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Enantioselective 1,6-Michael addition of anthrone to 3-methyl-4-nitro-5-alkenyl-isoxazoles catalyzed by bifunctional thiourea-tertiary amines

Hong-Wei Sun [a,c], Yu-Hua Liao [a,c], Zhi-Jun Wu [b], Hao-Yu Wang [a], Xiao-Mei Zhang [a], Wei-Cheng Yuan [a,*]

[a] Key Laboratory for Asymmetric Synthesis & Chirotechnology of Sichuan Province, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, PR China
[b] Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, PR China
[c] Graduate School of Chinese Academy of Sciences, Beijing 100049, PR China

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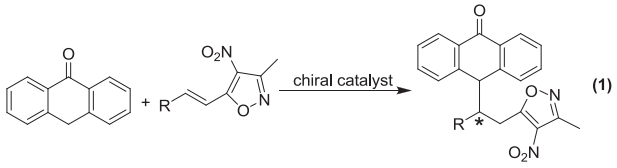
ABSTRACT

A simple and efficient method for the enantioselective 1,6-Michael addition reaction of anthrone to a series of 3-methyl-4-nitro-5-alkenyl-isoxazoles with a bifunctional thiourea-tertiary amine as catalyst is described. This transformation proceeds smoothly with 10 mol % catalyst and provides a series of Michael adducts bearing 3-methyl-4-nitro-isoxazole and anthrone units with good to high enantioselectivities (up to 96% ee) and in very high yields (up to 99%).

1. Introduction

Michael addition reaction of carbon-centered nucleophiles to various Michael acceptors represents a direct and powerful method for the C–C bond formation and has found widespread application in organic synthesis. Consequently, considerable effort has been devoted to the development of enantioselective versions of this transformation.[1] Despite the fact that remarkable advances have been made in the catalytic asymmetric Michael reaction,[1] the development of new Michael reaction for efficient construction of various new compounds is an important goal of research carried out in both academic and industrial laboratories. In this area, as for the Michael donor, various carbon-centered nucleophiles including aldehydes and ketones,[2] malonate esters,[3] ketoesters,[4] and 1,3-diketones[5] have been extensively reported, by comparison, little progress has been made in the development of using anthrone as a nucleophile for the Michael addition reaction.[6,7] In parallel, as for the Michael acceptor, in contrast to often-used electrophiles, such as nitro olefins, α,β-unsaturated aldehydes, α,β-unsaturated ketones, and maleimides,[1,8] the number of methods that involved 3-methyl-4-nitro-5-alkenyl-isoxazoles as Michael acceptor is rather limited.[9] Therefore, it is easy to understand why there is no report about the Michael reaction of anthrone with 3-methyl-4-nitro-5-alkenyl-isoxazoles leading to chiral products bearing 3-methyl-4-nitro-isoxazole units so far. This fact encouraged us to develop the protocol for the enantioselective conjugated addition of anthrone to 3-methyl-4-nitro-5-alkenyl-isoxazoles [Eq. 1].



(1)

Anthrones are important compounds in natural products and in medicinal chemistry.[10] From the chemical standpoint, anthrones and their enol tautomers, the 9-anthrols, play a central role in the chemistry of anthracenes, because by oxidation of the central ring they afford 9,10-anthraquinones, extremely valuable compounds as pigments or anticancer agents.[11] On the other hand, the reduction of anthrones provide anthracenes, useful in the preparation of dyestuffs and of optoelectronic materials.[12] And it also has been found that some anthrone derivatives may display various interesting biological properties[13] and possess some potent and

* Corresponding author. Tel./fax: +86 28 85232228; e-mail address: yuanwc@cioc.ac.cn (W.-C. Yuan).

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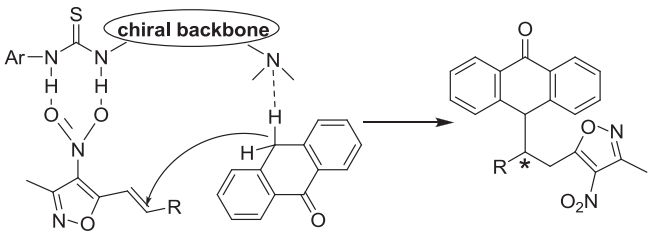
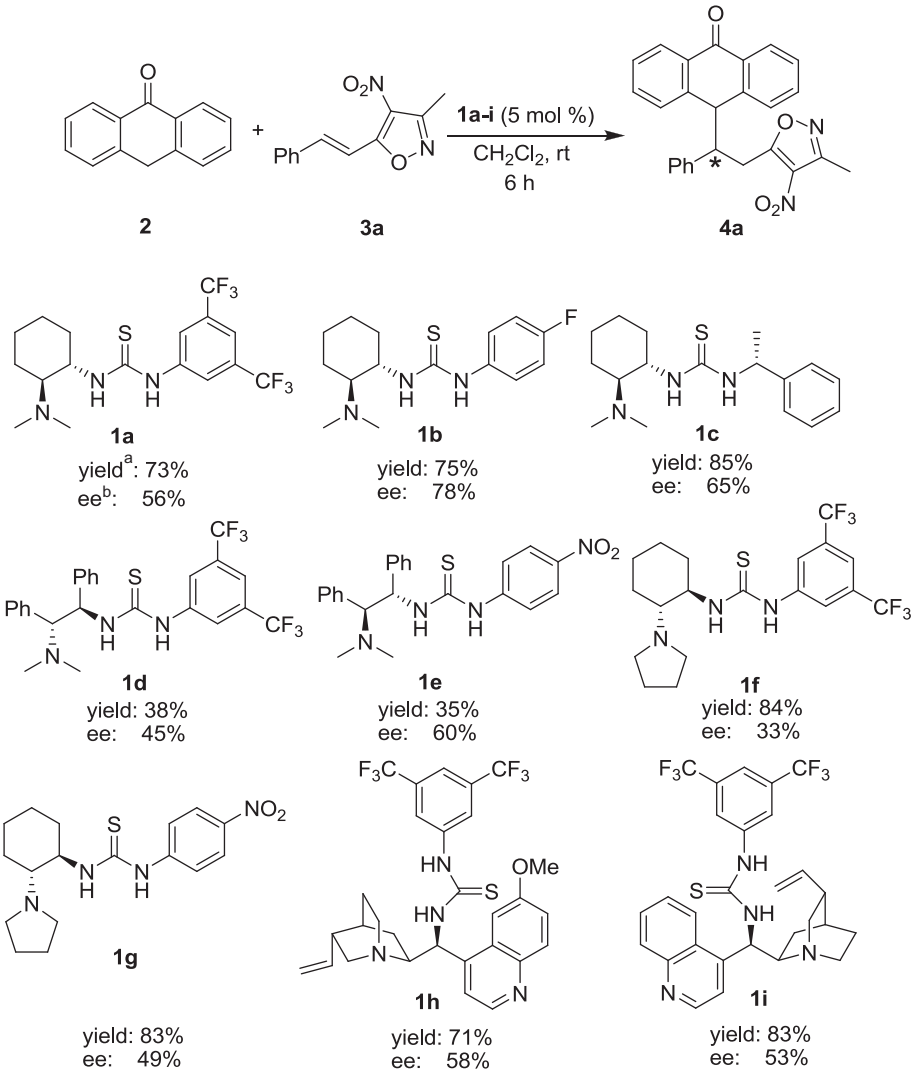
selective antitumor activity.[14] We also noted that 3-methyl-4-nitro-5-alkenyl-isoxazoles were able to be accepted as cinnamate equivalents that show high reactivity toward stabilized nucleophiles. However, only a few reports by Adamo and co-workers have addressed the Michael addition reaction with 3-methyl-4-nitro-5-alkenyl-isoxazoles as electrophiles.[9] Furthermore, over the past several years, numerous reports on the application of related tertiary amine thiourea frameworks as bifunctional catalysts in a wide variety of enantioselective catalytic reactions have been published.[15] Therefore, as a continuation of our efforts on the asymmetric organocatalysis,[7a,16] we became interested in the possible use of chiral bifunctional thiourea-tertiary amine catalysts for the enantioselective Michael addition of anthrone to various 3-methyl-4-nitro-5-alkenyl-isoxazoles. On the basis of our previous study, we thought that the tertiary amine group of the catalyst would function as a general base catalyst and activate the nucleophile (anthrone) while the thiourea group would simultaneously enable to activate the electrophile (3-methyl-4-nitro-5-alkenyl-isoxazoles) by double hydrogen bonding (Scheme 1), resulting in the Michael addition of nucleophile to electrophile. Herein, we hope to report the first example of a bifunctional thiourea-tertiary amine-catalyzed enantioselective 1,6-Michael addition of anthrone to various 3-methyl-4-nitro-5-alkenyl-isoxazoles, providing the corresponding adducts with good to high enantioselectivities (up to 96% ee) and in very high yields (up to 99%).



Scheme 1. Designation of the conjugated addition reaction catalyzed by chiral bifunctional thiourea-tertiary amine catalysts.

2. Results and discussion

The reaction between anthrone (**2**) and (*E*)-3-methyl-4-nitro-5-styrylisoxazole (**3a**)[17] was chosen as a model reaction for the catalysts study (Scheme 2). Takemoto's thiourea catalyst **1a**[3a,3c] and some other analogous bifunctional thiourea-tertiary amine catalysts **1b**–**i** with various chiral scaffolds, which have been previously reported by some chemists,[18] were screened in the model reaction with CH_2Cl_2 as solvent at room temperature for 6 h. All of the results were summarized in Scheme 2, and we found that the desired Michael adduct **4a** could be obtained in poor to good yields with acceptable enantioselectivities with 5 mol% catalyst. By comparison, bifunctional thiourea-tertiary amine catalyst **1b** proved to be the most effective catalyst in view of the reactivity (75% yield) and enantioselectivity (78% ee).



Scheme 2. Model reaction and catalysts study. Reaction conditions: **2** (0.20 mmol), **3a** (0.24 mmol), and chiral catalysts **1** (5 mol%) were stirred in CH_2Cl_2 (1.0 mL) at rt for 6 h. [a]Isolated yield. [b]Determined by chiral HPLC analysis.