Intramolecular Michael addition reaction for the synthesis of benzylbutyrolactones†

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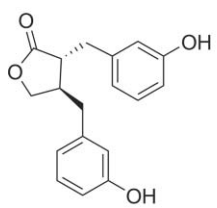
A convenient synthesis of benzyl-γ-butyrolactone derivatives *via* intramolecular Michael addition reaction of nitro-substituted aryl allyl β-ketocarboxylates is reported. The method features simple operation, mild reaction conditions and high efficiency.

Introduction

The lignan[1] lactones have attracted considerable interest over the years because of their broad biological activities.[2,3] Dibenzylbutyrolactones, such as enterolactone **1** and matairesinol **2**, are such examples of bioactive lignans. Recent investigations have shown that enterolactone **1** inhibits breast and colon cancer and suppresses the growth of prostate cancer cells.[4] Matairesinol **2** and its analogs have also been demonstrated to be potent inhibitors of HIV-type 1 integrase.[5] In addition to antitumor and antiviral activities, these compounds display phytoestrogenic,[6] immunoregulatory,[7] and neuroprotective properties.[8] Despite their enormous biological applications, there have been only a few synthetic studies documented in the literature.[9]



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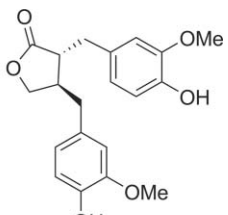

2

Recently, we reported the Ir-catalyzed decarboxylative alkylation of γ-substituted allyl β-ketocarboxylates.[10] Highly regio- and enantioselective allylation of ketone enolates has been achieved through Ir-catalyzed decarboxylative allylic alkylation of allyl β-ketocarboxylate (eqn (1)). Surprisingly, when 4-nitrocinnamyl 3-oxo-3-phenylpropanoate (**3a**) was tested under the same reaction conditions, no decarboxylative alkylation product was obtained but an intramolecular Michael reaction proceeded, affording γ-butyrolactone **4a**.

(1)

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† Electronic supplementary information (ESI) available: Experimental procedures and analysis data for new compounds. CCDC reference numbers 747012 (**4a**) and 747013 (**4j**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b924770j

The structure of the Michael addition product was further confirmed by an X-ray crystallographic analysis (Fig. 1).[11] Although various α,β-unsaturated compounds have been used in the Michael addition reaction, to our knowledge, this represents a rare example of the application of an electron-deficient phenyl alkene as the Michael acceptor. Notably, a similar cyclization reaction has also been observed by Craig and coworkers during their study on the decarboxylative Claisen rearrangement reactions of diallyl 2-sulfonylmalonates; however, only moderate yield was obtained.[12] An elegant study by Tan and Chen demonstrated that $Mn(OAc)_3$ could promote a similar cyclization efficiently *via* a radical process.[13] The extensive synthetic efforts towards γ-butyrolactone derivatives[14] emboldened us to carry out further studies into this Michael addition reaction.

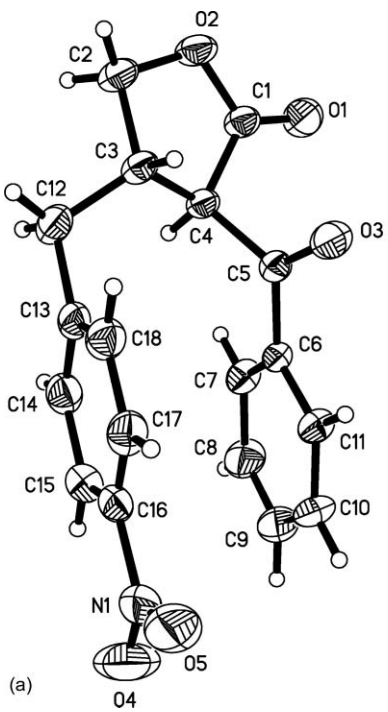
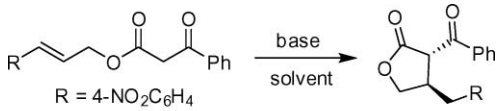


Fig. 1 X-Ray crystal structure of **4a** (thermal ellipsoids are set at 30% probability).

Further investigation of the reaction disclosed that DBU alone could catalyze the intramolecular Michael addition to afford *trans*-γ-butyrolactones (eqn (2)). Herein, we report our detailed

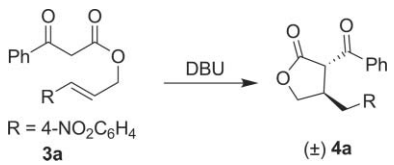
Table 1 Optimization of the reaction conditions for the Michael addition of **3a**[a]



Entry	Solvent	Base	Base (mol%)	T/°C	t/h	Yield (%)[b]
1	CH_2Cl_2	DBU	100	Reflux	2	79
2	CH_2Cl_2	Et_3N	100	25	12	Trace
3	CH_2Cl_2	Et_3N	100	Reflux	36	82
4	CH_2Cl_2	DBN	100	25	8	77
5	CH_2Cl_2	KOAc	100	25	12	NR
6	CH_2Cl_2	DABCO	100	25	12	NR
7	CH_2Cl_2	Cs_2CO_3	100	25	12	NR
8	CH_2Cl_2	K_2CO_3	100	25	12	NR
9	CH_2Cl_2	DIEA	100	25	12	NR
10	CH_2Cl_2	BSA	100	25	12	NR
11	CH_2Cl_2	TMP	100	25	12	NR
12	CH_2Cl_2	PS	100	25	12	NR
13	CH_2Cl_2	Quinine	100	Reflux	12	NR
14	CH_2Cl_2	DBU	100	25	4	86
15	CH_2Cl_2	DBU	20	Reflux	36	94
16	THF	DBU	20	Reflux	2	85
17	THF	DBU	10	Reflux	12	93
18	THF	DBU	5	Reflux	18	89
19	toluene	DBU	10	60	43	62
20	EtOH	DBU	10	60	43	48
21	DME	DBU	10	60	8	99
22	DMF	DBU	10	60	1.5	99
23	DMF	DBU	10	25	10	98

[a] Reaction conditions: 0.1 M of **3a**. [b] Isolated yields.

studies on this DBU-catalyzed intramolecular Michael addition reaction.



(2)

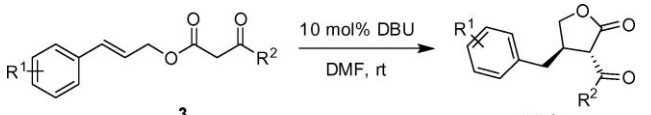
Results and Discussion

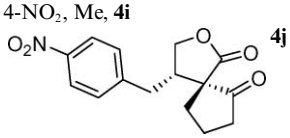
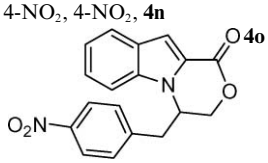
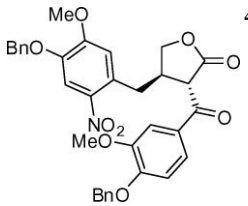
Initially, 4-nitrocinnamyl-3-oxo-3-phenylpropanoate (**3a**) was chosen as a model substrate to optimize the reaction conditions. The results are summarized in Table 1.

In the presence of 1 equiv. of DBU, refluxing **3a** in CH_2Cl_2 for 2 h afforded the cyclized product **4a** in 79% yield (entry 1, Table 1). We first examined different bases, as no reaction occurred without DBU. Most of the bases, such as KOAc, DABCO, Cs_2CO_3, K_2CO_3, DIEA, BSA, Proton Sponge and quinine were not suitable for this transformation (entries 5–13, Table 1), only DBN, Et_3N and DBU could promote this reaction (entries 1–4, Table 1). With Et_3N, the desired product **4a** was obtained only in trace amounts at 25 °C but in 82% yield in boiling dichloromethane (entries 2–3, Table 1). In the presence of 1 equiv. of DBN at 25 °C, **4a** was isolated in 77% yield (entry 4, Table 1). In general, a relatively strong base is needed for the Michael addition reaction.

After examining the loading of DBU, an excellent yield (93%) was obtained with 10 mol% of DBU (entries 14–18, Table 1). Different solvents such as toluene, THF, EtOH, DME and DMF, were all tolerated, and the reaction at 60 °C in DMF gave **4a** in almost quantitative yield (99%) in 1.5 h (entry 22, Table 1). Notably, the reaction in DMF with 10 mol% DBU at room temperature could also give **4a** in 98% yield (entry 23, Table 1). Given the mildness of these reaction conditions, they were chosen as the optimal reaction conditions.

Table 2 Substrate scope for the intramolecular Michael addition reaction[a]



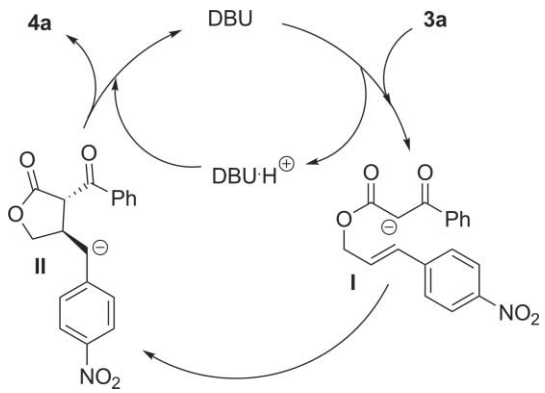
Entry	R^1, R^2, **4**	t/h	Yield (%)[b]
1	4-NO_2, Ph, **4a**	10	98
2	4-NO_2, 4-Me-C_6H_4, **4b**	36	90
3	4-NO_2, 4-MeO-C_6H_4, **4c**	3	96
4	4-NO_2, 4-Cl-C_6H_4, **4d**	8	96
5	4-NO_2, 4-Br-C_6H_4, **4e**	8	93
6	4-NO_2, 2-naphthyl, **4f**	8	99
7	4-NO_2, 2-furyl, **4g**	8	93
8	4-NO_2, *i*-Pr, **4h**	24	75
9[c]	4-NO_2, Me, **4i**	30	71
10[c]	 **4j**	14	83 (4 : 1)
11	2-NO_2, Ph, **4k**	12	92
12	3-NO_2, Ph, **4l**	n.r.	—
13	2-NO_2, 4,5-MeO,MeO Ph, **4m**	12	72
14	4-NO_2, 4-NO_2, **4n**	6	76
15	 **4o**	10	72
16	 **4p**	13	78

[a] Reaction conditions: 10 mol% of DBU, 0.1 M of **3** in DMF, rt. [b] Isolated yields. [c] Reaction was run at 60 °C.

In the presence of 10 mol% DBU in DMF at 25 °C, various substrates were tested and the results are summarized in Table 2. Substrates bearing either electron-donating groups (Me, MeO, entries 2–3, Table 2) or electron-withdrawing groups (Cl, Br, NO_2, entries 4, 5, and 14, Table 2) on the β-aryl keto esters were well tolerated and led to their corresponding products in excellent yields (76–96%). The reaction of 2-furyl and 2-naphthyl-substituted substrates **3f** and **3g** occurred also in excellent yields (93 and 99%, entries 6–7, Table 2). Under the same conditions, substrates **3h** and **3i**, derived from β-alkyl keto esters, could also be tolerated to afford the addition products in 71–75% yields (entries 8–9, Table 2). When substrate **3j** was used, a spiro product **4j** was obtained in 83% yield. The structure of the major diastereoisomer was confirmed by X-ray crystallographic analysis.[15]

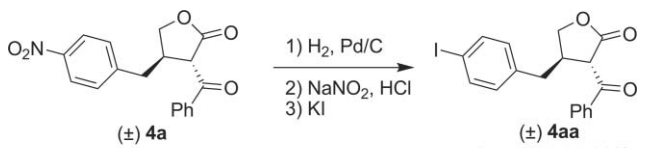
Moreover, 2-nitro- and 3-nitro-substituted substrates **3k** and **3l** were tested in this reaction (entries 11–12, Table 2). Substrate **3k** bearing a 2-nitro group underwent cyclization smoothly to give the corresponding product **4k** in 92% yield. However, the reaction with 3-nitro-substituted substrate **3l** failed to give the desired Michael addition product. Only starting material was recovered, even at elevated reaction temperature (60 °C). To our delight, substrates **3m** and **3p** proceeded the Michael addition reaction smoothly to give butyrolactones **4m** and **4p** in 72 and 78% yield respectively (entries 13 and 16, Table 2). The toleration of various substituents in the substrates highly broadens the utility of the current methodology. In addition to the Michael reaction for C nucleophiles, the aza-Michael reaction was explored. When substrate **3o** was used, the corresponding aza-Michael product **4o** was isolated in 72% yield (entry 15, Table 2).

A straightforward catalytic cycle was proposed as depicted in Scheme 1. Upon treatment with DBU, substrate **3a** will lead to the formation of the carbanion intermediate **I**. The strong electron-withdrawing nature of nitro group facilitates the intramolecular Michael addition generating intermediate **II**, which leads to the formation of product **4a** after the protonation and generates DBU to complete the catalytic cycle.



Scheme 1 DBU-catalyzed intramolecular Michael addition reaction.

The current methodology is particularly attractive in organic synthesis due to the versatile transformation of the nitro group. The synthetic transformation of γ-butyrolactone has also been explored. For instance, 3-benzoyl-4-(4-iodobenzyl)dihydrofuran-2(3H)-one **4aa** was prepared in three steps from **4a**, where the nitro group was converted to an iodo group (eqn (3)).



(3)

Conclusions

In summary, we have developed an efficient method for the preparation of benzyl-γ-butyrolactone derivatives through a Michael addition reaction of nitro-substituted aryl allyl β-ketocarboxylates. The reaction features simple operation, mild reaction conditions and atom economy. The versatile transformation of the nitro group in the products makes the current methodology particularly attractive in organic synthesis.

Experimental

General procedure for the synthesis of benzylbutyrolactone derivatives 4

A flame dried Schlenk tube was cooled to room temperature and filled with argon. To this flask, β-ketoesters **3** (0.2 mmol), DBU (0.02 mmol, 3 mg) and DMF (2 mL) were added. The reaction mixture was stirred at room temperature or 60 °C. After the reaction was complete (monitored by TLC), the reaction mixture was diluted with Et_2O and saturated NH_4Cl. The organic layer was separated, and the aqueous layer was extracted three times with Et_2O. The combined organic layers were dried over Na_2SO_4, and concentrated to afford the crude product. The residue was purified by silica gel column chromatography to afford the desired product **4**.

Full experimental details and characterization data are given in the ESI.†

Acknowledgements

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11 CCDC 747012 contains the supplementary crystallographic data for **4a**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk /data request/cif, and are in the ESI.† Crystal data for compound **4a**: $C_{18}H_{15}NO_5$, M = 325.31, Monoclinic, a = 5.8692(11) A, $\alpha = 90°$, b = 7.6984(14) A, $\beta = 94.634(3)°$, c = 34.643(7) A, $\gamma = 90°$, V = 1560.2(5) A^3, T = 293(2) K, space group = $P2_1/c$, $Z = 4$, Number of Reflections = 8662, Independent reflections = 3360 [R(int) = 0.1004], Final R indices [$I > 2\delta(I)$] $R_1 = 0.0607$, w$R_2 = 0.1486$, R indices (all data) $R_1 = 0.0919$, w$R_2 = 0.1601$.

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15 CCDC 747013 contains the supplementary crystallographic data for major diastereomer of **4j**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk /data request/cif, and are in the ESI.† Crystal data for compound **4j**: $C_{15}H_{15}NO_5$, M = 289.28, Monoclinic, a = 6.8274(9) A, $\alpha = 90°$, b = 8.8266(11) A, $\beta = 96.661(2)°$, c = 23.345(3) A, $\gamma = 90°$, V = 1397.3(3) A^3, T = 293(2) K, space group = $P2_1/c$, $Z = 4$, Number of Reflections = 7130, Independent reflections = 2597 [R(int) = 0.0997], Final R indices [$I > 2\delta(I)$] $R_1 = 0.0632$, w$R_2 = 0.1538$, R indices (all data) $R_1 = 0.0808$, w$R_2 = 0.1656$.

