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Samarium-induced reductive dimerization of methyl cinnamate: synthesis of 2,8-diamino chrysene

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Abstract—Samarium metal-induced reductive dimerization of methyl cinnamate was performed for the first time. A unique role for aluminum was indicated in the dimerization reaction. The intermediate adipate ester was converted to 2,8-diamino chrysene.

Despite nearly 60 years of research relating to the study of polycyclic aromatic hydrocarbons (PAH) only in recent years there has been a stronger focus on the use of compounds related to PAH as anticancer agents.[1] We and others performed a systematic analysis of structure–activity studies of chrysene and other PAH derivatives in the search for antitumor agents.[2,3] For example, we[2] reported the synthesis and biological evaluation of a number of chrysene and dibenzofluorene derivatives against several cancer cells. This study established that the biological activity depends on the position of the side chain in the aromatic systems, because experiments demonstrated that the 2-substituted chrysene derivatives are more potent than the 6-substituted isomers.

In the field of cancer chemotherapy, it was discovered that a ring system that has two side chains is considerably more active than an analogue that has only one identical chain.[4] Therefore, we hypothesized that the disubstituted chrysenes would be more potent than the monosubstituted analogue. Based on the superior activity of the 2-substituted chrysene over that of the 6-substituted isomer, we planned the synthesis of 2,8-disubstituted chrysene derivatives. Until now, there have been no reports that chrysene can be functionalized in this unusual position. This paper describes a facile synthetic method for the preparation of 2,8-diamino chrysene by samarium-induced reductive dimerization of methyl cinnamate as one of the key steps.

The most common way to introduce functionality in the aromatic system is by electrophilic substitution reaction.[1] However, electrophilic substitution of chrysene does not afford the 2-substituted isomer, since it is not the most reactive position. It is known that electrophiles always attack chrysene at the 6-position as the predominant site. The only method of preparing 2-substituted chrysene described in the literature is a photocyclization route.[5] However, synthesis of 2,8-diamino chrysene following this method would be very complicated. Realizing the importance of 2,8-disubstituted chrysenes and to broaden our perspective of our main target in developing novel anticancer agents, we decided to prepare 2,8-diamino chrysene using our metal-mediated reactions.

Organolanthanides have been extensively used as effective reagents in organic synthesis.[6] Increasing attention is being paid to performing synthetic reactions by direct reaction of metals since this represents a favorable approach that avoids the use of expensive organometallic reagents. For example, we have demonstrated the use of samarium[7] and indium[8] metal in organic synthesis. Parallel with our research, several other groups also showed the effectiveness of samarium metal in different types of organic transformation.[9,10] One of the most important reactions with samarium metal achieved thus far is the reductive dimerization of aldimines and carbonyl compounds.[7a,f,g] Interestingly, a similar reaction

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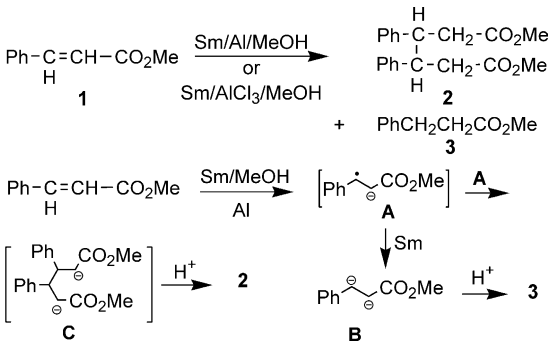
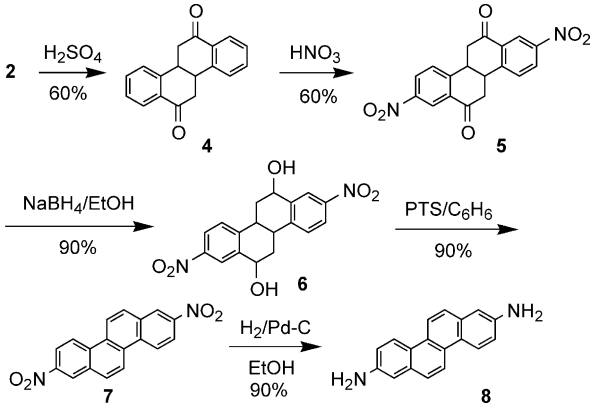
with methyl cinnamate (**1**) or ethyl cinnamate in alcohol could not produce the dimeric compound **2** at all; instead it produced 3-phenylpropionate (**3**).[9b] This has been attributed to a simple Birch-type reduction of the double bond. Kagan, the pioneer of samarium iodide-mediated reactions, also could not achieve the dimerization of ethyl cinnamate.[11] Facile reductive dimerization of conjugated acid derivatives was performed with a combination of samarium diiodide/THF/amine in alcohol.[10f] However, a similar reaction with methyl cinnamate, ethyl cinnamate, or cinnamic acid was not reported. Ytterbium iodide was also tested with these compounds, resulting in reduction products.[11a] Indium-mediated reaction also failed to give dimerization.[8] Our continued interest in the samarium metal-induced processes toward biologically active compounds prompted us to investigate the dimerization of methyl cinnamate further. It turned out that the dimeric product, if available, could be manipulated to the tetracyclic skeleton as present in chrysene.

From our study, it appears that the success of samarium-induced reactions and product distribution can be controlled with the selection of appropriate solvents.[7] Therefore, our aim is to promote dimerization of methyl cinnamate (**1**). Single-electron transfer across the carbon–carbon unsaturated bond by samarium can, in general produce the ion radical **A** in the first step. The generated ion radical **A** can follow two different pathways leading to two different products. The first pathway is the transfer of additional electron from the metal to create dianion **B** and subsequent protonation of the dianion **B** toward the reduction product **3**. The second pathway is a coupling process of the ion radical (**A**–**C**) and subsequent protonation of **C** to **2**. This mechanism clearly indicates that if a reaction follows the first pathway, the reduction product **3** (**A** to **B**) would be favorable (Scheme 1). Alternatively, if the reaction proceeds through the second pathway (**A**–**C**) the product would be dimeric. With this mechanistic rationale in mind, it is conceivable that the stability of the ion radical dictates the product distribution. An increase in the stability may help increase the yield of the dimer and achieve our goal.

To test this hypothesis, we investigated a few reactions using samarium metal in the presence of iodine, allyl bromide and methyl iodide in methanol and THF.



Scheme 1.



Scheme 2.

However, the dimer was not formed; only a low yield of the monomer was obtained. To our surprise, reaction of methyl cinnamate (**1**) with samarium metal in the presence of aluminum foil in methanol produced the dimer **2** in 60% isolated yield. The use of aluminum chloride/samarium produced a similar yield of the dimer. On the other hand, samarium iodide alone failed to produce the dimer, as the product was monomer **3**.[9b] Samarium diiodide in the presence of aluminum foil or aluminum chloride produced mostly monomer but only a trace of dimer. Aluminum alone also did not produce the dimer **2**. Therefore, it appears that the stability of the ion radical is high enough in the presence of the samarium–aluminum combination; as a result, coupling can occur, which is the key pathway for dimer formation (**A**–**C**). Most probably, aluminum or aluminum chloride coordinates to the ion radical **A**, increasing its stability, and therefore favors the coupling process.[10d] Alternatively, the dimer **2** may arise via a Michael-type addition of the initially formed ketyl with the cinnamate rather than dimerization of the two ketyls.[12]

Having a successful route for the dimerization reaction, our next step was a cyclization reaction of the diester **2**. This was conducted using strong acid, and the tetracyclic system **4** was obtained in good yield. Nitration and reduction-aromatization followed, resulting in 2,8-diamino chrysene in good yield (**4**–**8**, Scheme 2).

In conclusion, we have demonstrated facile synthesis of 2,8-diamino chrysene from readily available methyl cinnamate (**1**) by following a samarium-induced, mechanistically unique procedure as one of the key steps. The key feature is functionalization of chrysene at the 2 and 8 positions, which cannot be achieved with any other existing methods.[13,14] The chemistry described herein may open up the possibility of synthesizing many rare derivatives of chrysene and other PAHs with potent biologically active compounds.

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