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Highly Efficient Approach to 4-Ethoxy-5,6-dihydro-6,6-disubstituted Pyran-2-ones using a Combinational Lewis Acid-Base System

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Abstract: The first efficient approach to 5,6-dihydro-6,6-disubstituted pyran-2-ones was successfully achieved from the reaction between commercially available ethyl 3-ethoxybut-2-enoate and ketones in the presence of $BF_3 \cdot Et_2O$, $InBr_3$ and LDA. $BF_3 \cdot Et_2O$ and $InBr_3$ were employed as the Lewis acid to activate the ketone and LDA was employed as the Lewis base to activate ethyl 3-ethoxybut-2-enoate. Aromatic, aliphatic, and heterocyclic ketones were converted to the corresponding δ-lactones containing quaternary carbon atom centers in excellent yields (up to 99%) under mild conditions.

Keywords: dihydropyrones; dual activation; ketones; lactones; lithium diisopropylamide; quaternary carbon atom center

Introduction

The unequivocal chemical synthesis of δ-lactones, which are important intermediates in the synthesis of a variety of structures with biological and medical significance,[1,2] such as antifungal and antitumor agents, has attracted wide attention in organic chemistry. There are several synthetic methodologies to afford δ-lactones, such as the annulation of open-chain precursors,[3] the derivatization from a 2,3-dihydropyran-4-one,[3e] and the two-step addition reaction of enes to dicarbonyl compounds.[3f] One of the convenient routes to δ-lactones is based on a hetero-Diels–Alder reaction of Brassard's diene with suitable aldehydes and results in 5,6-dihydro-6-substituted pyran-2-ones as the products. Previously we reported an example of the highly enantioselective hetero-Diels–Alder reaction of Brassard's diene with aromatic aldehydes.[4] Later, another example of the hydrogen bond-promoted hetero-Diels–Alder reaction of aldehydes with Brassard's diene was also developed by Ding's group.[5] However, until recently only few examples of the synthesis of the 5,6-dihydro-6,6-disubstituted pyran-2-one have been reported.[6] The synthesis of δ-lactones with four non-hydrogen substituents, that is, quaternary carbon centers,[7] is still a challenge. These facts prompted us to search for an efficient route to synthesize 5,6-dihydro-6,6-disubstituted pyran-2-ones.

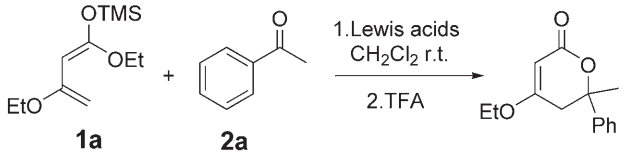
Results and Discussion

Preliminary Trials

Acetophenone was reacted with Brassard's diene in our initial study as outlined in Table 1. A series of Lewis acids was screened, but they inefficiently mediated the cycloaddition of carbonyl dienophiles with Brassard's diene.

To overcome the low reactivity of acetophenone, the dual activation strategy was used.[8] A Lewis base such as fluoride anion (TBAF) and *N*-oxides have been reported to activate the silylated nucleophiles.[9,10] Therefore we tested the combination of a fluoride anion (TBAF) or *N*-oxides and Lewis acid to activate Brassard's diene and acetophenone, respectively. But no product was observed. Considering the reactivity of Brassard's diene, ethyl 3-ethoxybut-2-enoate (**1b**), the intermediate for the synthesis of Brassard's diene, was investigated in this reaction. Ester **1b** could easily be converted to **1c** by treatment with lithium diisopropylamide (LDA). Compared with **1a**, the nucleophilicity of **1c** was much higher.[11] As shown by experiment, **1c** could smoothly react with acetophenone activated by a Lewis acid or two Lewis acids.

Table 1. Hetero-Diels–Alder reaction of brassard's diene with acetophenone catalyzed by Lewis acids.[a]



Entry	Lewis acid	Catalyst loading [mol %]	Time [h]	Yield [%][b]
1	$BF_3 \cdot Et_2O$	50	64	16
2	$TiCl_4$	50	64	N.D
3	$ZnCl_2$	50	64	N.D
4	$Yb(OTf)_3$	50	64	N.D
5	$Sc(OTf)_3$	50	64	N.D
6	Et_2AlCl	50	64	N.D
7	$BF_3 \cdot Et_2O/Et_2AlCl$	50/20	48	12
8	$BF_3 \cdot Et_2O/TiCl_4$	50/20	48	10
9	$BF_3 \cdot Et_2O/Yb(OTf)_3$	50/20	48	N.D
10	$BF_3 \cdot Et_2O/InCl_3$	50/20	48	7

[a] All reactions were performed with acetophenone (0.25 mmol) and Brassard's diene (0.375 mmol) in the presence of a Lewis acid (50 mol %) at room temperature in CH_2Cl_2 (1.0 mL) for 48 or 64 h.
[b] Yield of isolated products.

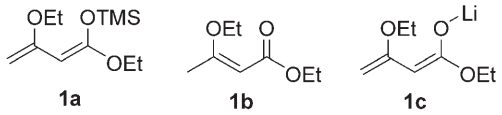
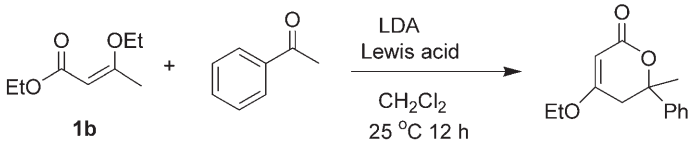


Figure 1. Structures of compounds **1a**, **1b**, and **1c**.

Lewis Acid Survey

A variety of Lewis acids was screened as catalysts for the reaction (Table 2). The initial attempt revealed that $BF_3 \cdot Et_2O$ possessed catalytic ability. 26% adduct was obtained after 12 hours (Table 2, entry 1). In the course of this reaction, THF was a necessary solvent to convert **1b** to **1c**. It had an adverse effect in the next addition step with acetophenone. In another parallel experiment, when THF was removed before the Lewis acid and ketone were added, the yield was raised to 41% (Table 2, entry 2). This result indicated that $BF_3 \cdot THF$ was formed, and this complex led to a lower catalytic activity. As the catalyst loading increased, the yield rose steadily

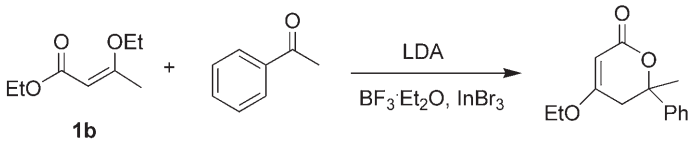
Table 2. The reaction of ethyl 3-ethoxybut-2-enoate with acetophenone.[a]



Entry	Catalyst	Catalyst loading [mol %]	Yield [%][b]
1[c]	$BF_3 \cdot Et_2O$	50	26
2	$BF_3 \cdot Et_2O$	50	41
3	$BF_3 \cdot Et_2O$	100	61
4	$InBr_3$	20	54
5	$InBr_3$	50	27
6	$BF_3 \cdot Et_2O/Zr(O\text{-}i\text{-}Pr)_4$	50/20	30
7	$BF_3 \cdot Et_2O/Zn(OTf)_2$	50/20	53
8	$BF_3 \cdot Et_2O/LiCF_3SO_3$	50/20	43
9	$BF_3 \cdot Et_2O/AlEt_2Cl$	50/20	55
10	$BF_3 \cdot Et_2O/TiCl_4$	50/20	93
11	$BF_3 \cdot Et_2O/InCl_3$	50/20	50
12	$BF_3 \cdot Et_2O/InBr_3$	50/20	99

[a] All the reactions were carried out according to the given standard procedure (see Method 2 in the Experimental Section).
[b] Yield of isolated product.
[c] THF was not removed.

Table 3. Effects of the conditions on the reaction.[a]



1b

Entry	Catalyst loading [mol %]	Solvent	Time [h]	Temp. [°C]	Yield [%][b]
1	50/20	CH_2Cl_2	12	25	99
2	50/20	Et_2O	12	25	31
3	50/20	toluene	12	25	24
4	50/20	CH_2Cl_2	12	0	30
5	50/20	CH_2Cl_2	12	50	0
6	50/20	CH_2Cl_2	2	25	70
7	20/20	CH_2Cl_2	12	25	50
8	50/10	CH_2Cl_2	12	25	81
9	50/5	CH_2Cl_2	12	25	71
10[c]	50/20	CH_2Cl_2	12	25	32
11[d]	50/20	CH_2Cl_2	12	25	trace
12[e]	50/20	CH_2Cl_2	12	25	0
13[e]	50/20	THF	12	25	0

[a] All the reactions were carried out according to the given standard procedure (see Method 2 in the Experimental Section).
[b] Yield of isolated product.
[c] The ratio of **1b** to **2a** was 2:1.
[d] The ratio of **1b** to **2a** was 1.5:1.
[e] $BF_3 \cdot Et_2O$, $InBr_3$, LDA were added to the reaction system together.

(Table 2, entry 3). Further improvement, however, was not achieved by increasing the catalyst loading. $InBr_3$ also exhibited a certain catalytic ability with moderate yield (Table 2, entries 4 and 5). To our delight, when $BF_3 \cdot Et_2O$ and other Lewis acid were employed at the same time, the yield was dramatically improved (Table 2, entries 5–12). A Lewis acid-assisted process may occur in this system.[12] On the basis of these results, the combination of $BF_3 \cdot Et_2O$ and $InBr_3$ was a good system for this reaction.

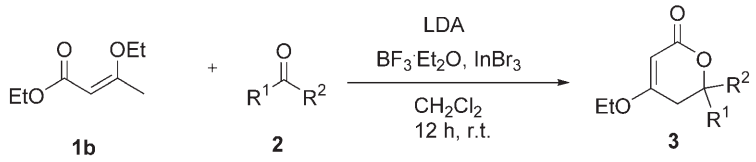
Optimization of the Conditions

Having identified $BF_3 \cdot Et_2O$ and $InBr_3$ as viable activators, an optimization of other the reaction conditions was undertaken to lead to further improvements in the reaction. Solvent screening revealed that CH_2Cl_2 could provide products in 99% yield, and other solvents, such as Et_2O, toluene gave rather poor yields (Table 3, entries 1–3). The reaction temperature evidently influenced the yields (Table 3, entries 4 and 5). By lowering the temperature, the reactivity was reduced. However, no product was detected at 50 °C. $InBr_3$ might play an important role in this reaction. With reducing the loading of $InBr_3$, the yield decreased from 99% to 71% (Table 3, entries 8 and 9). Otherwise, as the ratio of **1b** to **2a** reduced to 1.5:1, the yield decreased sharply (Table 3, entries 10 and 11). Unfortunately, on changing the procedure of this reaction whereby $BF_3 \cdot Et_2O$, $InBr_3$, LDA were added to the reaction system together, the reaction did not occur (Table 3, entries 12 and 13). In summary, extensive screening showed that the optimized catalytic reaction conditions were 0.25 mmol of ketones, 3 equivs. of **1b**, 50 mol % $BF_3 \cdot Et_2O$, 20 mol % $InBr_3$ and 3 equivs. of LDA in 2.0 mL of CH_2Cl_2 at room temperature.

Substrate Generality

Encouraged by the result obtained from acetophenone, we investigated the reactions of **1b** with a variety of ketones, most of which gave rise to products in high yields (up to 99%, Table 4). The transformation proceeded with a similar reaction time of 12 hours (Table 4). As can be seen from the data, the reactivity was associated with electronic and steric effects closely. With the enhancement of group's electron-donating capability from Cl, CH_3 to OCH_3, the reactivity increased (Table 4, entries 4, 6, 7). Interestingly, with the enhancement of group's electron-withdrawing capability from Cl to NO_2, the reactivity also increased (Table 4, entries 4 and 5). This indicated that appropriate electronegative groups on substituted ketones could give high yields. The bulkier *ortho*-group, like isopropyl and *tert*-butyl, could achieve only moderate yield (Table 4, entries 12 and 13), which could be attributed to the steric effect. The results from the Table 4 suggested that aromatic ketones were superior to aliphatic ketones. Moreover, it is worthwhile to note that the heterocyclic ketone was

Table 4. Catalytic reactions of ethyl 3-ethoxybut-2-enoate with different ketones catalyzed by $BF_3 \cdot Et_2O$, $InBr_3$, and LDA.[a]



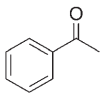
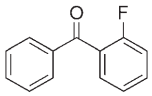
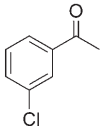
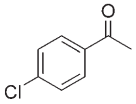
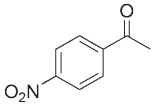
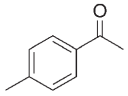
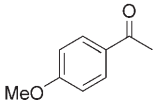
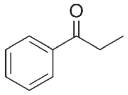
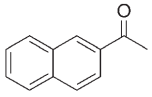
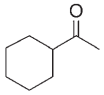
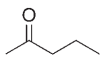
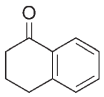
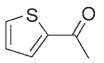
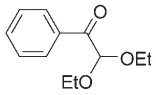
Entry	Ketones		Products	Yield [%][b]
1		**2a**	**3a**	99
2		**2b**	**3b**	72
3		**2c**	**3c**	65
4		**2d**	**3d**	68
5		**2e**	**3e**	82
6		**2f**	**3f**	99
7		**2g**	**3g**	98
8		**2h**	**3h**	98
9		**2i**	**3i**	88
10		**2j**	**3j**	81
11		**2k**	**3k**	85
12		**2l**	**3l**	75
13		**2m**	**3m**	65
14		**2n**	**3n**	66

Table 4 (cont.)

Entry	Ketones		Products	Yield [%][b]
15		**2o**	**3o**	86
16		**2p**	**3p**	63
17		**2q**	**3q**	65

[a] All the reactions were carried out according to the given standard procedure (see Method 2 in the Experimental Section).
[b] Yield of isolated product, satisfactory spectral data were obtained for the new compounds (see Supporting Information).

transformed with moderate yield (Table 4, entry 16). However, the active ketone gave the corresponding product only in 65% yield (Table 4, entry 17), which might be due to its steric hindrance.

Conclusion

In summary, we have developed an efficient synthetic method for the formation of 5,6-dihydro-6,6-disubstituted pyran-2-ones with excellent yields. Moreover, the preparation of the oxygen-heterocycle adducts from commercially available materials (ethyl 3-ethoxybut-2-enoate) with short reaction times, mild conditions and good substrate adaptability make this approach highly practical. The corresponding products containing a quaternary carbon atom center are key structural subunits of some natural products. Further mechanistic studies and realization of the enantioselective version of this transformation are underway in our laboratory.

Experimental Section

General Remarks

^{1}H NMR spectra were recorded at 300 and 400 MHz. The chemical shifts are reported in ppm downfield to the $CDCl_3$ resonance ($\delta = 7.27$) for ^{1}H NMR. ^{13}CNMR data were collected at 100 and 75 MHz with complete proton decoupling. The chemical shifts are reported in ppm downfield to the central $CDCl_3$ resonance ($\delta = 77.0$) for ^{13}C NMR. Coupling constants in ^{1}H NMR spectra are given in Hz. HR-MS were recorded on a Bruker-APEX-2 (SIMS). Ketones obtained from commercial sources were used directly without further purification. Toluene, THF, Et_2O were distilled freshly from sodium/benzophenone ketyl. CH_2Cl_2 was distilled freshly from CaH_2. Brassad's diene 1a was prepared from ethyl 3-ethoxybut-2-enoate[13] according to a literature procedure.[14]

Typical Procedure for the Synthesis of 5,6-Dihydro-6,6-disubstituted Pyran-2-ones

4-Ethoxy-5,6-dihydro-6-methyl-6-phenylpyran-2-one **(3a); Method 1:** $BF_3 \cdot Et_2O$ (15 μL, 0.125 mmol) (or other Lewis acids) was stirred with acetophenone (30 μL, 0.25 mmol) in CH_2Cl_2 (0.5 mL) at room temperature for 30 min under an N_2 atmosphere, followed by addition of Brassard's diene **1a** (85 μL, 0.375 mmol).The reaction mixture was stirred for 64 h at room temperature, before being quenched with 5 drops of TFA. After stirring for additional 2 h, the mixture was neutralized with saturated $NaHCO_3$ (2.0 mL) and partitioned between CH_2Cl_2 and water twice. The combined organic layers were washed with saturated brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (eluent 3:1 petroleum ether:ethyl acetate) to afford the cycloadduct **3a**; yield: 16%.

4-Ethoxy-5,6-dihydro-6-methyl-6-phenylpyran-2-one **(3a); Method 2:** To a solution of ethyl 3-ethoxybut-2-enoate (**1b**) (118 mg, 0.75 mmol) in dry THF (1.0 mL) was added LDA (0.4 mL, 2 M in hexane, 0.75 mmol) at $-78\,^\circ$C under an N_2 atmosphere. After the mixture had been stirred for 1 h, the solvents were removed under vacuum. The residue was redissolved in CH_2Cl_2 (1.0 mL) and then treated with a solution containing 15 μL (0.125 mmol) of $BF_3 \cdot Et_2O$, 30 μL (0.25 mmol) of acetophenone, and 17.7 mg (0.05 mmol) of $InBr_3$ in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at room temperature for 12 h and monitored by TLC. After completion, the reaction mixture was concentrated under reduced pressure and purified by flash chromatography (petroleum ether:ethyl acetate, 3:1) to afford **3a**.

Acknowledgements

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