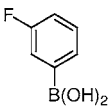
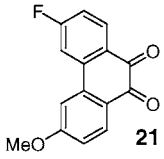
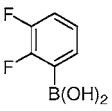
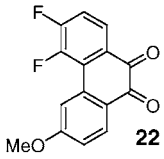
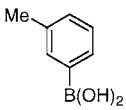
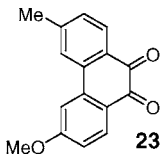
With the oxalyl group installed at the desired position, the formation of the phenanthrene skeleton was examined by the intramolecular Friedel−Crafts type reaction (Scheme 3). First of all, the direct cyclization of the acid (**12**) was

Scheme 3. Cyclization



attempted by using a mixture of H_3PO_4 and trifluoroacetic anhydride.[17] Although rapid consumption of the acid was observed, the reaction produced no phenanthrenequinones, giving rise to a complex mixture. An attempt to convert the carboxylic acid to the corresponding acid chloride (**15**) by treatment with thionyl chloride resulted in the formation of an unidentified byproduct. On the other hand, the treatment of the same acid (**12**) with thionyl chloride in the presence of benzotriazole[18] cleanly produced the corresponding benzotriazolide (**16**), whose structure was judged by ^{1}H NMR. The resulting benzotriazolide, which was stable at 20 °C, rapidly underwent a cyclization reaction upon activation of the carbonyl group by treatment with $TiCl_4$ to afford the

Table 1. Synthesis of Phenanthrenequinones with Different Substituents

boronic acid	product	overall yield from **10** (regioselectivity)
	 **13**	77% (98:2)
	 **18**	42%
	 **19**	44%
	 **20**	70% (99:1)
	 **21**	82% (>99:1)
	 **22**	61%
	 **23**	53% (84:16)

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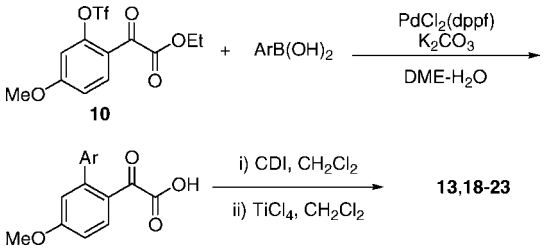
desired phenanthrenequinone (**13**) in 80% yield (2 steps from **12**). The other regioisomer (**14**) was formed in 3%. Although this result was encouraging for us, there was a safety concern about the use of benzotriazole on a large scale. Thus, we examined the use of 1,1′-carbonyldiimidazole (CDI) as an alternative reagent. Using a similar procedure, the phenanthrenequinone (**13**) was obtained in an improved yield (85%) with a slightly better selectivity (regioisomer ~2%).

The process to prepare **13** from **10** has been demonstrated in a large scale (>20 kg) with an overall yield of 77%. No purification or isolation of intermediates was necessary, and the final phenanthrenequinone (**13**) was isolated by simple crystallization. Using triflate **10** as the starting material, the present process has been extended to the synthesis of other substituted phenanthrenequinones using different boronic acids (Scheme 4 and Table 1).

Scheme 4. Improved One-Pot Process for the Suzuki−Miyaura Coupling and Hydrolysis



The Suzuki−Miyaura coupling and hydrolysis steps proceeded well for all boronic acids, giving the corresponding carboxylic acids. The crude acids were again subjected to the subsequent cyclization step without further purification. When boronic acids having a π-donor at the 3-position were employed, the cyclization tended to proceed more rapidly and cleanly (Table 1). The phenanthrenequinones (**13**, **20**, and **21**) were generally obtained in excellent yields (70−82%) from these boronic acids. The efficiency of the cyclization was not as good when 4-methoxyphenylboronic acid and phenylboronic acid were used. The yields of the phenanthrenequinones from triflate **10** were 42% and 44%, respectively. Although 2,3-difluorophenylboronic acid, which has an electron deficient aromatic ring, had a significantly lower reactivity in the cyclization, we were able to obtain the corresponding phenanthrenequinone (**22**) in 61% (from **10**) after an extended reaction time. Boronic acids with electron deficient aromatic ring such as 3-formylphenylboronic acid failed to give the corresponding phenanthrenequinones.

In summary, a Friedel−Crafts type acylation has proven to be effective to construct the phenanthrenequinone skeleton for the first time. The substrates for the cyclization were synthesized through an orthoselective Friedel−Crafts acylation of 3-methoxyphenol with ethyl chlorooxoacetate promoted by $TiCl_4$, followed by a Suzuki−Miyaura coupling and hydrolysis. The method can be applied to boronic acids with nonelectron-deficient aromatic ring. Further studies to exploit this methodology using other phenols are currently underway.

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Supporting Information Available: Experimental procedures and spectral data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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