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Preparation of 2-heteroatom substituted-4-oxo-4-arylbutanoates *via* thio- and aza-Michael addition

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Abstract: Efficient regioselective conjugate additions of thiophenols and benzotriazole to 4-aryl-4-oxobut-2-enoates were achieved under mild conditions. Thus, a variety of 2-(arylthio)-4-oxo-4-arylbutanoates and 2-benzotriazolyl-4-oxo--4-arylbutanoates were conveniently synthesized in good to excellent yields.

Keywords: Michael addition; thiophenol; benzotriazole; 4-aryl-4-oxobut-2-enoate.

INTRODUCTION

4-Aryl-4-oxobut-2-enoates, which can be readily prepared from low-cost and readily available materials,[1,2] have aroused great interest because of their biological activity and applications in the field of synthetic chemistry.[3–6] The conjugate addition using 4-aryl-4-oxobut-2-enoates as Michael acceptors has received significant attention since the adducts are usually multi-functional compounds and are potentially synthetically or medicinally valuable. The addition of amino acids to 4-aryl-4-oxobut-2-enoates (*γ*-oxo-*γ*-phenylbutyrate) could produce useful intermediates for the synthesis of angiotensin-converting enzyme (ACE) inhibitors.[7,8] Indoles underwent conjugate addition to 4-aryl-4-oxobut-2-enoates, forming a C–C bond, catalyzed by a Lewis acid.[9] The facile Michael addition of other *C*-nucleophiles, such as active methylene compounds to 4-aryl-4-oxobut-2--enoates was also reported.[10]

In our recent program focused on the selective reduction of 2-heteroatom-substituted carbonyl compounds, some 2-heteroatom-substituted 4-oxo-4-arylbutanoates were required. Although thio-Michael addition has been intensively studied,[11–19] only a few unusual approaches to certain specific 2-arylthio-4-oxo--4-arylbutanoates have been reported. Yoshimatsu *et al.* found that scandium(III) triflate ($Sc(OTf)_3$), *i.e.*, scandium(III) trifluoromethanesulfonate, could facilitate the reaction between trimethyl((1-phenylvinyl)oxy)silane and ethyl 2-fluoro-2-

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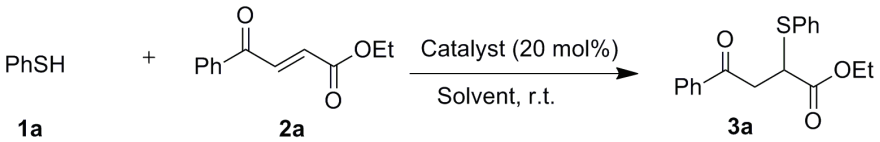
-(phenylthio)acetate to afford ethyl 4-oxo-4-phenyl-2-(phenylthio)butanoate.[20,21] Mukaiyama *et al*. reported that methyl 4-oxo-4-phenyl-2-(phenylthio)butanoate was synthesized in low yield (23 %) *via* $Sn(OTf)_2$-promoted rearrangement of a *β*-keto sulfoxide.[22] In addition, methyl 4-oxo-4-aryl-2-(arylthio)butanoates could be prepared from the substitution between *α*-chloro-*α*-phenylthioketone and silyl enol ethers.[23,24] Nevertheless, the above methods might suffer from special substrates, expensive (or special) catalysts, low efficiency, and/or harsh conditions.

On the other hand, to the best of our knowledge, a method for the synthesis of 2-benzotriazolyl-4-oxo-4-arylbutanoates is unknown. Although a variety of 2-heterocycle (C–N bond) substituted 4-oxo-4-arylbutanoates could be synthesized *via* 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) catalyzed redox isomerization of ethyl 4-aryl-4-hydroxybut-2-ynoate, followed by aza-Michael addition of *N*-containing heterocyclic compounds to the isomerized product, unfortunately the reaction of benzotriazole failed and the desired 2-benzotriazolyl-4-oxo-4-arylbutanoates could not be obtained.[25]

Herein, the preparations of 2-(arylthio)-4-oxo-4-arylbutanoates and 2-benzotriazolyl-4-oxo-4-arylbutanoates *via* regioselective conjugate addition of thiophenol and benzotriazole to 4-aryl-4-oxobut-2-enoates are reported.

RESULTS AND DISCUSSION

This investigation focused first on the catalytic conjugate addition of thiophenols to 4-aryl-4-oxobut-2-enoates. The conjugate addition between thiophenol **1a** and ethyl 4-phenyl-4-oxobut-2-enoate **2a** was employed as a model reaction. It is of interest that all the examined bases (DBU, 1,4-diazabicyclo[2.2.2]octane (DABCO), triethylamine (TEA), pyridine (PyH) and K_2CO_3) led to the formation of the desired **3a** (Scheme 1, Table I). Among them, TEA proved to be the most efficient (Table I, entry 3). Furthermore, screening of the solvents showed that in CH_2Cl_2 an excellent yield of **3a** was obtained (Table I, entry 7). Therefore, CH_2Cl_2 was chosen as the most suitable solvent.



Scheme 1. The catalytic conjugate addition of thiophenol to ethyl 4-phenyl-4-oxobut-2-enoate.

With the optimized conditions in hand, various 4-aryl-4-oxobut-2-enoates were employed as the substrates to test the generality of the reaction (Scheme 2). The results are given in Table II.

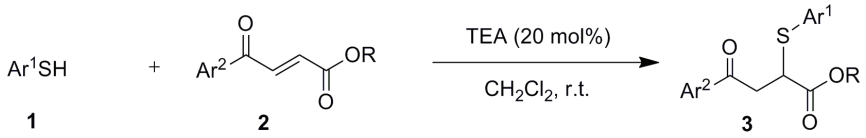
Generally, aryls with electron-donating groups and electron-withdrawing group at the 4-position of substrate **2** exerted little influence on the efficiency of

the reaction (entries 3, 5, 7, 8 and 10, Table III). Exceptionally, 2-furyl caused the corresponding substrate **2** to react more slowly and afforded a lower yield (entry 6). The more nucleophilic *p*-methoxythiophenol was also employed, and the desired product was smoothly obtained in a shorter reaction time (entry 7).

TABLE I. The catalytic conjugate addition of thiophenol to ethyl 4-phenyl-4-oxobut-2-enoate under different conditions

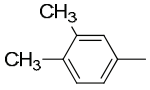
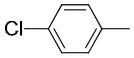
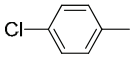
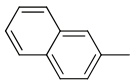
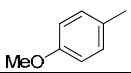
Entry	Catalyst[a]	Solvent	Yield, %[b,c]
1	DBU	THF	76
2	DABCO	THF	65
3	TEA	THF	82
4	PyH	THF	49
5	K_2CO_3	THF	37
6	TEA	EtOH	57
7	TEA	CH_2Cl_2	90
8	TEA	PhMe	52

[a]Catalyst loading: 20 mol %; [b]the runs were performed at room temperature for 6 h; [c]isolated yields



Scheme 2. The catalytic conjugate addition of thiophenols to 4-aryl-4-oxobut-2-enoates.

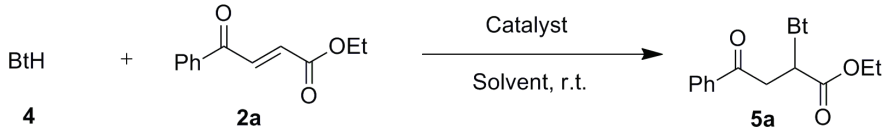
TABLE II. TEA promoted conjugate addition of thiophenols to 4-aryl-4-oxobut-2-enoates (reaction conditions: thiophenol **1** (1 mmol), 4-aryl-4-oxobut-2-enoate **2** (1 mmol), CH_2Cl_2 (10 mL), TEA (0.2 mmol, 20 mol %), room temeprature)

Entry	Ar^1	Ar^2	R	Product	Time, h	Yield, %[a]
1			Et	**3a**	6	90
2			Et	**3b**	6	95
3			Et	**3c**	6	89
4			CH_2Ph	**3d**	6	93
5			Et	**3e**	6	92
6			Et	**3f**	8	62
7			Et	**3g**	4	88

[a]Isolated yields

With the successful preparation of 2-(arylthio)-4-oxo-4-arylbutanoates, the conjugate addition between 1*H*-benzotriazole (BtH) and 4-aryl-4-oxobut-2-enoates was then explored.

Since BtH is also weakly acidic, the above base-catalyzed conditions for thio-Michael addition was tentatively applied to the aza-Michael addition. However, the reaction of BtH (**4**) and ethyl 4-phenyl-4-oxobut-2-enoate (**2a**) under the above optimized conditions, afforded **5a** in only 53 % yield (Scheme 3) (Table III, entry 1). Other bases, such as DBU, DABCO, PyH, cyclohexylamine, and K_2CO_3 were also tested, but the yield could not be improved (Table III, entries 2–6).



Scheme 3. The catalytic conjugate addition of BtH to ethyl 4-phenyl-4-oxobut-2-enoate.

TABLE III. The catalytic conjugate addition of BtH to ethyl 4-phenyl-4-oxobut-2-enoate under different conditions

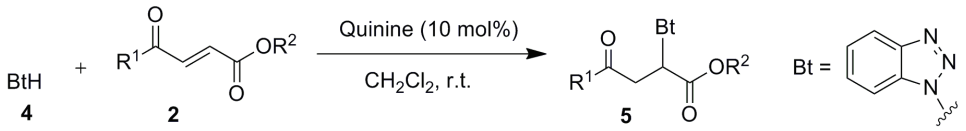
Entry	Catalyst[a]	Solvent	Yield, %[b,c]
1	TEA	CH_2Cl_2	53
2	DBU	CH_2Cl_2	47
3	DABCO	CH_2Cl_2	20
4	PyH	CH_2Cl_2	33
5	Cyclohexylamine	CH_2Cl_2	46
6	K_2CO_3	CH_2Cl_2	35
7	Quinine	CH_2Cl_2	93
8	Quinine	THF	73
9	Quinine	PhMe	51
10	Quinine	CH_2Cl_2	92[d]
11	Quinine	CH_2Cl_2	80[e]

[a]Catalyst loading: 20 mol %; [b]the runs were performed at r.t. for 24 h; [c]isolated yields; [d]catalyst loading: 10 mol %; [e]catalyst loading: 5 mol %

In light of the fact that quinine could promote many Michael additions due to its special bi-functional structure,[26–30] it was introduced as a base catalyst for the addition of BtH with **2a**. Encouragingly, the yield of **5a** increased to 93 % yield with quinine as the catalyst (Table III, entry 7). Other solvents were also screened. THF and toluene seemed to be inferior to CH_2Cl_2 (entries 8–10). Reducing the amount of the catalyst to 10 mol % had hardly any influence on the efficiency (entry 10). However, the yield sharply decreased when the amount of the catalyst was reduced to 5 mol % (entry 11).

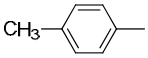
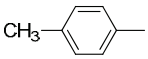
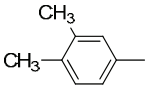
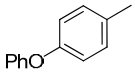
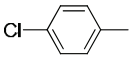
Therefore, the conjugate addition of BtH to various substituted 4-oxobut-2--enoates was performed at room temperature in CH_2Cl_2 with 10 mol % of qui-

nine as the catalyst (Scheme 4). The results are summarized in Table IV. With regard to the substituents on the aryl in substrate **2**, the electron properties seemed to only slightly affect the efficiency of the reactions and good to excellent yield of product **5** could be isolated (Table IV, entries 1–6). The substrate with 2-furyl substitution afforded a lower yield (entry 7). An alkyl substituted substrate was also tried and moderate yield of the desired adduct was obtained (entry 8).



Scheme 4. The catalytic conjugate addition of BtH to 4-phenyl-4-oxobut-2-enoates.

TABLE IV. Quinine promoted conjugate addition of BtH to 4-aryl-4-oxobut-2-enoates (reaction conditions: thiophenol **1** (1 mmol), 4-aryl-4-oxobut-2-enoate **2** (1 mmol), in CH_2Cl_2 (10 mL) with TEA (0.2 mmol, 20 mol %) as catalyst, stirred at room temperature)

Entry	R^1	R^2	Product	Yield, %[a]
1		Et	**5a**	92
2		Et	**5b**	90
3		CH_2Ph	**5c**	80
4		CH_2Ph	**5d**	88
5		Et	**5e**	83
6		Et	**5f**	90
7		Et	**5g**	57
8	Me	Et	**5h**	62

[a]Isolated yields

A plausible mechanism of this quinine catalyzed aza-Michael addition was proposed (Fig. 1). The hydroxyl on the quinine could form a hydrogen bond with the *γ*-carbonyl of the 4-aryl-4-oxobut-2-enoate, and the tertiary nitrogen of quinine acts as a base, which deprotonates the BtH to give a benzotriazole anion (Bt^-). The combination of these factors could double-activate the aza-Michael addition, thereby making the reaction highly efficient.

It is noteworthy that the above catalytic conjugate reactions exhibited complete regioselectivity. The *S*- and *N*- nucleophiles selectively attacked the *β*-po-

sition of the ketone carbonyl. In addition, no product resulting from addition to the *β*-position of the ester carbonyl was observed under the employed catalytic conditions. Furthermore, attacks of *S*- and *N*- nucleophiles on the carbonyls were not observed.

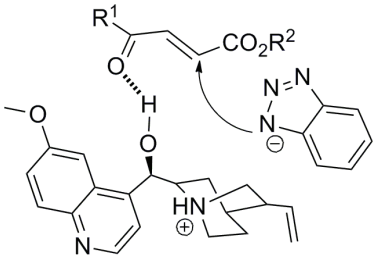


Fig. 1. Proposed mechanism for the conjugate addition between BtH and 4-aryl-4-oxobut-2-enoate.

Thiophenol was more nucleophilic towards 4-aryl-4-oxobut-2-enoate than BtH. Thus, by employing simple TEA as the base catalyst, thiolphenol underwent efficient regioselective thio-Michael addition and 2-arylthio-4-oxo-4-arylbutanoates were prepared in good to excellent yields. Using quinine as the catalyst, the regioselective aza-Michael addition between BtH and 4-aryl-4-oxobut-2--enoate proceeded efficiently and afforded the desired 2-benzotriazolyl-4-oxo-4--arylbutanoates in satisfactory yields.

EXPERIMENTAL

Reagents were commercially available and used without further purification unless otherwise indicated. 4-Aryl-4-oxobuten-2-oic acid,[31] and the corresponding esters **2** were prepared according to literature procedures.[32] TLC was performed on silica gel plates with F-254 indicator; viewing was by UV light (254 nm). Flash column chromatography was performed on silica gel (200–300 mesh), using ethyl acetate/petroleum ether mixtures as eluents. The ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. The elemental analyses were recorded on a Varian-ELIII elemental analyzer. The HRMS spectra were obtained on a Bruker APEXIII 7.0 Tesla FTMS.

*General procedure for the conjugation of thiophenols **1** to 4-aryl-4-oxobut-2-enoates **2**. Synthesis of compounds **3***

To a solution of 4-aryl-4-oxobut-2-enoate **2** (1 mmol) and thiophenol **1** (1 mmol) in CH_2Cl_2 (10 mL) was added TEA (0.20 mmol, 20 mol %) at room temperature. The mixture was stirred at room temperature and monitored by TLC. After the starting material **2** had been completely consumed, the solvent was evaporated under vacuum and the residue purified by flash column chromatography on silica gel to give the desired product **3**.

*General procedure for the conjugation of BtH **4** to 4-aryl-4-oxobut-2-enoates **2**. Synthesis of compounds **5***

To a solution of 4-aryl-4-oxobut-2-enoate **2** (1.0 mmol) and BtH **4** (1.0 mmol) in CH_2Cl_2 (10 mL) was added quinine (0.1 mmol, 10 mol %). The mixture was stirred at room temperature and monitored by TLC. After the starting material **2** had been completely consumed, the

reaction was quenched by aq. HCl. The mixture was extracted with ethyl acetate. The combined organic layers were washed with aq. Na_2CO_3 and then with saturated NaCl. The obtained organic layer was dried over anhydrous Na_2SO_4. After the solvent had been evaporated under vacuum, the residue was purified by flash column chromatography on silica gel to give the desired product **5**.

CONCLUSIONS

In summary, efficient and facile conjugate addition reactions of thiophenols and benzotriazole to various 4-aryl-4-oxobut-2-enoates were developed. The obtained multi-functionalized adducts might be valuable for synthetic or pharmaceutical utilization. The addition reactions proceeded with complete regioselectivity and tolerated various substituents. The readily available materials, simplicity of the procedure, high efficiency, and potentially valuable adducts make the method convenient and useful to synthetic chemists.

SUPPLEMENTARY MATERIAL

Spectral data of the products are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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И З В О Д

СИНТЕЗА 2-ХЕТЕРОАТОМ-СУПСТИТУИСАНИХ 4-ОКСО-4-АРИЛБУТАНОАТА ТИО- И АЗА-МАЈКЛОВОМ АДИЦИЈОМ

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*Р*азвијен је ефикасан поступак региоселективне коњуговане адиције тиофенола и бензотриазола, под благим реакционим условима, при чему су добијени 4-арил-4-оксобут-2-еноати. Овим поступком добијени су различити 2-(арилтио)-4-оксо-4-арилбутаноати и 2-бензотриазолил-4-оксо-4-арилбутаноати у добром до одличном приносу.

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