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A new method for enol lactone synthesis by a Michael addition/cyclization sequence

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Abstract—Reactions of cyclic 1,3-dicarbonyl compounds with 1-(2-alkenoyl)-4-bromo-3,5-dimethylpyrazoles under the double catalytic activation conditions using both catalytic amounts of Lewis acid and amine catalysts provide a new direct synthetic route to enol lactones. Thus, 1,3-cyclohexanedione is allowed to react with 4-bromo-1-crotonoyl-3,5-dimethylpyrazole, in tetrahydrofuran at room temperature in the presence of both catalytic amounts (10 mol% each) of nickel(II) perchlorate hexahydrate and 2,2,6,6-tetramethylpiperidine, to give 4,7,7-trimethyl-3,4,5,6,7,8-hexahydrobenzopyran-2(*H*),5-dione in a good yield. This reaction does not proceed or is too slow under the reaction conditions other than the double catalytic activation conditions.

Enol lactone is an important functionalized substructure found in the skeletons of neoflavonoid and coumarin family which often shows a variety of interesting biological and pharmaceutical activities.[1,2] Although many synthetic routes have been developed for the construction of enol lactones, effective synthetic reactions are quite limited. Thermal condensation reactions between cyclic 1,3-dicarbonyl compounds and α,β-unsaturated esters require heating at a high temperature such as under reflux in *o*-xylene.[3] When 1-(2-alkenoyl)azoles derived from imidazoles or 1,2,4-triazoles are employed instead of esters in the presence of DBU, the reaction becomes much faster. However, a mixture of the *O*- and *C*-acylation products is produced.[4] Reactions between cyclic 1,3-dicarbonyl compounds and α,β-unsaturated acid chlorides in the presence of amines[5] or montmorillonite K-10[6] provide one of the most direct and effective accesses. The Michael additions of the enols of 1,3-dicarbonyl compounds to α,β-unsaturated esters, followed by hydrolysis of the ester and activation of the resulting substituted acids by acetic anhydride, are an alternative.[7] Reactions of phenols with α,β-unsaturated acids in the presence of montmorillonite K-10 is also useful.[8] These reactions are usually performed under severe reaction conditions and the yields are only modest. The most effective accesses so far reported includes the condensation reactions of meldrumic acid (isopropylidene malonate) with aromatic aldehydes followed by the Michael addition of 5,5-dimethyl-1,3-cyclohexanedione under microwave irradiation, where meldramic acid works as reactive condensation reagent.[9]

On the other hand, we have recently developed a new enantioselective Michael addition of nitromethane[10] or malononitrile[11] to unsaturated carbonyl compounds such as 3-(2-alkenoyl)-2-oxazolidinones and 1-(2-alkenoyl)-3,5-dimethylpyrazoles, which can be highly activated by use of both catalytic amounts of amine and chiral Lewis acid. For example, the reaction of malononitrile with 4-bromo-1-crotonoyl-3,5-dimethylpyrazole was performed in the presence of both catalytic amounts (10 mol% each) of 2,2,6,6-tetramethylpiperidine and the (*R*,*R*)-DBFOX/Ph complex of nickel(II) perchlorate hexahydrate to produce 4-bromo-1-(4,4-dicyano-3-methylbutanoyl)-3,5-dimethylpyrazole as Michael adduct in a good yield with high enantioselectivity. The authors have expected that the Michael addition methodology under the double catalytic activation conditions[10–12] should work well as the synthetic method of enol lactones, or their precursors at least, if acceptors and catalysts are appropriately selected.

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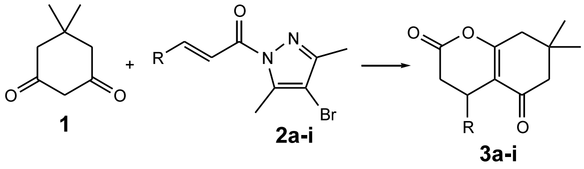
Here in this communication, we will report a new enol lactone synthesis through the reactions between cyclic 1,3-dicarbonyl donors and α,β-unsaturated carbonyl acceptors under the double catalytic activation conditions. When 5,5-dimethyl-1,3-cyclohexanedione was treated with 1-(2-alkenoyl)-4-bromo-3,5-dimethylpyrazole in the presence of nickel(II) perchlorate hexahydrate and 2,2,6,6-tetramethylpiperidine (both in 10 mol% amounts), 4-substituted 7,7-dimethyl-3,4,5,6,7,8-hexahydrobenzopyran-2(*H*),5-diones were produced as the corresponding enol lactones in good yields.

The reaction between 5,5-dimethyl-1,3-cyclohexanedione (**1**) and 4-bromo-1-crotonoyl-3,5-dimethylpyrazole (**2a**) did not take place at room temperature under uncatalyzed conditions; use of a catalytic amount of 2,2,6,6-tetramethylpiperidine (TMP, 10 mol%) as amine catalyst was not totally effective either (Table 1, entry 1). A catalytic amount of nickel(II) perchlorate hexahydrate (10 mol%) employed as Lewis acid promoted the reaction, but the yield of product **3a** was only in a low yield (8%, entry 2). To our delight, however, the yield of **3a** was much improved to 67% in the presence of both catalytic amounts of nickel(II) perchlorate hexahydrate and TMP (10 mol% amounts each), indicating that employment of both Lewis acid and amine catalysts is essential for the production of **3a** (entry 3). Use of excess amount of donor **1** (2 equiv.) made the reaction faster to produce **3a** in a satisfactory yield (4 h, 77%, entry 4). This reaction can be specifically promoted by the use of nickel(II) perchlorate hexahydrate as Lewis acid catalyst, while a variety of bulky amines can be successfully employed.[13] Other perchlorate salts such as copper(II), zinc(II), and iron(III) perchlorate hexahydrates as well as magnesium(II) perchlorate were totally ineffective as Lewis acid catalysts, while cobalt(II) perchlorate hexahydrate showed a weak reaction rate enhancement to give **3a** in 32% yield (32% after 48 h, entry 5).

It was found that the product **3a** isolated was not a simple Michael adduct but was characterized to be a compound resulting from elimination of a pyrazole unit from the corresponding Michael adduct. On the basis of the elemental analysis as well as other spectral data, two structures were probable: either 4,7,7-trimethyl-3,4,5,6,7,8-hexahydrobenzopyran-2(*H*),5-dione or 2,7,7-trimethyl-2,3,5,6,7,8-hexahydrobenzopyran-4(*H*),5-dione. The carbonyl stretching vibrations of **3a** were recorded at 1649 and 1784 cm^{-1}, indicating the existence of functionalities of both β-oxyenone and enol lactone moieties, respectively. Finally, the structure of **3a** was confirmed to be 4,7,7-trimethyl-3,4,5,6,7,8-hexahydrobenzopyran-2(*H*),5-dione on the basis of the X-ray crystallography based structure of its derivative **3h** as shown in Figure 1.

Reaction path for the production of enol lactone **3a** may involve the following steps (Scheme 1): (1) The generation of enolate **A** by deprotonation of diketone **1** with TMP catalyst, (2) the Lewis acid catalyzed

Table 1. Reactions of 5,5-dimethyl-1,3-cyclohexanedione (**1**) with 4-bromo-1-crotonoyl-3,5-dimethylpyrazoles (**2a**–**i**) under the double catalytic activation conditions producing enol lactones **3a**–**j**[a]



Entry	**2** (R)	Metal salt (equiv.)	Donor (equiv.)	Time (h)	**3**	Yield (%)
1[b]	**2a** (Me)	None	1	48	**3a**	–
2[c]		$Ni(ClO_4)_2{\cdot}6H_2O$	1	48		8
3		$Ni(ClO_4)_2{\cdot}6H_2O$	1	10		67
4		$Ni(ClO_4)_2{\cdot}6H_2O$	2	4		77
5		$Co(ClO_4)_2{\cdot}6H_2O$	2	48		32
6		$Cu(ClO_4)_2{\cdot}6H_2O$	2	12		Trace
7		$Zn(ClO_4)_2{\cdot}6H_2O$	2	12		Trace
8		$Fe(ClO_4)_3{\cdot}nH_2O$	2	12		–
9		$Mg(ClO_4)_2$	2	12		–
10	**2b** (Et)	$Ni(ClO_4)_2{\cdot}6H_2O$	2	4	**3b**	74
11	**2c** (*n*-Pr)	$Ni(ClO_4)_2{\cdot}6H_2O$	2	72	**3c**	75
12	**2d** (*i*-Pr)	$Ni(ClO_4)_2{\cdot}6H_2O$	2	96	**3d**	50
13	**2e** (c-C_6H_{11})	$Ni(ClO_4)_2{\cdot}6H_2O$	2	96	**3e**	52
14	**2f** (1-Propenyl)	$Ni(ClO_4)_2{\cdot}6H_2O$	2	96	**3f**	55
15	**2g** (Ph)	$Ni(ClO_4)_2{\cdot}6H_2O$	2	12	**3g**	97
16	**2h** (4-BrC_6H_4)	$Ni(ClO_4)_2{\cdot}6H_2O$	2	12	**3h**	94
17	**2i** (Furyl)	$Ni(ClO_4)_2{\cdot}6H_2O$	2	12	**3i**	89

[a] Conditions: metal salt/TMP (10 mol% each), at rt, in THF (0.1 M).

[b] Only TMP was added.

[c] Only $Ni(ClO_4)_2{\cdot}6H_2O$ was added.

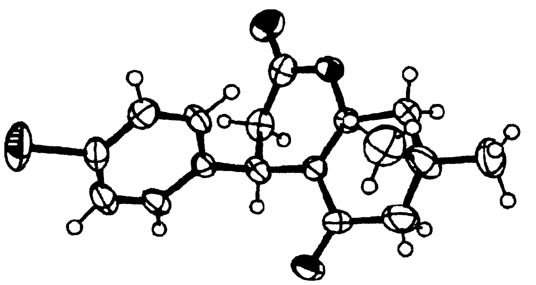
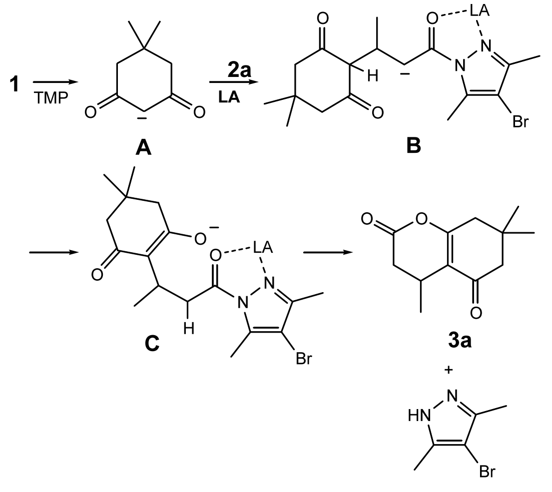


Figure 1. X-Ray based structure of 4-(*p*-bromophenyl)-7,7-dimethyl-3,4,5,6,7,8-hexahydrobenzopyran-2(*H*),5-dione (**3h**).



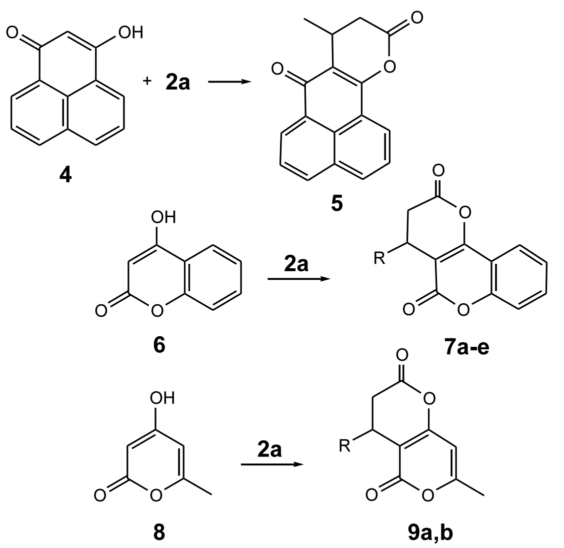
Scheme 1.

Michael addition reaction of **A** to acceptor **2a**, (3) the intramolecular protonation of **B** to give enolate **C**, (4) lactonization of **C** giving enol lactone **3a**. The 1,3-diketone-stabilized anion **C**, or ketone-stabilized enolate, should be much less basic than amide enolate anion **B** causing the ready proton migration in the transformation of **B** to **C**. Both the nucleophilic carbonyl addition and pyrazole elimination steps involved in the esterification step of **C** leading to **3a**, are also activated by coordination of the Lewis acid catalyst (LA) to the *N*-acyl pyrazole group. The reason that nickel(II) perchlorate hexahydrate was an especially active catalyst may be because of the fast ligand exchange occurring on the cationic nickel(II) metal center having water ligands.[14]

A variety of substituents can be successfully employed as β-substituents of acceptors **2**. Not only primary alkyl substituents (**2b**,**c**) but also secondary alkyl (**2d**,**e**) and alkenyl substituents (**2f**) worked well, albeit in moderate yields of **3b**–**f**. Reactions of substrates having aryl (**2g**,**h**) and heteroaryl substituents (**2i**) provided especially excellent yields of enol lactones **3g**–**i** (Table 1).

The reaction of 3-hydroxy-1*H*-phenalen-1-one (**4**) as the ring-fused 1,3-diketone with 4-bromo-1-crotonoyl-3,5-dimethylpyrazole (**2a**) under the double catalytic activation conditions using $Ni(ClO_4)_2 \cdot 6H_2O$ and TMP in THF at room temperature for 6 h gave enol lactone **5** in 65% yield (Table 2). In the cases of β-keto esters such as 4-hydroxycoumarin (**6**) and 4-hydroxy-6-methyl-2-pyrone (**8**), there are two possible cyclization modes. It was found that the enol lactones based on ketone enols such as **7a**–**e** and **9a**,**b** were produced predominantly rather than those derived from the corresponding ester enols. The structures of **7a**–**e** and **9a**,**b** were based on the X-ray determined structure of **7e** as shown in Figure 2.

Table 2. Reactions of cyclic diketone **4** and keto esters **6** and **8** with 4-bromo-1-crotonoyl-3,5-dimethylpyrazole **2a** under the double catalytic activation conditions producing enol lactones, **5**, **7a**–**e**, and **9a**,**b**, respectively



	R	Time (h)	Yield (%)
5	Me	6	65
7a	Me	3	81
7b	Ph	48	85
7c	$4\text{-}BrC_6H_4$	48	83
7d	$3,5\text{-}Br_2C_6H_3$	48	41
7e	$2\text{-}MeO\text{-}5\text{-}BrC_6H_3$	144	76
9a	Me	3	81
9b	$3,5\text{-}Br_2C_6H_3$	48	81

Conditions: $Ni(ClO_4)_2 \cdot 6H_2O$/TMP (10 mol% each), at rt, in THF (0.1 M).

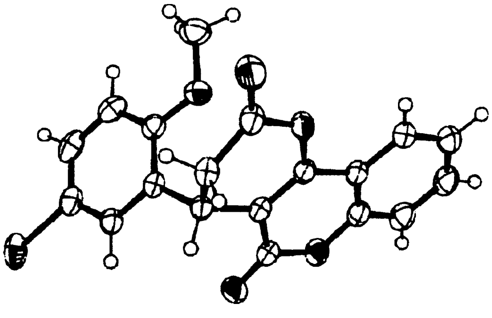


Figure 2. X-Ray based structure of 4-(5-bromo-2-methoxyphenyl)-3,4,5,6-tetrahydronaphtho[1,2-*b*]pyran-2(*H*),5-dione (**7e**).

In conclusion, a combined use of nickel(II) perchlorate hexahydrate and TMP, both in catalytic amounts (10 mol% each), in the reactions of cyclic 1,3-dicarbonyl compounds with 1-(2-alkenoyl)-4-bromo-3,5-dimethylpyrazoles was especially effective in the synthesis of enol lactones under mild reaction conditions (in THF at room temperature). Extension of this reaction to enantioselective enol lactone synthesis under the double catalytic activation conditions is now in progress. Detailed results will be reported soon elsewhere.

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