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I^--Catalyzed Methyl−Oxygen Bond Cleavage in 2-Methoxyfurans. An Efficient Synthesis of Butenolides

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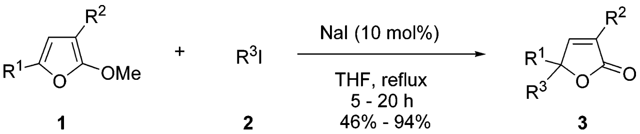

An efficient I^--catalyzed methyl-oxygen bond cleavage in 2-methoxyfurans was observed. The subsequent C−C bond formation occurred at the 5-position to afford substituted butenolides. The structures of the final products were determined by the X-ray diffraction study.

Butenolides are an important structure unit in natural products and intermediates in organic synthesis.[1] Butenolide-containing compounds are considered as potential insecticides, bactericides, fungicides, antibiotics, cyclooxygenase inhibitors, phospholiphase A_2 inhibitors, etc.[2] Chemists have developed many ways to synthesize these interesting compounds.[3] Recently, our group also has reported some methods for the synthesis of butenolides by transition metal-promoted or -catalyzed cyclization reactions of 2,3-allenoic acids/esters.[4] In this paper, we wish to report a I^--catalyzed reaction of 2-alkoxyfurans with organic iodides to form substituted butenolides.

Under the catalysis of a Lewis acid, the O−X bond (X = Si, COMe) of 2-substituted furans, such as 2-siloxy[5−7] and 2-acetoxy,[8] was cleaved to react with electrophiles at the 5-position of furans. For 2-boroxyfurans,[9] these reactions can occur in the absence of a catalyst. However, similar reactions with 2-alkoxyfurans are limited to protonation with TsOH[10,11] or oxidation with MnO_2−HCl.[12] A stoichiometric TMSI-mediated reaction of 2-methoxyfuran with α,β-unsaturated ketones has been reported.[13] BF_3-mediated reactions of 2-methoxyfuran with allylic alcohols have also been reported.[14] Recently, our group has reported that inorganic halides can serve as catalysts in the cleavage of C−C bonds in a series of reactions, such as the ring-opening of cyclopropenes[15] and

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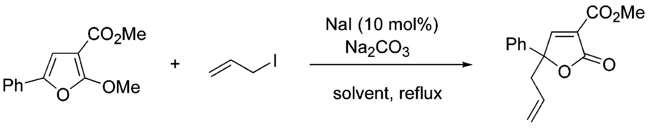
10.1021/jo048430l CCC: $30.25

TABLE 1. Effects of Solvents on the Reaction of 1a and 2a[a]

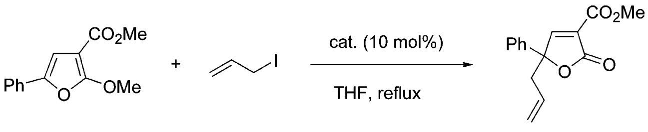


1a **2a** **3aa**

entry	cat.	Na_2CO_3 (equiv)	allylic iodide (equiv)	solvent	time (h)	yield (%)
1	NaI[b]	1.0	1.2	DMF[c]	11	15
2	NaI	0.6	2.0	CH_2Cl_2	18	NR
3	NaI	0.5	2.0	CH_3CN	34	8
4	NaI	0.5	2.0	toluene[c]	14.5	trace
5	NaI	0.5	2.0	dioxane[c]	34	39
6	NaI	0.5	2.0	acetone	10	60
7	NaI	0.5	2.0	THF	15	70
8	NaI	0.1	1.2	THF	13	72
9	NaI	–	1.2	THF	10.5	79
10	–	–	1.2	THF	10	NR

[a] The reaction was carried out using 0.25–0.5 mmol of **1a**, Na_2CO_3, and **2a** in 1–2 mL of solvent under reflux. [b] 20 mol % NaI was used. [c] The reaction was conducted at 80 °C.

TABLE 2. Effects of Catalysts on the Reaction of 1a and 2a[a]

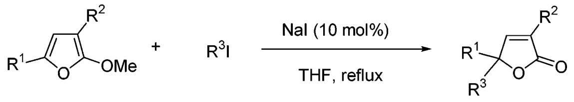


1a **2a** **3aa**

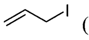
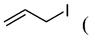
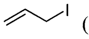
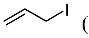
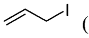
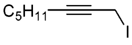
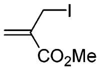
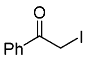
entry	cat.	allylic iodide	time (h)	yield (%)
1	NaI	1.2	10.5	79
2	LiI	1.2	48	60
3[b]	KI[c]	2.0	33	57
4	LiBr	1.2	22	60
5	NaBr[d]	1.2	14.5	75
6	LiCl	1.2	22	61

[a] The reaction was carried out using 0.25–0.5 mmol of **1a** and **2a** in 1–2 mL of solvent under reflux. [b] The solvent was acetone. [c] 0.5 equiv of K_2CO_3 was used. [d] 20 mol % NaBr was used.

TABLE 3. NaI-Catalyzed Reaction of 2-Methoxy 3,5-Disubstituted Furans with Organic Iodides[a]



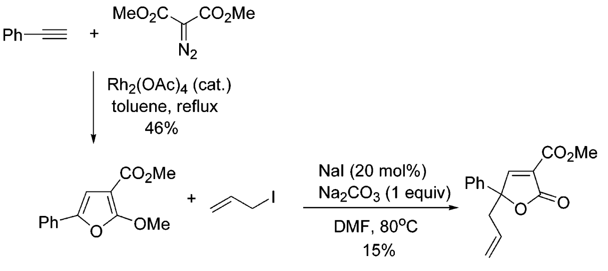
1 **2** **3**

entry	R^1	R^2	R^3I	Time (h)	Yield of **3** (%)
1	Ph	CO_2Me (**1a**)	 (**2a**)	10.5	79 (**3aa**)
2[b,c]	Ph	SO_2Ph (**1b**)	 (**2a**)	9.5	46 (**3ba**)
3	C_4H_9	CO_2Me (**1c**)	 (**2a**)	14.5	73 (**3ca**)
4	C_5H_{11}	CO_2Me (**1d**)	 (**2a**)	25.5	71 (**3da**)
5	Bn	CO_2Me (**1e**)	 (**2a**)	9.5	71 (**3ea**)
6[d]	Ph	CO_2Me (**1a**)	MeI (**2b**)	51.5	79 (**3ab**)
7	Ph	CO_2Me (**1a**)	ICH_2CO_2Et (**2c**)	12	82 (**3ac**)
8	Ph	CO_2Me (**1a**)	 (**2d**)	6.5	82 (**3ad**)
9[b]	Ph	CO_2Me (**1a**)	 (**2e**)	10	84 (**3ae**)
10	Ph	CO_2Me (**1a**)	 (**2f**)	5	94 (**3af**)

[a] The reaction was carried out using 0.25–0.5 mmol of **1a** and **2a** in 1–2 mL of solvent under reflux. [b] 2.0 equiv of allylic iodide were used. [c] 10 mol % Na_2CO_3 was used. [d] The reaction was carried out with 3.0 equiv of MeI in a sealed tube.

cycloisomerization of alkylidene cyclopropyl ketones.[16] In this context, an I^--catalyzed direct alkyl–oxygen cleavage of 2-alkoxyfurans and the subsequent reaction with organic halides will be reported.

2-Methoxy-3-methoxycarbonyl-5-phenylfuran **1a**, which was easily available from the reaction of phenylacetylene with diazomethylmalonate under the catalysis of $Rh_2(OAc)_4$,[17] could react with allylic iodide **2a** to form 5-allyl-3-methoxycarbonyl-5-phenylbutenolide **3aa** in 15% yield under the catalysis of NaI in DMF (eq 1).



1a **2a** **3aa** (1)

On the basis of this promising result, the solvent effects were further investigated and some typical results are listed in Table 1. Among the solvents tested, THF and acetone were the best, while CH_2Cl_2, CH_3CN, toluene, and dioxane were all inferior (Table 1). Further research proved that the base was not necessary in this reaction (Table 1, entry 9) while in the absence of NaI, no reaction was observed (Table 1, entry 10). Different inorganic catalysts were also tested in this reaction (Table 2) with NaI affording the best results (Table 2, entry 1).

With the optimized conditions in hand, the scope of this reaction was explored. Some typical results are summarized in Table 3. It could be seen from Table 3 that R^1 can be an alkyl group, benzyl, or an aryl group. Different organic iodides were tested in this reaction (entries 2–10, Table 3). Basically, reactive sp^3 organic iodides all could participate the reaction. However, the alkyl iodides showed much lower reactivity. The structures of **3** were established by a single-crystal X-ray diffractional study of **3ae**.[18] It should be noted that the

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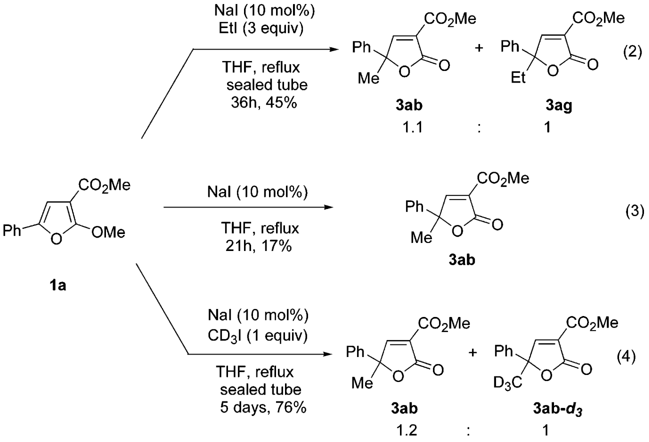
(18) X-ray data for compound **3ae**: $C_{17}H_{16}O_6$, Mw = 316.30, monoclinic, space group $P2(1)/n$, Mo Kα, final R indices $[I > 2\sigma(I)]$, R1 = 0.0455, wR2 = 0.0801, a = 904395(11) Å, b = 11.5890(14) Å, c = 15.0764(18) Å, α = 90°, β = 104.516(2)°, γ = 90 ° V = 1596.6 3) Å^3, T = 293(2) K, Z = 4, reflections collected/unique: 9566/3722 (R_{int} = 0.0605), parameters 273. CCDC 244480 contains the supplementary crystallographic data.

in-situ formed MeI may leave the reaction mixture due to its low bp (41−43 °C) under the current reaction conditions, which excluded the formation of 5-methylbutenolides.

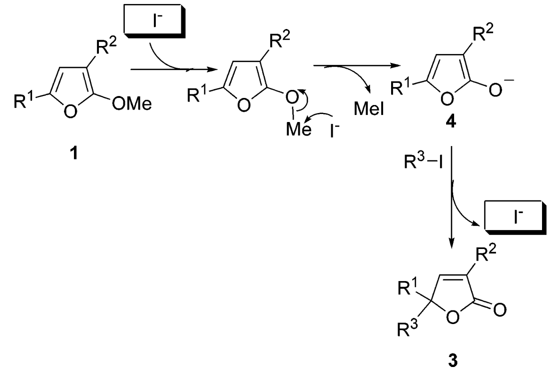
A detailed study showed that a mixture of 4-methyl-substituted and 4-ethyl-substituted products **3ab** and **3ag** was formed when EtI was used as the iodide (eq 2), indicating that MeI was generated in situ in this NaI-catalyzed reaction. Indeed, **3ab** was formed in 17% yield after 21 h from the treatment of **1a** with 10 mol % NaI in the absence of any organic iodide (eq 3). To explore the source of Me in the structure of the product **3ab** in eq 2, we designed a deuterium-labeling experiment. From eq 4, it can be concluded that both the added CD_3I and the in-situ-generated MeI participated the reaction.



According to the results mentioned above, a plausible catalytic cycle for this reaction is depicted in Scheme 1. The attack of I^- at the methyl group[19] led to the cleavage of the methyl−oxygen bond with the formation of MeI and intermediate **4**,[7d,9] which would react with an organic iodide to afford **3**.

In conclusion, we have observed a very mild cleavage of the methyl−oxygen bond of 2-methoxyfurans under the catalysis of I^-, which was followed by the formation of a new C−C bond with organic halides at the 5-position of the furans to afford butenolides. The higher reactivity of the targeted carbon−methoxy bond than that of the C−O bond in the ester group may be attributed to the acetal-like structure. Due to the easy availability of the starting materials, simple operation, and mild conditions, this method will show its utility in the synthesis of butenolides. Further studies in this area are being pursued in our laboratory.

SCHEME 1. A Plausible Mechanism for the Reaction of 1 and 2



Experimental Section

General Procedure for NaI-Catalyzed Reaction of 2-Methoxyfuran with Organic Iodides. In a flame-dried argon-flushed flask, a solution of **1a** (116 mg, 0.5 mmol), **2a** (101 mg, 0.6 mmol), and NaI (8 mg, 0.05 mmol) in 2 mL of dry THF was stirred for 10.5 h under reflux. After evaporation, the residue was purified by column chromatography (eluent: petroleum ether/Et_2O = 5/1) on silica gel to afford **3aa** (102 mg, 79%): liquid; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58−7.66 (m, 2 H), 7.37−7.44 (m, 3 H), 5.84 (s, 1 H), 5.63−5.77 (m, 1 H), 5.12−5.25 (m, 2 H), 3.77 (s, 3 H), 2.93 (dd, J = 13.8, 6.9 Hz, 1 H), 2.80 (dd, J = 13.8, 7.8 Hz, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.3, 167.9, 154.1, 130.6, 130.2, 128.7, 127.4, 125.1, 120.6, 101.9, 60.2, 53.3, 38.6; MS m/z 258 (M^+, 9.08), 217 (100); IR (neat) 1806, 1743, 1648, 1235 cm^{-1}. Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.79; H, 5.46. Found: C, 69.53; H, 5.57.

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Supporting Information Available: Typical experimental procedure and analytical data for all products not listed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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