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K_2CO_3-Catalyzed Michael Addition–Lactonization Reaction of 1,2-Allenyl Ketones with Electron-Withdrawing Group Substituted Acetates. An Efficient Synthesis of α-Pyrone Derivatives

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ABSTRACT

α-Pyrone derivatives were synthesized via the base catalyzed or promoted reaction of 1,2-allenyl ketones and electron-withdrawing group substituted acetates. The reaction was believed to proceed through a Michael addition C–C double-bond migration–lactonization process.

α-Pyrone is a commonly observed structural unit in many naturally occurring products that show a broad range of biological activities.[1,2] Due to the existence of functional groups such as conjugated dienes and the ester group, α-pyrones are usually utilized as important intermediates in organic synthesis.[3,4] Thus, much attention has been paid to the development of new methodology for the efficient synthesis of α-pyrones. In summary, the following are typical methodologies for the synthesis of α-pyrone: (1) lactonization reaction of various functionalized α,*β*-unsaturated enones, which were prepared via various methods from different starting materials;[5] (2) cyclization of 3,5-diketocarboxylic acids;[6] (3) Pd-catalyzed coupling−lactonization of 3-halo-(2*Z*)-enoic acids with 1,2-allenic tins;[7] and (4) Pd-catalyzed carbometalation−lactonization of 3-halo-(2*Z*)-

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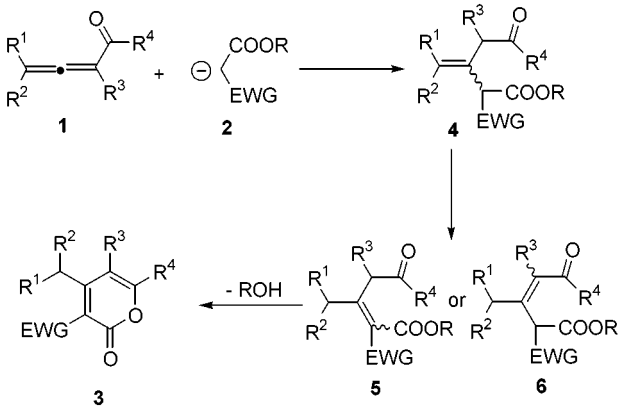
enoates with alkynes.[8] The most obvious disadvantages for some of these methodologies are either low-yielding or lacking diversity and regioselectivity.

Recently, during the course of our study of the chemistry of allenes,[9] we have demonstrated that electron-deficient allenes can easily accept the nucleophilic attack of a halide anion to afford β-halo-β,γ-unsaturated functionalized alkenes.[10] On the basis of these results, we reasoned that 1,2-allenyl ketones may accept the nucleophilic attack of compounds with active methylene groups (Scheme 1).

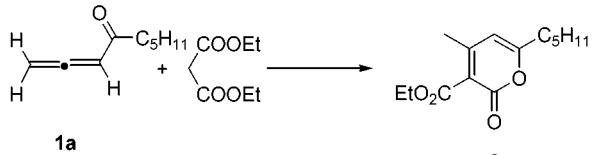
Scheme 1



However, for this reaction, due to the existence of three carbonyl groups, there is a tendency that the carbon−carbon double bond may migrate to form intermediate **5** or **6**. If we can control the selectivity of this reaction, it may be possible for us to develop an efficient method for the synthesis of α-pyrone.[11] If this is feasible, diversity and regioselectivity is the advantage for this reaction since the allenyl ketones can accommodate four different substituents at the different locations and compounds with an active methylene group **2** have one EWG group, which can be organized into the different locations of α-pyrones.

Using 1,2-nonadien-4-one and diethyl malonate as the starting point, we screened many combinations of solvents and bases; fortunately, the corresponding reaction in DMF with 0.5 or 1.0 equiv of K_2CO_3 afforded the expected α-pyrone **3a** in 31% yield. Better results were obtained when the reaction was run in the presence of 1.0 equiv of K_2CO_3 in acetone under reflux. A preparation of **3a** in 79% yield was realized when only a catalytic amount (10 mol %) of K_2CO_3 was utilized (Table 1).[12]

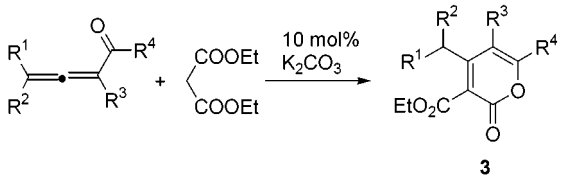
Table 1. Base-Promoted Reaction of 1,2-Nonadien-4-one and Diethyl Malonate



entry	K_2CO_3 (equiv)	solvent	temp (°C)	time (h)	yield (%)
1	0.5	DMF	50	13	31
2	1.0	DMF	80	3	31
3	1.0	acetone	reflux	12	67
4	0.1	acetone	reflux	20	79

Some typical results are summarized in Table 2. The following points should be noted. (1) Although K_2CO_3 was a commonly used base for this chemical transformation, the generality of the reaction parameters for this methodology is poor. Even for very similar substrate, different solvents should always be tried until a satisfactory result is obtained.

Table 2. K_2CO_3 Catalyzed or Promoted 1,4-Addition C−C Double-Bond Migration−Lactonization Reaction of 1,2-Allenyl Ketones with Diethyl Malonate



	1							
entry	R^1	R^2	R^3	R^4	solvent	temp (°C)	time (h)	yield of **3** (%)
1	H	H	H	Me (**1b**)	EtOH	60	1.5	74 (**3b**)
2	H	H	H	Ph (**1c**)	acetone	reflux	4	71 (**3c**)
3	H	H	H	Ph (**1c**)	EtOH	reflux	1.5	56 (**3c**)
4	H	H	H	Bn (**1d**)	CH_2Cl_2	reflux	40	69 (**3d**)
5	H	H	C_4H_9	Me (**1e**)	acetone	reflux	48	64 (**3e**)
6[a]	H	H	C_4H_9	Me (**1e**)	DMF	80	7	55 (**3e**)
7	H	H	C_2H_5	Me (**1f**)	EtOH	reflux	12	53 (**3f**)
8	H	H	C_2H_5	Me (**1f**)	DMF	80	12	50 (**3f**)
9	H	H	C_2H_5	Me (**1f**)	acetone	reflux	20	33 (**3f**)
10	H	H	Bn	Me (**1g**)	acetone	reflux	21	92 (**3g**)
11	H	H	Bn	Me (**1g**)	DMF	60	2.5	90 (**3g**)
12	H	H	allyl	Me (**1h**)	EtOH	reflux	15	54 (**3h**)
13	H	H	allyl	Me (**1h**)	acetone	reflux	20	90 (**3h**)
14	H	C_4H_9	H	Me (**1i**)	EtOH	80	7	38 (**3i**)
15	H	C_4H_9	H	Me (**1i**)	DMF	80	13	54 (**3i**)

[a] One equiv of K_2CO_3 was used.

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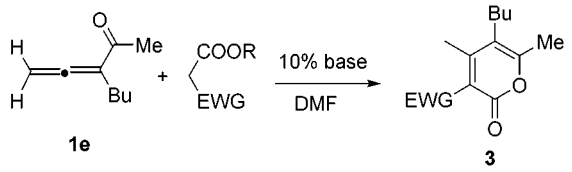
Table 3. Cyclization Reaction of 1,2-Dienyl Ketone **1E** with $CH_2(CO_2R)(EWG)$



1e **3**

entry	$CH_2(CO_2R)(EWG)$	base	temp (°C)	time (h)	yield of **3** (%)
1	$CH_2(CO_2Me)_2$	K_2CO_3	80	4	88 (**3j**)
2	$CH_2(CO_2Me)_2$	NaH	rt	5 days	87 (**3j**)
3	$CH_2(CO_2Me)_2$	NaH	80	4	88 (**3j**)
4	$CH_2(CO_2Me)_2$	NaOH	80	1	87 (**3j**)
5	$CH_2(CN)(CO_2Et)$	NaH	50	3	69 (**3k**)
6	$CH_2(CN)(CO_2Et)$	NaH	80	4	39 (**3k**)
7	$CH_2(CN)(CO_2Et)$	NaOAc	50	7	61 (**3k**)
8	$CH_2(CN)(CO_2Et)$	K_2CO_3	50	2	60 (**3k**)
9	$CH_2(COMe)(CO_2Me)$	NaH	80	23	38 (**3l**)

Solvents used were EtOH, DMF, acetone, THF, CH_2Cl_2, etc. (2) Even when R^4 = Ph, the reaction also afforded the corresponding product **3d** in 71% yield (entry 2, Table 2). (3) For substrates with non-H R^3 and R^4, the best yields for every reaction range from 53 to 92% (entries 5−13, Table 2). (4) For substrates with non-H R^2 and R^4, the yields are also reasonable (entries 14 and 15, Table 2).

The present protocol can also be extended to dimethyl malonate, ethyl cyanoacetate, and ethyl acetoacetate to afford differently substituted α-pyrone derivatives (Table 3).

In conclusion, we have developed an efficient methodology for the synthesis of differently substituted α-pyrones starting from the easily available 1,2-allenic ketones and compounds with an active methylene group. The scope and limitation of this reaction as well as its synthetic application are being carried out in our laboratory.

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Supporting Information Available: Typical experimental procedure and analytical data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0170859

(12) A typical procedure for the synthesis of **3a** is as follows: A solution of 166 mg (1.2 mmol) of 1,2-nondien-4-one, 160 mg (1.0 mmol) of diethyl malonate, and 14 mg (10 mol %) of K_2CO_3 in 1 mL of acetone was heated to reflux with stirring. After the reaction was complete (monitored by TLC, eluent = 6:1 hexane/ethyl acetate), the solvent was evaporated and the crude product was purified by chromatography on silical gel (6:1 hexane/ethyl acetate) to afford 199 mg (79%) of **3a**.