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Facile and efficient conjugate additions of β-dicarbonyl compounds and nitroalkanes to 4-aryl-4-oxobut-2-enoates

XIN LV, YAOHONG ZHANG, LIEJIN ZHOU and XIAOXIA WANG*

Zhejiang Key Laboratory for Reactive Chemistry on Solid Surfaces, College of Chemistry and Life Sciences, Zhejiang Normal University, Jinhua 321004, P. R. China

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Abstract: Facile and efficient conjugate additions of carbon nucleophiles, such as β-dicarbonyl compounds and nitroalkanes, to 4-aryl-4-oxobut-2-enoates have been achieved under simple base catalysis. A variety of multi-functional γ-keto esters could be conveniently obtained in good to excellent yields with complete regioselectivity.

Keywords: conjugate addition; multi-functional γ-keto ester; β-dicarbonyl compound; nitroalkane; 4-aryl-4-oxobut-2-enoate.

INTRODUCTION

The catalytic conjugate addition of carbon nucleophiles to electron-deficient alkenes is one of the most important synthetic strategies for direct C–C bond formation,[1–3] and many of the corresponding adducts are of great value in biological chemistry and in the field of pharmaceutical.[4]

Both β-dicarbonyl derivatives and nitroalkanes are important sources of stabilized carbanions and the employment of these C-nucleophiles for conjugate addition has drawn much attention.[4] The addition of β-dicarbonyl compounds to activated carbonyl systems could afford potential precursors for a variety of biologically active substances or medicinal intermediates;[4–6] the adducts from nitroalkanes could be conveniently converted to amines, ketones, aldehydes, hydrides, and other useful building blocks.[4,7–11]

4-Aryl-4-oxobut-2-enoates are known as biologically and medicinally important small molecules.[12] These substrates can be conveniently synthesized from readily available and low-cost materials.[12–17] In recent years, Michael addition reactions employing 4-aryl-4-oxobut-2-enoates as the acceptors have been of great interest in modern chemistry, because the corresponding multi-functionalized adducts are of potential value in synthetic or pharmaceutical

* Corresponding author. E-mail: wangxiaoxia@zjnu.cn
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areas.[18–23] For example, Han developed a practical synthesis of 2-azolyl substituted 4-oxo-4-arylbutanoates using azoles as the nucleophiles.[18] The conjugate addition between indoles and 4-aryl-4-oxobut-2-enoates facilitated by a Lewis acid was recently found.[20]

The addition of 1,3-dicarbonyl compounds to 4-aryl-4-oxobut-2-enoates could afford various synthetically or medicinally useful multi-carbonyl derivatives. For example, Tan *et al*. reported bicyclic guanidines-catalyzed Michael reaction of dimethyl malonate with fumaric derivatives, but only one example was the reaction with a 4-aryl-4-oxobut-2-enoate.[21] However, to the best of our knowledge, no systematic study on this type of addition has been reported.

Conjugate addition reactions of nitroalkanes to 4-aryl-4-oxobut-2-enoates are rare in the literature.[7,22,23] Xiao successfully employed a Cinchona alkaloid--based thiourea catalyst for the Michael addition of nitroalkanes to 4-oxo-2-enoates.[7] Tishkov *et al*. reported the 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-catalyzed addition of nitromethane to methyl 4-phenyl-4-oxobut-2-enoate.[22] Feng and coworkers recently reported that a chiral *N*,*N*'-dioxide-Sc(OTf)$_3$ complex worked well for Michael additions of β-dicarbonyl compounds and nitromethane to 4-aryl-4-oxobut-2-enoates.[23] However, to the best of our knowledge, β-keto esters have not been employed as the C-nucleophiles for conjugate addition with 4-oxo-2-enoates.

Other approaches to these multi-functional γ-keto esters have also been developed. For example, Smirnov *et al*. reported that the reactions of 3-bromo-3--nitroacrylates with 2-phenyl-1,3-indanedione under the catalysis of triethylamine (TEA) could afford 2-[1-(alkoxycarbonyl)-2-nitroethyl]-2-phenyl-1,3-indanediones.[24] Ballini and coworkers found that polyfunctionalized nitroalkanes could be synthesized from the addition of active methylene compounds to β-nitroacrylates.[25] They also synthesized multi-functional β-nitro esters using β-nitroacrylates and silyl enol ethers as the starting materials.[26]

However, in spite of these developments, the previously described methods might suffer from harsh conditions (such as low temperatures), poor yields, narrow scopes, expensive (or special) catalysts, and/or tedious procedures. Therefore, more convenient, versatile and efficient strategies for the synthesis of multi--functional γ-keto esters derived from 4-aryl-4-oxobut-2-enoates are still in demand (Fig. 1).

Herein, as a continuation of ongoing studies on catalytic conjugate additions employing 4-aryl-4-oxobut-2-enoates as strategic starting materials, the conjugate addition of various β-dicarbonyl compounds or nitroalkanes to 4-aryl-4--oxobut-2-enoates using a common inorganic base catalyst is presented as a facile protocol to generate multi-functionalized γ-keto esters with complete regioselectivity and high efficiency.

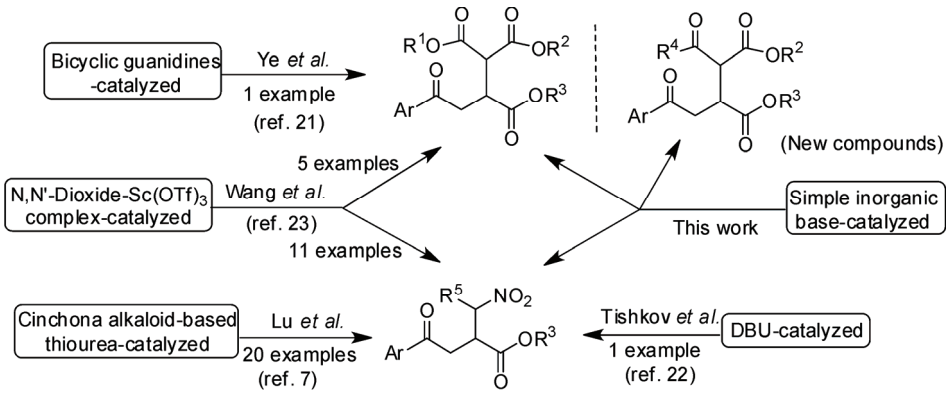
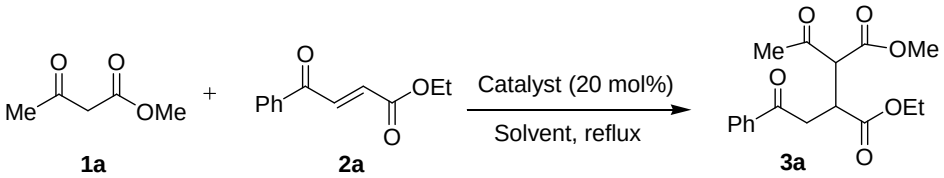


Fig. 1. Recently reported catalytic conjugate addition reactions of 4-aryl-4-oxobut-2-enoates with *β*-dicarbonyl compounds and nitroalkanes.

RESULTS AND DISCUSSION

Initially, the work focused on the catalytic conjugate addition of methyl acetoacetate **1a** to ethyl 4-phenyl-4-oxobut-2-enoate **2a**. In the first attempt performed in tetrahydrofuran, THF, with Et_3N (20 mol %) as the catalyst at room temperature, the desired product **3a** was obtained but in unsatisfactory yield (Scheme 1, Table I). Then, attempts were made to optimize the reaction conditions. Evidently, the key point in the reaction is the choice of solvent. Various solvents (THF, benzene, CH_3CN, Et_2O, CH_2Cl_2, and EtOH) were examined and the result was remarkably improved when EtOH was used as the solvent. After screening a range of bases (Et_3N, pyridine, KOH, 1,4-diazabicyclo[2.2.2]octane (DABCO), DBU and *t*-BuOK), the weak inorganic base K_2CO_3 was found to be the optimal base to promote the conjugate addition.



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

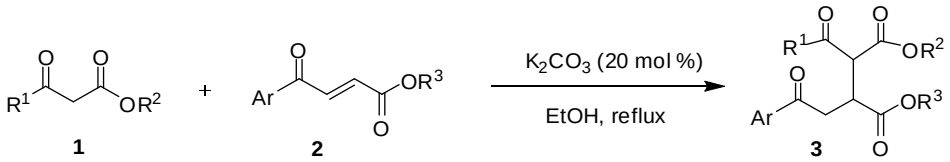
Under the optimized conditions, various *β*-dicarbonyl derivatives and 4-aryl--4-oxobut-2-enoates were employed as the substrates to test the generality of the reaction (Scheme 2, Table II). Both *β*-keto esters and malonic esters undergo the conjugate additions smoothly to give the corresponding adducts in good to excellent yields within a short reaction time (within 2.5 h). Generally, neither electron--donating groups (4-Me, 3,4-dimethyl) nor electron-withdrawing groups (4-Cl,

4-Br) on the aromatic ring seemed to exert an apparent influence on the efficiency of the reaction (entries **3**, **5**, **7**, **8** and **10**), although the reaction of the 4--aryl-4-oxobut-2-enoate bearing a strong electron-donating group, such as PhO–, required a little longer time and gave a relatively lower yield (entries **4** and **9**).

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

Entry	Catalyst[a]	Solvent	Yield[b], %
1	Et_3N	THF	40
2	Et_3N	PhH	22
3	Et_3N	CH_3CN	18
4	Et_3N	Et_2O	33
5	Et_3N	CH_2Cl_2	49
6	Et_3N	EtOH	60
7	Pyridine	EtOH	42
8	DABCO	EtOH	16
9	DBU	EtOH	53
10	*t*-BuOK	EtOH	81
11	K_2CO_3	EtOH	88

[a]Catalyst load: 20 mol %; [b]isolated yields, the runs were performed under reflux conditions for 2.5 h



Scheme 2. K_2CO_3 catalyzed Michael addition of 1,3-dicarbonyl compounds to 4-aryl-4-oxobut-2-enoates.

TABLE II. K_2CO_3 catalyzed Michael addition of 1,3-dicarbonyl compounds to 4-aryl-4-oxobut-2-enoates (reaction conditions: β-dicarbonyl compound **1** (1 mmol), 4-aryl-4-oxobut-2--enoate **2** (1 mmol) in EtOH (10 mL) with K_2CO_3 (0.2 mmol, 20 mol %) as catalyst, stirred under reflux)

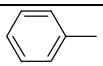
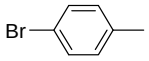
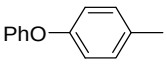
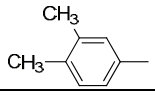
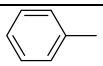
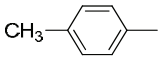
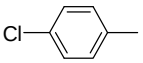
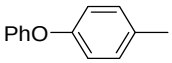
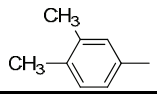
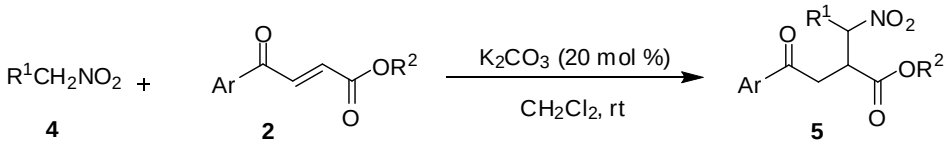
Entry	R^1	R^2	Ar	R^3	Product	Time, h	Yield[a], %
1	Me	Me		Et	**3a**[b]	2.0	88
2	Me	Et		CH_2Ph	**3b**[b]	2.0	85
3	Me	Et		Et	**3c**[b]	2.0	82
4	Me	Et		CH_2Ph	**3d**[b]	2.5	77
5	Me	Et		Et	**3e**[b]	2.0	89

TABLE II. Continued

Entry	R^1	R^2	Ar	R^3	Product	Time, h	Yield[a], %
6	OEt	Et		Et	**3f**	2.0	90
7	OEt	Et		Et	**3g**[b]	2.5	82
8	OEt	Et		Et	**3h**[b]	2.0	86
9	OEt	Et		CH_2Ph	**3i**[b]	2.5	81
10	OEt	Et		Et	**3j**[b]	2.5	85

[a]Isolated yields; [b]new compound

Using 4-aryl-4-oxobut-2-enoates as the acceptors, it was decided to investigate the addition of other carbon nucleophiles, such as nitroalkanes. Fortunately, it was found that the reactions could also proceed efficiently with K_2CO_3 as the catalyst (Scheme 3, Table III) and that CH_2Cl_2 is a superior solvent for the reactions. Various substituted 4-aryl-4-oxobut-2-enoates and nitroalkanes were employed as the substrates to examine the scope of the addition and the results are summarized in Table III. Both nitromethane and nitroethane reacted successfully with 4-aryl-4-oxobut-2-enoates and gave the corresponding products in good yields at room temperature within 3 h. With regard to the substituents on the aryl moiety in 4-aryl-4-oxobut-2-enoates, their electron properties seem to only slightly affect the efficiency of the reactions.



Scheme 3. K_2CO_3 catalyzed Michael addition of nitroalkanes to 4-aryl-4-oxobut-2-enoates.

TABLE III. K_2CO_3 catalyzed Michael addition of nitroalkanes to 4-aryl-4-oxobut-2-enoates (reaction conditions: nitroalkane **4** (1 mmol), 4-aryl-4-oxobut-2-enoate **2** (1 mmol), in CH_2Cl_2 (10 mL) with K_2CO_3 (0.2 mmol, 20 mol %) as catalyst, stirred at room temperature

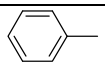
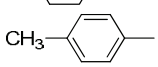
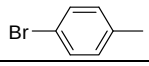
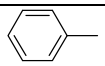
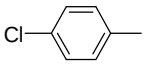
Entry	R^1	Ar	R^2	Product	Time, h	Yield[a], %
1	H		Et	**5a**	3.0	81
2	H		Et	**5b**	3.0	80
3	H		Et	**5c**	2.0	86

TABLE III. Continued

Entry	R^1	Ar	R^2	Product	Time, h	Yield[a], %
4	H		CH_2Ph	**5d**	2.5	85
5	H		CH_2Ph	**5e**[b]	1.5	87
6	Me		CH_2Ph	**5f**[b]	3.0	82

[a]Isolated yields; [b]new compound

It is noteworthy that the above catalytic conjugate reactions exhibited complete regioselectivity. The carbon nucleophiles selectively attacked the β-position of the ketone carbonyl and no product from the addition on the β-position of the ester carbonyl was observed under the employed catalytic conditions.

Among the results, most of the products, including all adducts (**3a**–**e**) derived from the reactions with β-keto esters, are new compounds.

EXPERIMENTAL

The employed reagents were commercially available and used without further purification unless otherwise indicated. EtOH was treated with magnesium before distillation. 4--Aryl-4-oxobuten-2-oic acid,[27] and the corresponding esters **2** were prepared according to literature procedures.[28] TLC was performed on silica gel plates with F-254 indicator; viewing was by UV light (254 nm). Flash column chromatography was realized over 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 solvent and TMS as the internal standard. The infrared (IR) spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer. The elemental analyses were performed on a Various-ELIII elemental analyzer.

General procedure for the conjugation of β*-dicarbonyl compounds **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 β-dicarbonyl compounds **1** (1 mmol) in anhydrous EtOH (10 mL) was added K_2CO_3 (0.2 mmol, 20 mol %) at room temperature. The mixture was stirred under reflux and monitored by TLC. After the starting material **2** had been completely consumed, the reaction mixture was cooled to room temperature and quenched by HCl (0.03 mol L^{-1}). The solvent was evaporated under vacuum and the residue was extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl. Then, the organic layer was dried over anhydrous $MgSO_4$. After solvent evaporation under vacuum, the residue was purified by flash column chromatography on silica gel to give the desired products **3**.

*General procedure for the conjugation of nitroalkanes **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 mmol) and nitroalkane **4** (1 mmol) in CH_2Cl_2 (10 mL) was added K_2CO_3 (0.2 mmol, 20 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 HCl (0.03 mol L^{-1}). The mixture was extracted with ethyl acetate.

The combined organic layers were washed with saturated NaCl and then dried over anhydrous $MgSO_4$. After solvent evaporation under vacuum, the residue was purified by flash column chromatography on silica gel to give the desired products **5**.

CONCLUSIONS

In summary, a facile and efficient conjugate addition of β-dicarbonyl compounds and nitroalkanes to 4-aryl-4-oxobut-2-enoates was achieved. The obtained multi-functionalized adducts might be synthetically or pharmaceutically important. Compared with the reported methods using expensive or unavailable organic catalysts, a common and inexpensive inorganic base (K_2CO_3) was employed as the base catalyst. The presented reaction proceeded with complete regioselectivity and various substituents were tolerated. In addition, the methodology could be successfully applied to reactions with various C-nucleophiles, including β-keto esters. The common catalyst, the ready availability of the materials, the simplicity of the procedure and the potentially valuable adducts make the protocol potentially practical and useful to synthetic chemists.

SUPPLEMENTARY MATERIAL

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

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И З В О Д

ЈЕДНОСТАВНА И ЕФИКАСНА КОНЈУГОВАНА АДИЦИЈА β-ДИКАРБОНИЛНИХ ЈЕДИЊЕЊА И НИТРОАЛКАНА НА 4-АРИЛ-4-ОКСОБУТ-2-ЕНОАТЕ

XIN LV, YAOHONG ZHANG, LIEJIN ZHOU и XIAOXIA WANG

Zhejiang Key Laboratory for Reactive Chemistry on Solid Surfaces, College of Chemistry and Life Sciences, Zhejiang Normal University, Jinhua 321004, P. R. China

Остварена је једноставна и ефикасна конјугована адиција угљеникових нуклеофила као што су β-дикарбинилна једињења и нитроалкани на 4-арил-4-оксобут-2-еноате, у базно-катализованим реакционим условима. Под примењеним условима могу се добити различити више-функционални γ-кето естри у добром до одличном приносу, уз потпуну региоселективност реакције.

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