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Asymmetric Aza-Mannich Addition: Synthesis of Modified Chiral 2-(Ethylthio)-thiazolone Derivatives with Anticancer Potency

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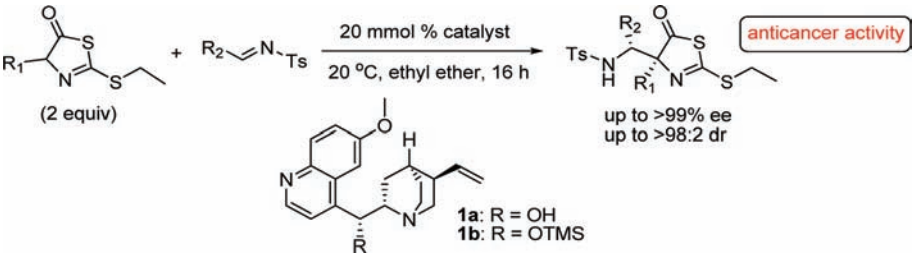
ABSTRACT



An easily prepared cinchona alkaloid derivative was found to be an effective organocatalyst in a direct, enantioselective aza-Mannich addition. By establishing a quaternary carbon stereocenter, a series of modified chiral 2-(ethylthio)-thiazolone derivatives have been obtained with excellent diastereo- and enantioselectivities. And these derivatives have been found to show anticancer activities against five different cancer cell lines using the MTT assay.

One of the fundamental objectives of organic and medicinal chemistry has been the design, synthesis, and production of molecules having value as human therapeutic agents. In the past 10 years, the number of chiral, nonracemic pharmaceuticals on the market was consistently increasing. Many new single enantiomer drugs with a well-timed chiral switch were produced to offer enhanced therapy, more predictable pharmacokinetics, and reduced toxicity.[1] It is becoming more and more important to prepare these compounds using new enantioselective technologies to minimize the losses incurred from making racemic mixtures. And organocatalysis has emerged to be an effective way. Due to its operational and economic advantages, the asymmetric organocatalysis has had a significant impact in chemical synthesis and has developed into a practical synthetic paradigm associated with the pharmaceutical industry.[2]

With proven utility in biological chemistry, heterocyclic compounds have received special attention gradually.[3] There are numerous biologically active molecules with

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five-membered rings, containing two heteroatoms. And the thiazole ring is the most widely existing one. According to the literature, the thiazole ring is an important scaffold associated with several biological active compounds.[4] For instance, several natural molecules with a thiazolidinone moiety are known to possess significant antitumor, immunosuppressive, and antibiotic properties.[5] In addition, the aminothiazole ring system has found application in the drug development for the treatment of allergies, hypertension, and HIV infections.[6] However, to the best of our knowledge, the research on modified thiazolone derivatives has mainly focused on racemic ones. Only one example using 2-benzyloxythiazol-5(4*H*)-ones as substrates in asymmetric addition was reported by Ooi's group in 2010.[7] Therefore, the development of new highly efficient organic synthetic methods to access optically active thiazolone derivatives would be of great value for the drug-lead synthesis.

According to Lin's report,[8] in addition to the main keto form, 2,4-disubstituted thiazolones can also exist in other tautomeric forms in the solvent (mainly having an enol form and a conjugated keto form). When the electron-donating group was introduced into the C-2 position, less likely tautomerism was observed. Thus in order to eliminate the undesired reactions, we chose the 2-(ethylthio)-thiazolones which have an ethylthio- group at the C-2 position as the nucleophile to explore this aza-Mannich reaction in the nonpolar solvents.

Furthermore, in the previous communication we have described the asymmetric addition of oxazolones with

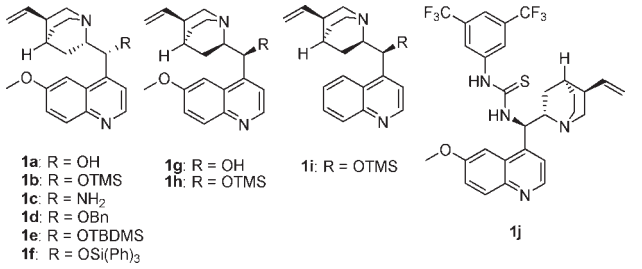

Figure 1. Chiral cinchona alkaloid derived catalysts screened in this work.

N-tosyl aldimines,[9] and it was proven that the cinchona alkaloid derivatives were highly efficient catalysts in the chiral α-disubstituted α,*β*-diamino acid synthesis. On the basis of this, we decided to investigate the cinchona alkaloid catalyst system in this reaction to see whether it is viable for the synthesis of masked chiral 2-(ethylthio)-thiazolone derivatives.

At the outset of the study, a variety of chiral cinchona alkaloid catalysts (Figure 1) were tested in the selected reaction of substrates **1a** and **2a** in the ethyl ether at 30 °C.

Initially, as is shown in Table 1, at 20 mmol %, all of quinine derived catalysts **1a**−**d** could catalyze this model reaction well except **1c** (entry 4), and catalyst **1b** was the most effective one affording the product **4a** with a high diastereomeric ratio of 95:5 and good enantioselectivity (entry 2). Replacing the −OTMS group at the R position with the sterically bulky groups (−OTBDMS and −OSi-$(Ph)_3$) resulted in longer reaction times and an obvious decrease of enantioselectivities. Subsequently, we investigated the other cinchona alkaloid catalysts **1g**−**i** derived from the quinidine and cinchonine, and none of them could perform better than the catalyst **1b** as well.

In addition, when the bifunctional thiourea-tertiary amine **1j** was used in this model reaction (entry 9), only a racemic product was obtained. It suggested that the thiourea functionality was disadvantageous in this reaction because of its strongly basic effect. To further improve the enantioselectivity, we conducted a cursory examination of the influence of the reaction temperature. Interestingly, except for a slightly prolonged reaction time, a higher ee value of

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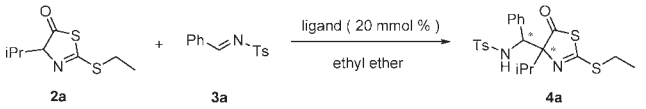
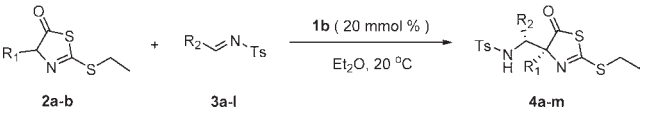
Table 1. Representative Screening for the Addition of 2-(Ethylthio)-thiazolone **2a** to *N*-Tosyl Imine **3a**[a]



entry	cat. (20 mmol %)	temp (°C)	time (h)	dr[b]	ee[c]
1	**1a**	35	8	92:8	57
2	**1b**	35	16	95:5	86
3[d]	**1b**	35	16	95:5	85
4	**1c**	35	16	90:10	13
5	**1d**	35	16	96:4	81
6	**1e**	35	24	95:5	77
7[e]	**1f**	35	32	95:5	60
8	**1g**	35	8	82:18	35
9	**1h**	35	16	90:10	67
10	**1i**	35	36	80:20	17
11	**1j**	35	8	78:22	0
12	**1b**	20	18	95:5	90
13	**1b**	0	20	91:9	81
14[f]	**1b**	−40	48	nd	nd

[a] Unless indicated otherwise, all reactions were performed with 0.20 mmol of **2a**, 0.10 mmol of **3a**, and 20 mmol % of catalyst in 1.0 mL of ethyl ether for 8−36 h, and full conversion was observed in all cases. [b] Determined by ^{1}H NMR measurements after purification. [c] Determined by chiral HPLC on a Chiralpak AD column. [d] 0.40 mmol of **2a** was used. [e] The conversion rate of the reactant was under 80% after 32 h. [f] The conversion rate of the reactant was under 30% after 48 h. nd: not determined.

Table 2. Aza-Mannich Addtion of 2-(Ethylthio)-thiazolones and *N*-Tosyl Aldimines[a]



entry	**2**, R_1	**3**, R_2	yield [%][b]	dr[c]	ee [%][d]
1	**2a**, *i*Pr	**3a**, Ph	**4a**, 79	95:5	90
2	**2a**, *i*Pr	**3b**, *o*-F-Ph	**4b**, 86	>98:2	86
3	**2a**, *i*Pr	**3c**, *o*-Cl-Ph	**4c**, 87	>98:2	98
4	**2a**, *i*Pr	**3d**, *m*-Cl-Ph	**4d**, 67	>98:2	80
5	**2a**, *i*Pr	**3e**, *p*-Cl-Ph	**4e**, 73	95:5	>99
6[e]	**2a**, *i*Pr	**3f**, *o*-Me-Ph	**4f**, 88	90:10	>99
7[e]	**2a**, *i*Pr	**3g**, *m*-Me-Ph	**4g**, 80	92:8	82
8	**2a**, *i*Pr	**3h**, *o*-Br-Ph	**4h**, 78	>98:2	>99[g]
9	**2a**, *i*Pr	**3i**, *p*-CN-Ph	**4i**, 83	>98:2	>99
10[e]	**2a**, *i*Pr	**3j**, 3,4-$(Me)_2$-Ph	**4j**, 85[f]	83:17	90
11	**2a**, *i*Pr	**3k**, 2-naphthyl	**4k**, 78	91:9	92
12	**2a**, *i*Pr	**3l**, 2-furyl	**4l**, 94	>98:2	96
13	**2b**, *i*Bu	**3a**, Ph	**4m**, 90[f]	75:25	90/85

[a] Unless indicated otherwise, all reactions were performed with 0.20 mmol of **2**, 0.10 mmol of **3**, and 0.02 mmol of **1b** in 1.0 mL of ethyl ether for 16 h, and full conversion was observed in all cases. [b] Yield of the major diastereoisomer isolated by silica-gel column chromatography. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Determined by chiral HPLC on a Chiralcel column. [e] The reaction was carried out with 0.02 mmol of quinine as catalyst under 0 °C for 18 h. [f] The yield of both diastereoisomers. [g] The absolute configuration of **4h** was determined by X-ray crystal-structure analysis. The absolute configurations of the other products were assigned by analogy.

90% with a maintained diastereomeric ratio was gained when the reaction temperature was lowered to 20 °C (entry 12). However, both the ee value and diastereomeric ratio have shown an obvious decrease when the reaction temperature was further cooled down to 0 °C. And under −40 °C, the conversion rate of the reactant was still under 30% after 2 days of reaction.

With the optimized conditions established, the scope of *N*-tosyl aldimines and 2-(ethylthio)-thiazolones in the presence of 20 mmol % catalyst **1b** was explored.

As is shown in Table 2, a majority of the reactions proceeded smoothly to furnish the corresponding masked chiral 2-(ethylthio)-thiazolone derivatives in moderate to good yields and excellent diastereo- and enantioselectivities. For the reactions with the nucleophile 2-(ethylthio)-thiazolone **2a**, a wide range of substituents could be present at the aryl position on the *N*-tosyl imines. All of the aryl-substituted substrates, whether electron-rich or electron-deficient at different sites, seemed to have little influence on the results of the diastereo- and enantioselectivity of the reaction. A series of aza-Mannich adducts were obtained in excellent diastereomeric ratios and ee values (entries 1−9). The additions of more sterically hindered imines derived from 3,4-dimethylbenzaldehyde and 2-naphthaldehyde proceeded equally well with high enantioselectivities and good diastereoselectivities. Outstanding diastereo- and

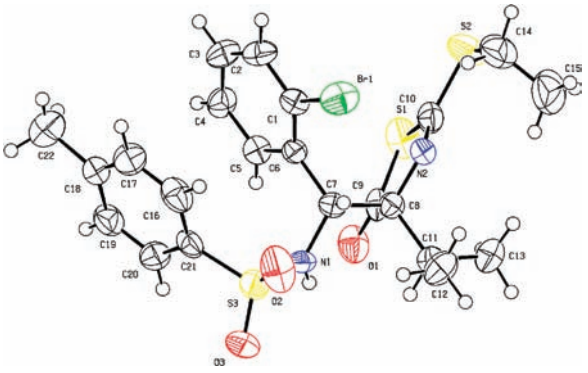


Figure 2. X-ray Structure of the adduct **4h**.

enantioselectivity were also observed for the 2-(ethylthio)-thiazolone with the 2-furanyl *N*-tosyl imine. In addition, a high enantioselectivity with a moderate diastereomeric ratio (75:25) was obtained when the 2-(ethylthio)-thiazolone had an isobutyl substituent at the R_2 position.[10]

(10) Under the optimized conditions, the alkyl-substituted isobutyl *N*-tosyl imine showed no reactivity toward 2-(ethylthio)-thiazolone **2a**.

Table 3. IC_{50} Values of Masked Chiral 2-(Ethylthio)-thiazolone Derivatives on the Growth of Human Cancer Cell Lines[a]

Compound	4a	4b	4c	4f	4h	4i	4l
EJ	25	32	20	28	22	26	30
PC-3	29	34	23	30	27	25	33
MDA-MB-231	49	57	38	59	41	47	68
HepG-2	26	23	20	24	22	25	24
Jurkat	29	27	17	29	19	28	28

[a] Values are means of three experiments each done in duplicate. IC_{50} values are expressed in μM. EJ, PC-3, MDA, HepG-2, and Jurkat cells were seeded at a density of 5000 cells in 96-well plates. Compounds were added 24 h after seeding. After 2 days in culture, the MTT stock solution (5 mg/mL in PBS) was added to each well and incubated at 37 °C for 4 h. The medium was removed carefully, and dimethyl sulfoxide was added to each well to dissolve formazan. The absorbance of each well at 490 nm was measured by using a Bio-Rad Model 680 microplate reader.

The constitution and absolute configuration of the product **4h** were determined by X-ray crystallography (Figure 2) as well as by NMR spectroscopic studies.[11]

In view of the case in which we were able to access diverse enantiopure masked 2-(ethylthio)-thiazolone derivatives, we decided to evaluate the biological activities of them. The compounds **4a**, **4b**, **4c**, **4f**, **4h**, **4i**, and **4l** were prepared to test for their cytotoxic activity on five human cancer cell lines using the MTT assay. A summary of the IC_{50} values is shown in Table 3. To all of the cancer cell lines we tested, masked 2-(ethylthio)-thiazolone derivatives presented a dose-dependent inhibitory effect.[12] A majority of them showed inhibition on EJ, PC-3, HepG-2, and Jurkat with an IC_{50} range of 20 to 30 μM (Table 3). And the analogues **4c** and **4h** having one *ortho*-halogen substituted phenyl group showed significant inhibitory effects on the Jurkat with IC_{50} values of 17 and 19 μM. Although **4c** and **4h** exhibited weaker inhibitory activity (IC_{50} = 38 μM, 41 μM) on the breast cancer cell MDA-MB-231, they were still the most effective ones. Moreover, the different cytotoxicities suggested that the cancer cell lines displayed different sensitivities to chiral masked 2-(ethylthio)-thiazolone derivatives.

In conclusion, it has been uncovered that, in the aza-Mannich addition of 2-(ethylthio)-thiazolones and *N*-tosyl aldimines, the cinchona alkaloid catalyst system could perform efficiently. By establishing a carbon- and nitrogen-substituted quaternary carbon stereocenter, a series of masked chiral 2-(ethylthio)-thiazolone derivatives have been synthesized with high levels of diastereo- (up to >98:2) and enantioselectivities (up to >99%) for the first time. Several new derivatives have been found to show potential anticancer activities. This preliminary study provided a foundation for the further development of new single enantiomer anticancer drugs.

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Supporting Information Available. Experimental details, characterization data for the products, and crystal structure data of the adduct **4h** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

(11) CCDC 800993 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/daa_request/cif.

(12) The dose-dependent growth inhibition ability was shown in the Supporting Information.