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Stereoselective thio-Michael addition to chalcones in water catalyzed by bovine serum albumin

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ABSTRACT

A biomimetic, inexpensive, and simple method for the stereoselective thio-Michael addition of thiols to chalcones has been developed using bovine serum albumin (BSA) as a catalyst. Optically active products are obtained in high yield and with enantiomeric excesses of up to 70%.

1. Introduction

The distinct redox, catalytic, and metal-binding properties of sulfur containing compounds ensure their major role in biology. Many of these substances show antibiotic, antifungal, and anticancer activities and are interesting from a pharmacological perspective.[1,2] Moreover, organic and metallo-organic catalysis, natural product synthesis, chiral auxiliaries, synthesis of pharmaceutically important compounds, such as Diltiazem[3] are but a few of the applications of sulfur containing compounds in organic chemistry.[4,5] The thio-Michael reaction, which involves the conjugate addition of sulfur nucleophiles to electron-deficient olefins, is a straightforward route for the generation of carbon–sulfur bonds. The stereoselective version of this reaction benefits from both stoichiometric and catalytic methods.[6,7]

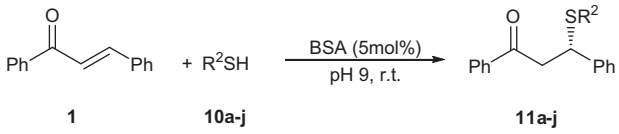
Biomimetic reactions constitute a challenging approach with regard to environmental concerns, which demand clean reaction processes that do not use harmful organic solvents, toxic metals, and other extreme experimental conditions, such as temperatures much lower or higher with respect to ambient, dry reaction conditions or complex work-up operations. To the best of our knowledge, only a single example of a biomimetic thio-Michael addition has been reported by using stoichiometric amounts of chemically modified β-cyclodextrin.[8] In this regard, bovine serum albumin (BSA), a ubiquitous non-enzymic transport protein in biological systems, constitutes a worthwhile choice since it is able to bind organic molecules by reversible non-covalent complexation in its hydrophobic pockets, providing a chiral environment for a number of asymmetric oxidations and reductions.[9]

On the basis of our previous experience on the exploitation of BSA as a catalyst in stereoselective oxidations,[10,11] we decided to explore the ability of BSA to promote the thio-Michael reaction, thus expanding upon the range of reactions catalyzed by this protein.

Herein we report a novel, biomimetic procedure for the addition of aliphatic and aromatic thiols to α,β-unsaturated ketones in a stereoselective fashion and excellent yield.

2. Results and discussion

The addition of thiophenol **10a** to *trans*-calchone **1**, chosen as a model reaction, has been carried out in aqueous borate buffer (pH 9) at room temperature and in the presence of 5% mol equiv of BSA (Scheme 1).



1 **10a-j** **11a-j**

Scheme 1.

After 18 h 1,3-diphenyl-3-phenylsulfanyl-propan-1-one **11a** was recovered in quantitative yield and 40% ee (Table 1, entry 1). Moreover, evaporation of the mother liquor recovered from a single crystallization of the crude adduct allowed isolation of the enriched (−)-enantiomer in 75% yield and 65% ee.[12] The absolute configuration was established as (*S*) by comparison of the $[\alpha]_D$ value with the literature data.[12] When the reaction was carried out at lower temperature (4 °C), no improvement in ee was noticed (Table 1, entry 2). Only a slight increase in enantioselectivity was observed when 10% BSA loading was used (Table 1, entry 3). To verify that BSA acts as a true catalyst, we carried out a control experiment in the absence of the protein. Under these reaction conditions, racemic **11a** was obtained in fairly good chemical yield (Table 1, entry 4).

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Table 1
Thiols addition to *trans*-chalcone[a]

Entry	R^2	Product	Yield (%)	ee [b,c] (%)
1	C_6H_5 **10a**	**11a**	99	40 (65)
2	C_6H_5 **10a**	**11a**	81[d]	40
3	C_6H_5 **10a**	**11a**	99[e]	46
4	C_6H_5 **10a**	**11a**	64[f]	rac.
5	4-CH_3-C_6H_4- **10b**	**11b**	66	22
6	2,6-$(CH_3)_2$-C_6H_3- **10c**	**11c**	77	40
7	4-OCH_3-C_6H_4- **10d**	**11d**	99	70 (86)
8	2-OCH_3-C_6H_4- **10e**	**11e**	85	57
9	4-NO_2-C_6H_4- **10f**	**11f**	5[g]	—
10	C_6H_5-CH_2- **10g**	**11g**	70	26
11	*n*-C_4H_9- **10h**	**11h**	71	19
12	*n*-C_8H_{17}- **10i**	**11i**	75	10
13	C_6H_5-CO- **10j**	**11j**	85	rac.

[a] Reaction conditions: BSA (5 mol %), aqueous borate buffer pH 9, 18 h, rt.
[b] Determined by chiral HPLC analysis.
[c] Ee of compound after a single crystallization is reported in brackets.
[d] At 4 °C.
[e] 10% equiv mol BSA, 15 h.
[f] Without BSA.
[g] After 48 h.

The reaction scope was investigated by using different aliphatic and aromatic thiols in the addition to *trans*-chalcone **1**, under the reaction conditions set up with thiophenol which we considered as an optimal compromise with regard to the Michael adduct yield and ee and the amount of BSA used (Table 1). In all of the experiments the only materials recovered were the Michael adducts and, in some instances, the starting chalcones. In no case, were the formation of disulfides or by-products resulting from the undesired 1,2-addition and/or bis-addition observed.

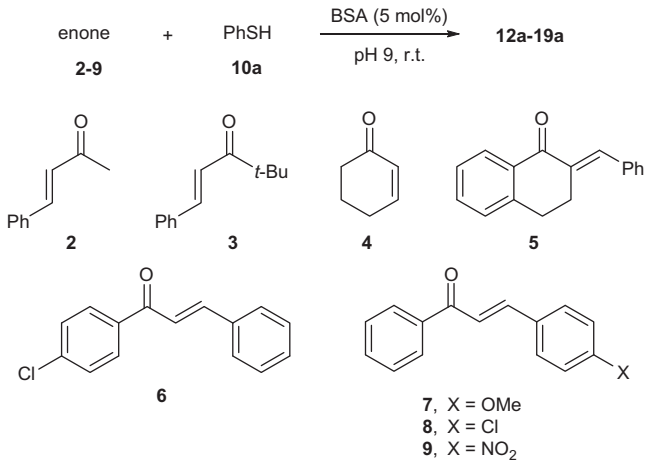
A series of *para*-substituted aryl thiols underlines that the electronic effects seem to have a significative influence on the observed stereoselectivity. The use of *p*-methoxythiophenol **10d** provided the desired product in quantitative yield and 70% ee. It is worth mentioning that the enantiomeric purity of (*S*)-**11d** was enhanced to 86% ee after a single crystallization (Table 1, entry 7). On the other hand, *p*-nitrothiophenol **10f** reacted sluggishly (Table 1, entry 9). The presence of a methyl group at the *ortho*-, *ortho*′- positions of the thiol group has an unfavorable effect on the chemical yield, but no influence on the enantioselectivity when compared to thiophenol **10a** (Table 1, entry 6).

Aliphatic thiols, such as *n*-butyl and *n*-octyl mercaptan **10h**, **i**, afforded Michael adducts in good yield but low ee's (Table 1, entries 11 and 12), thus suggesting the importance of the aromatic ring for the complexation of the Michael donor in the binding site of the protein.

From a synthetic perspective, thioesters can be readily transformed into versatile SH groups under various, mild reaction conditions. However, the addition of the less nucleophilic thiobenzoic acid **10j** to *trans*-chalcone afforded the corresponding adduct **11j** in racemic form, although in good chemical yield (Table 1, entry 13).

In order to evaluate the influence of the structure of the Michael acceptor on the outcome of the reaction, the addition of thiophenol **10a** to various α,β-unsaturated ketones **2–9** was investigated (Scheme 2).

4-Phenyl-3-buten-2-one **2** and 4,4-dimethyl-1-phenyl-pent-1-en-3-one **3** were examined to verify whether different steric requirements with respect to *trans*-chalcone **1** could affect the enantioselectivity. On the basis of molecular mechanics calculations, the *s-trans* conformation is more stable for **2**; *s-trans* and *s-cis* conformations are nearly equally stable for chalcone **1**, while the sterically demanding *tert*-butyl group in ketone **3** favors the *s-cis* form.[13] Enones **2**,**3** afforded the corresponding Michael adducts in excellent yields with 35% and 45% ee, respectively (Table 2, entries 2 and 3). These results suggest that the *s-cis* conformation ensures higher stereocontrol, although in a moderate amount.



Scheme 2.

Table 2
Thiophenol addition to enones **1–10**[a]

Entry	Enone	Product	Yield (%)	ee[b] (%)
1	**1**	**11a**	99	40
2	**2**	**12a**	99	35
3	**3**	**13a**	98	45
4	**4**	**14a**	99	—
5	**5**	**15a**	—	—
6	**6**	**16a**	65	14
7	**7**	**17a**	77	14
8	**8**	**18a**	79	40
9	**9**	**19a**	40	2

[a] Reactions and conditions: BSA (5 mol %), 18 h, rt.
[b] Determined by chiral HPLC analysis.

In accordance with this hypothesis, cyclohexen-2-one **4**, bearing an *s-trans* conformation, afforded the corresponding racemic adduct. Enone **5**, bearing an *s-cis* conformation did not react under standard conditions, presumably because of unfavorable steric interactions with the BSA binding pocket.

Moderate to good chemical yields were obtained with chalcones **6–9** bearing substituents on the aromatic moieties (Table 2, entries 6–9). Higher enantioselectivity was observed with 3-(4-chlorophenyl)-1-phenyl-2-propen-1-one **8** with respect to 1-(4-chlorophenyl)-3-phenyl-2-propen-1-one **6** (Table 2, entries 6 and 8).

3. Conclusion

In conclusion the method described herein offers a novel biomimetic route to enantio-enriched Michael adducts from easily available and inexpensive starting materials and catalyst. The simplicity of this procedure, the use of water as a solvent, and the benign nature of the catalyst make this method environmentally friendly. Moreover, this work underlines that proteins without a catalytic site, such as BSA, can be an interesting alternative to enzymes which often show narrow substrate specificity, high cost, commercial unavailability, and insufficient stability.

4. Experimental

4.1. Materials and characterization

All enones and thiols are commercially available compounds and were used as received. Lyophilized BSA Cohn V fraction was

used throughout the work. NMR spectra were recorded on a Bruker AC 300 operating at 300.13 MHz for ^{1}H NMR and 75.3 MHz for ^{13}C NMR. Chemical shifts were reported by using $CHCl_3$ as the external standard (7.24 ppm for ^{1}H NMR and 77.0 for ^{13}C NMR). Optical rotations were measured with a Perkin Elmer 241 polarimeter; the $[\alpha]_D$ values are reported in 10^{-1} deg cm^{-2} g^{-1}, concentration (c) is reported in g per 100 mL. Chiral HPLC separations were performed on a Agilent HP 1100 apparatus, equipped with a diode array detector, using mixtures of hexane/2-propanol as eluant, detection at 230 nm unless otherwise stated. The flux was set to 1 ml min^{-1} and the volume of injection was 20 μL.

4.2. General procedure for BSA-catalyzed thio-Michael addition

The synthesis of (*S*)-1,3-diphenyl-3-(*p*-methoxyphenylsulfanyl)-propan-1-one **11d** is typical.

At first, *trans*-chalcone **1** (0.208 g, 1 mmol) was added to a magnetically stirred solution of BSA (3.30 g, 0.05 mmol) in 12.5 mL of 20 mM sodium tetraborate buffer solution (pH 9). The mixture was stirred for 30 min, then 4-methoxythiopenol **10d** (0.14 g, 1 mmol) was added. The reaction was stirred at room temperature for 18 h, then extracted with ethyl acetate (4 x 20 mL) and the organic phase dried ($MgSO_4$) and concentrated under vacuum. The crude product **11d** (0.35 g, yield 99%) obtained was chemically pure (by ^{1}H NMR). HPLC (Lux Cellulose 2, *i*PrOH-hexane 1–99) t_R (*S*) 25.2 min, t_R (*R*) 27.2, ee 70%. The adduct **11d** was crystallized from *n*-hexane/dichloromethane; concentration of the mother liquor allowed us to recover **11d** (0.23 g, 66% yield) in 86% ee, $[\alpha]_D^{20} = -100.6$ (c 1, CH_2Cl_2).

All Michael adducts **11–19** are known compounds (except for **11e** whose data are reported below) and have been isolated in pure form (as revealed by NMR comparison to data reported in the literature) following the general procedure described above. Determination of ee's has been performed by HPLC by using Chiralcel OD-H or Lux Cellulose 2 columns (Table 3).

4.2.1. 1,3-Diphenyl-3-(*o*-methoxyphenylsulfanyl)-propan-1-one 11e

Yield 85%, mp >400 °C, $[\alpha]_D^{25} = -6.0$ (c 0.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 3.58 (dd, 1H, J_1 = 5.6 Hz, J_2 = 17.0 Hz), 3.69 (dd, 1H, J_1 = 8.5 Hz, J_2 = 17.0 Hz), 3.82 (s, 3H), 5.09 (dd, 1H, J_1 = 5.6 Hz, J_2 = 8.5 Hz), 6.82 (m, 2H), 7.13–7.53 (m, 10H), 7.86 (d, 2H, J = 7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 44.9 (CH_2), 46.1 (CH), 55.7 (CH_3), 110. 8 (CH), 120.9 (CH), 121.2 (CH), 127.0 (CH), 128.0 (CH), 128.3 (CH), 128.5 (CH), 129.1 (CH), 136.9 (C), 141.2 (C), 159.0 (C), 197.1 (C). ESI-MS m/z 348 $(M+Na)^+$.

Table 3
HPLC analysis of Michael adducts **11–19**

	Column[a]	Eluant	t_R Major (min)	t_R Minor (min)
11a	A	1% *i*-PrOH	11.0	13.1
11b	A	1% *i*-PrOH	12.0	13.2
11c	A	1% *i*-PrOH	12.1	17.1
11d	B	1% *i*-PrOH	25.2	27.2
11e	A	1% *i*-PrOH	9.0	10.1
11g	A	2% *i*-PrOH	17.2	18.1
11h	A	1% *i*-PrOH	9.0	18.1
11i	A	1% *i*-PrOH	8.5	9.4
12a	A	2% *i*-PrOH	14.2	17.0
13a	A	2% *i*-PrOH	5.7	6.1
16a	B	1% *i*-PrOH	24.6	18.6
17a	B	1% *i*-PrOH	38.6	31.4
18a	A	1% *i*-PrOH	15.2	16.8
19a	A	1% *i*-PrOH	62.5	59.4

[a] A = Chiralcel OD-H; B = Lux cellulose 2.

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