CuX_2-Mediated Cyclization Reaction of 2,3-Allenoic Acids. An Efficient Route to β-Halobutenolides†

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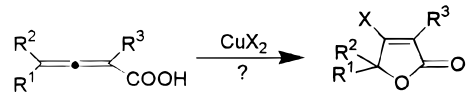
Unsaturated five-membered lactones, i.e., butenolides, are an important class of compounds because they are pivotal skeletons in many natural products with an unusual range of biological activities. Butenolides with different substitution patterns are considered as potential insecticides, bactericides, antibiotics, anticancer agents, antiinflammatories, allergy inhibitors, antipsoriasis agents, cyclooxygenase inhibitors, phospholipase A_2 inhibitors, etc.[1] Recently, much attention has been focused on the efficient and diverse synthesis of these valuable heterocyclic compounds.[1,2]

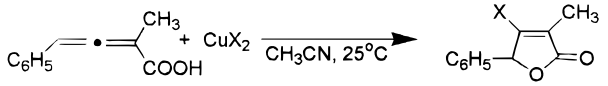
Although β-halobutenolides occur rarely in nature, some of them exhibit certain biological activities.[3] Moreover, from the viewpoint of retrosynthesis, they appear as a class of important building blocks for the connection of different types of R with butenolides at the β-position. Several routes have been available for the synthesis of β-halobutenolides, e.g., the addition of a *stoichiometric amount* of mercuric chloride to an acetylenic alcohol followed by carbonylation of the resulting vinylmercurial in the presence of a *stoichiometric amount* of $PdCl_2$,[4] and X^+ (X = Br or I)-mediated low-yielding lactonization of 2,3-allenoic carboxylic acids and esters.[5] Recently, we have developed a high-yielding procedure for the synthesis of β-halobutenolides (X = Br or I)[6] and have studied their Pd(0)-catalyzed coupling reactions with terminal alkynes[6] and organozinc reagents.[7] However, the utility of these methods suffers from certain drawbacks such as restricted generality, need for toxic or expensive chemicals, further resource consumption encountered in separation, etc. In this paper, we wish to report our recent observations that β-halobutenolides can be prepared conveniently and efficiently by the CuX_2-mediated halolactonization reaction of 2,3-allenoic acids.

Halogenation of alkenes and alkynes by $CuCl_2$ or $CuBr_2$ is well documented.[8] On the basis of these results and the proposed mechanism for these transformations, we reasoned that the reaction of 2,3-allenoic acids with CuX_2 might be expected to form β-halobutenolides (Scheme 1).

Scheme 1



Scheme 2

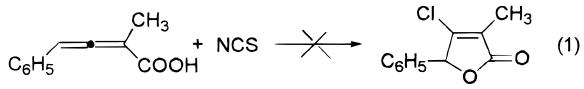


1a **2a**

2aa, X = Cl, 24 h, 83%
92% (with the addition of 4 equiv of LiCl)

2ab, X = Br, 12 h, 70% (with the addition of 4 equiv of LiBr)
84%

To test the feasibility of this halocyclization approach, 2-methyl-4-phenyl-2,3-butadienoic acid **1a** was chosen as the starting material. It should be pointed out that the corresponding reaction of 2,3-allenoic acid **1a** with NCS under the conditions[6] described previously did not afford chlorobutenolide **2aa** (eq 1).



(1)

1a **2aa**

In our first try, when **1a**[9] was treated with 4 equiv of $CuCl_2$ in acetonitrile at 25 °C for 24 h, β-chlorobutenolide **2aa** was obtained in 83% yield. To increase the solubility of $CuCl_2$ in acetonitrile, LiCl (4 equiv) was added, and **2aa** was isolated in 92% yield. Similarly, using $CuBr_2$ and LiBr instead of the corresponding chlorides, the β-bromobutenolide **2ab** was also obtained in 70% yield. Nevertheless, a more impressive result was received upon treatment of **1a** only with $CuBr_2$ in acetonitrile. In this case the yield of **2aa** was increased to 84% (Scheme 2).

Using these reaction conditions (defined as conditions A), we examined the behaviors of other 2,3-allenoic acids. However, the reaction of 2,3-undecadienoic acid **1b**[10] gave β-halobutenolide **2ba** and **2bb** in low yields (37−52%) (entries 1−4, Table 1). To improve the yield of this halocyclization reaction, several conditions were screened, including using DMF as the reaction solvent, but the results were still disappointing (entries 5−8, Table 1).

On the assumption that these results might be associated with the easy dihalogenation of C=C bonds in nonaqueous solvents,[8a−b,f] we investigated the reaction conducted in aqueous solvent. Treatment of **1b** with 4

† China patent pending (99119945.6).

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(9) For the synthesis of **1a** and **1d**−**f**, see: Bestmann, H.-J.; Hartung, H. *Chem. Ber.* **1966**, *99*, 1198.

(10) For the synthesis of **1b** and **1c**, see: Venkruijsse, H. D.; Brandsma, L. *Synthesis of Acetylenes, Allenes annd Cumulenes. A Laboratory Manual;* Elsevier: Amsterdam, The Netherlands, 1981; p 33.

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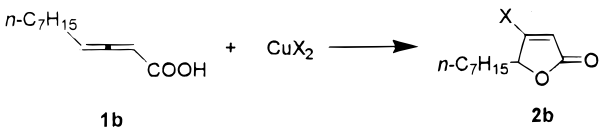
Table 1. Reaction of 2,3-Undecadienoic Acid with CuX_2[a]



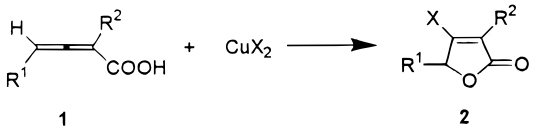
1b **2b**

2ba, X = Cl
2bb, X = Br

entry	solvent	LiX (equiv)	temp (°C)	time (h)	product	yield (%)
1	CH_3CN	4	25	50	**2ba**	52
2	CH_3CN	4	25	8	**2bb**	43
3[b]	CH_3CN	0	25	24	**2ba**	41
4[b]	CH_3CN	0	25	12	**2bb**	37
5	CH_3CN	4	40	48	**2ba**	43
6[c]	CH_3CN	4	25	48	**2ba**	50
7[c]	CH_3CN	4	40	13	**2ba**	34
8	DMF	4	40	51	**2ba**	14
9[d]	acetone/H_2O	0	65−70	6.5	**2ba**	87
10[d]	acetone/H_2O	0	65−70	2	**2bb**	85

[a] **1a**:CuX_2:LiX = 1:4:4 (X = Cl, Br). [b] **1a**:CuX_2 = 1:4 (X = Cl, Br). [c] With 1 equiv $NaHCO_3$. [d] **1a**:CuX_2 = 1:4 (X = Cl, Br); acetone:H_2O = 2:1

Table 2. Synthesis of β-halobutenolides[a]



1 **2**

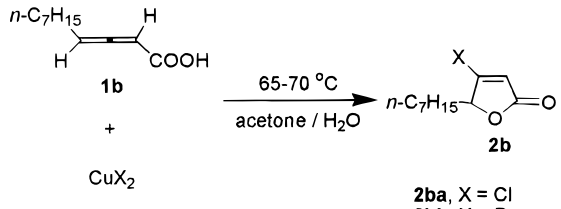
entry	1 R1	1 R2	X	time (h)	product	yield (%)
1	C_6H_5	CH_3 (**1a**)	Cl	4	**2aa**	93
2	**1a**		Br	2	**2ab**	96
3	*c*-C_6H_{11}	H(**1c**)	Cl	4	**2ca**	92
4	**1c**		Br	2	**2cb**	94
5	C_6H_5	*n*-C_3H_7(**1d**)	Cl	4	**2da**	100
6	**1d**		Br	2	**2db**	99
7	1-naphthyl	CH_3 (**1e**)	Cl	4	**2ea**	90
8	**1e**		Br	2	**2eb**	89
9	1-naphthyl	*n*-C_3H_7 (**1f**)	Cl	4	**2fa**	96
10	**1f**		Br	2	**2fb**	98

[a] The reaction was carried out using CuX_2 (4 equiv), acetone:H_2O (2:1), 65−70 °C.

equiv of $CuCl_2$ in acetone/water (2:1) at 65−70 °C gave the best result. The reaction was much faster, and the corresponding β-chlorolobutenolide **2ba** was isolated in 87% yield (entry 9, Table 1). The bromocyclization of **1b** with $CuBr_2$ also gave the corresponding β-bromobutenolide **2bb** in high yield (85%) within 2 h (entry 10, Table 1). The halogenation of the solvent, i.e., acetone, was not observed under the present reaction conditions though the chlorination of acetone with $CuCl_2$ has been reported.[11] Thus, these standard reaction conditions (defined as conditions B) were established. With such a procedure we have been able to extend the scope of this halocyclization reaction to a number of additional 2,3-allenoic acids with different substitution pattern at different locations (**1a** and **1c**−**f**) for the synthesis of β-halobutenolides (X = Cl and Br). The results are summarized in Table 2. Several points should be noted:

1. The starting materials, 2,3-allenoic acids, are fully converted, and the yields are excellent.

Scheme 3



2ba, X = Cl
2bb, X = Br
3b, X = H

entry	Reagents	Time (h)	Yield (%) of **2b**[10]	Yield (%) of **3b**
1	$CuCl_2$ (4 eq.)	6	86 (**2ba**)	0
2	$CuCl_2$ (2 eq.)	4	58 (**2ba**)	36
3	$CuCl_2$ (2 eq.)[a]	6	71 (**2ba**)	0
4	CuCl (2 eq.)	4	0 (**2ba**)	72
5	$CuBr_2$ (4 eq.)	2	85 (**2bb**)	0
6	$CuBr_2$ (2 eq.)	2	73(**2bb**)	7

[a] 1 equivalent of $NaHCO_3$ was added.

2. $CuBr_2$ is more reactive than $CuCl_2$ (by comparison of their reaction times).

3. Four equivalents of CuX_2 are needed. In control experiments, **1b** reacted with 2 equiv of CuX_2 to give **2ba** (or **2bb**) and the direct cyclization product **3b**[12] in 58% (or 73%) and 36% (or 7%) yields (entries 2 and 6, Scheme 3), respectively. When CuCl was used instead of $CuCl_2$, **3b** was formed exclusively in 72% yield (entry 4, Scheme 3), demonstrating that the excess of $CuCl_2$ can suppress the Cu(I)-catalyzed direct cyclization of 2,3-allenoic acid, probably by the formation of complexes of $CuCl_2$ and CuCl.[13] It is interesting to observe that the Cu(I)-catalyzed cyclization of 2,3-allenoic acid was also suppressed by the addition of $NaHCO_3$ in the reaction system. In the presence of 1 equiv of $NaHCO_3$, the reaction afforded **2ba** in 71% yield even with 2 equiv of $CuCl_2$ (compare entries 2 and 3 in Scheme 3).

Some plausible mechanisms for this reaction were proposed as follows: (1) The interaction of allenoic acid **1** with CuX_2 forms a coordination complex **3**. In this complex, the linear geometry of the allene moiety is twisted to a certain extent,[5c,d,8f,14] and thus, the hydroxy oxygen atom acting as an intramolecular nucleophile attacks the γ-position of the allenoic acid (5-*endo*-*trig*[5c,d,8f,14]) to give butenolide-containing copper anoinic intermediate **4**. Single-electron transfer from **4** to another molecule of CuX_2 forms **5** and CuX. Reductive elimination of **5** affords β-halobutenolide **2** together with CuX (Scheme 4). (2) A stereoselective intermolecular reaction of the excess amount of H_2O in the reaction mixture with the coordination complex **3** followed by a similar SET processs and a reductive elimination reaction[8f] would form (*E*)-γ-hydroxy carboxylic acid **6**. Lactonization of *E*-**6** would afford the final butenolides **2**.[15]

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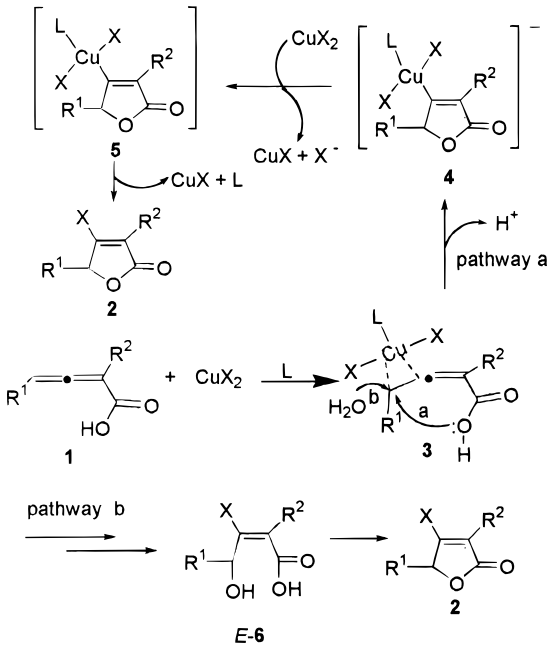
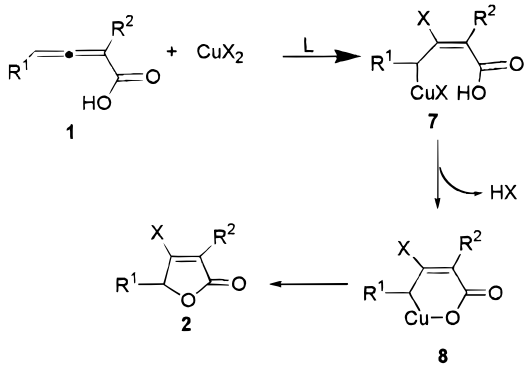
Scheme 4



Scheme 5



Another possibility is that the stereoselective halocupration reaction of 1,2-allenic carboxylic acid afforded the Cu-containing intermediate *E*-**7** (Scheme 5). Intramolecular attack of the hydroxyl group on cupper would form the six-membered intermediate **8**, which would provide butenolides **2** after reductive elimination reaction.[15]

In conclusion, we have developed a convenient and efficient method for the synthesis of β-halobutenolides. Both β-chloro- and β-bromo-butenolides can be obtained in high to excellent yields by the reaction of 2,3-allenoic acids and CuX_2 in aqueous acetone within a short period of time of several hours. The control experiments have shown that an excess amount of CuX_2 was required to suppress the Cu(I)-catalyzed direct cyclization reaction forming β-unsubstituted butenolide.

Experimental Section

Starting Materials. 2,3-Undecadienoic acid (**1b**) and 4-cyclohexyl-2,3-butadienoic acid (**1c**) were prepared according to a published procedure[10] via the reaction of CO_2 with the corresponding 1,2-allenic lithiums, which, in turn, were prepared from the treatment of the corresponding 1,2-allenes with *n*-BuLi. The other allenic acids (**1a** and **1d**−**f**) were prepared according to the known method[9] by treatment of the acid chlorides with ethyl 2-(triphenylphosphoranylidene)propionate and subsequent hydrolysis of the 2,3-allenoic esters with *2* N NaOH.

Typical Procedure. Conditions A. A solution of **1a** (44 mg, 0.25 mmol) with $CuCl_2$ (134 mg, 1.0 mmol) and LiCl (42 mg, 1.0 mmol) in CH_3CN (2.5 mL) was stirred at 25 °C for 24 h. The mixture was then filtered through a short column of silica gel, and the solvent was removed. The residue was subjected to flash chromatography on silica gel with petroleum ether/ethyl acetate (15:1) as the eluent to give 49 mg (93% yield) of **2aa**.

Using the same procedure, except that $CuBr_2$ and LiBr were used instead of the corresponding chlorides, starting from 42 mg (0.24 mmol) of **1a**, the reaction gave 43 mg (70% yield) of **2ab** within 12 h.

Using the same procedure, but without the addition of LiCl or LiBr, starting from 44 mg (0.25 mmol) and 43 mg (0.25 mmol) of **1a**, the reactions gave 44 mg (83%) of **2aa** or 53 mg (84%) of **2ab**, respectively.

General Procedures. Conditions B. A solution of **1** (0.25 mmol) and CuX_2 (1.0 mmol) in acetone/H_2O (2:1, 4.5 mL) was stirred at 65−70 °C for 4−6 h (in the case of $CuCl_2$) or 2 h (in the case of $CuBr_2$). The mixture was then diluted with saturated NH_4Cl and extracted three times with diethyl ether. The ether phases were combined and dried over $MgSO_4$. After evaporation, the residues were purified via flash chromatography on silica gel with petroleum ether/ethyl acetate (15:1) as the eluent to afford the β-halobutenolides. All of the solid products were recrystallized from *n*-hexane.

4-Chloro-3-methyl-5-phenyl-2(5*H*)-furanone (2aa): starting from **1a** (43 mg, 0.25 mmol) to afford 48 mg (93% yield) of **2aa**; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.41(m, 3H), 7.30−7.26(m, 2H), 5.73(d, J = 1.7 Hz, 1H), 1.99(d, J = 1.7 Hz, 3H); EIMS *m*/*z* 208[M^+ (^{35}Cl), 81.18], 210[M^+(^{37}Cl), 27.45], 173(100); HRMS calcd for $C_{11}H_9{}^{35}ClO_2$ 208.0291, found 208.0266; calcd for $C_{11}H_9{}^{37}ClO_2$ 210.0261, found 210.0256; IR(neat) 1767, 1661 cm^{-1}.

4-Chloro-5-(*n*-heptyl)-2(5*H*)-furanone (2ba): starting from **1b** (45 mg, 0.25 mmol) to afford 46 mg (87% yield) of **2ba**; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.29(d, J = 1.5 Hz,-1H), 4.99−4.95(m, 1H), 2.06−1.97(m, 1H), 1.66−1.56(m, 1H), 1.40−1.26(m, 10H),0.88(t, J = 6.5 Hz, 3H); EIMS *m*/*z* 217[M^+ + 1 (^{35}Cl), 1.99], 219[M^+ + 1 (^{37}Cl), 0.63], 57(100); IR(neat) 1769,-1610 cm^{-1}; HRMS(EI) calcd for $C_{11}H_{17}{}^{35}ClO_2$ 216.0917, found 216.0902; calcd for $C_{11}H_{17}{}^{37}ClO_2$ 218.0887, found 218.0850.

4-Chloro-5-cyclohexyl-2(5*H*)-furanone(2ca): starting from **1c** (83 mg, 0.5 mmol) to afford 92 mg (92% yield) of **2ca**; white solid, mp 34−35 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06(d, J = 1.2 Hz, 1H), 4.75(t, J = 1.9 Hz, 1H), 1.90−0.95(m, 11H); EIMS *m*/*z* 201[M^+ + 1 (^{35}Cl), 0.57], 203[M^+ + 1 (^{37}Cl), 0.18], 55(100); IR(KBr) 1768, 1610 cm^{-1}. Anal. Calcd for $C_{10}H_{13}ClO_2$: C 59.86, H 6.53. Found: C 59.71, H 6.56.

4-Chloro-3-(*n*-propyl)-5-(phenyl)-2(5*H*)-furanone(2da): starting from **1d** (50 mg, 0.25 mmol) to afford 58 mg (100% yield) of **2da**; oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.40(m, 3H), 7.29−7.26(m, 2H), 5.72(s, 2H) 2.40(t, J = 7.6 Hz, 2H) 1.72−1.60-(m, 2H); 0.97(t, J = 7.4 Hz, 3H). EIMS *m*/*z* 236[M^+(^{35}Cl), 22.52], 238[M^+ (^{37}Cl), 9.64], 77(100); IR(KBr) 1746, 1650 cm^{-1}; HRMS calcd for $C_{13}H_{13}{}^{35}ClO_2$ 236.0604, found 236.0628.

4-Chloro-3-methyl-5-(1-naphthyl)-2(5*H*)-furanone (2ea): starting from **1e** (56 mg, 0.25 mmol) to afford 58 mg (90% yield) of **2ea**; white solid, mp 108−109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12−8.10(d, J = 8.1 Hz,1H), 7.94−7.91(d, J = 8.0 Hz, 2H), 7.63−7.46(m, 3H), 7.36−7.34(d, J = 6.2 Hz, 1H), 6.62(s, 1H), 2.06−2.05(d, J = 1.1 Hz, 3H); EIMS *m*/*z* 258[M^+(^{35}Cl), 100.00], 260[M^+(^{37}Cl), 38.17]; IR(KBr) 1748, 1662 cm^{-1}. Anal. Calcd for $C_{15}H_{11}ClO_2$: C 69.62, H 4.32. Found: C 69.82, H 4.20.

4-Chloro-3-(*n*-propyl)-5-(1-naphthyl)-2(5*H*)-furanone (2fa): starting from **1f** (63 mg, 0.25 mmol) to afford 69 mg (96% yield) of **2fa**; white solid, mp 74−75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08−8.06(d, J = 8.2 Hz,1H), 7.90−7.87(d, J = 8.0 Hz, 2H), 7.60−7.43(m, 3H), 7.32−7.30(d, J = 7.1 Hz, 1H), 6.57(s, 1H), 2.46−2.40(td, J = 0.8, 7.6 Hz, 2H), 1.73−1.61(m, 2H), 0.97(t, J = 7.4 Hz, 3H); EIMS *m*/*z* 286[M^+(^{35}Cl), 100.00], 288[M^+(^{37}Cl), 34.44]; IR(KBr) 1734, 1646 cm^{-1}. Anal. Calcd for $C_{17}H_{15}ClO_2$: C 71.21, H 5.27. Found: C 71.28, H 5.19.

4-Bromo-3-methyl-5-phenyl-2(5*H*)-furanone (2ab): starting from **1a** (45 mg, 0.26 mmol) to afford 63 mg (96% yield) of

(15) We thank the referee for his suggestion on these mechanisms.

2ab; white solid, mp 57−58 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.35(m, 3H), 7.23−7.20(m, 2H), 5.72(d, J = 1.7 Hz, 1H), 1.94(d, J = 1.9 Hz, 3H); EIMS m/z 252[M^+ (^{79}Br), 32.44], 254-[M^+(^{81}Br), 32.33], 173(100); IR(KBr) 1746, 1650 cm^{-1}. Anal. Calcd for $C_{11}H_9BrO_2$: C 52.20, H 3.58. Found: C 52.00, H 3.46.

4-Bromo-5-(*n*-heptyl)-2(5*H*)-furanone (2bb):[7] starting from **1b** (46 mg, 0.25 mmol) to afford 56 mg (85% yield) of **2ba**; white solid, mp 37−38 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.29(d, J = 1.7 Hz, 1H), 4.98−4.94(m, 1H), 2.08−1.97(m, 1H), 1.68−1.56-(m, 1H), 1.42−1.26(m, 10H), 0.87(t, J = 6.7 Hz, 3H).

4-Bromo-5-cyclohexyl-2(5*H*)-furanone (2cb): starting from **1c** (42 mg, 0.25 mmol) to afford 68 mg (94% yield) of **2cb**; white solid, mp 68−69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25−6.24(d, J = 1.7 Hz,1H), 4.79(t, J = 2.0 Hz, 1H), 2.00−0.95(m, 11H); EIMS m/z 245[$M^+ - 1$ (^{79}Br), 27.14], 247[$M^+ - 1$ (^{81}Br), 28.74], 55(100); IR(KBr) 1768, 1596 cm^{-1}. Anal. Calcd for $C_{10}H_{13}BrO_2$: C 49.00, H 5.35. Found: C 48.81, H 5.27.

4-Bromo-3-(*n*-propyl)-5-(phenyl)-2(5*H*)-furanone (2db): starting from **1d** (49 mg, 0.25 mmol) to afford 67 mg (99% yield) of **2db**; white solid, mp 76−77 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.41(m, 3H), 7.28−7.26(m, 2H), 5.76(s, 2H) 2.40(t, J = 7.5 Hz, 2H), 1.70−1.57(m, 2H), 0.98(t, J = 7.4 Hz, 3H); EIMS m/z 280[M^+(^{79}Br), 2.52], 282[M^+ (^{81}Br), 2.63], 77(100); IR(KBr) 1742, 1644 cm^{-1}. Anal. Calcd for $C_{13}H_{13}BrO_2$:C 55.54, H 4.66. Found: C 55.38, H 4.57.

4-Bromo-3-methyl-5-(1-naphthyl)-2(5*H*)-furanone (2eb): starting from **1e** (55 mg, 0.25 mmol) to afford 74 mg (89% yield) of **2eb**; white solid, mp 125−126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14−8.11(d, J = 8.2 Hz,1H), 7.95−7.93(d, J = 8.0 Hz, 2H), 7.65−7.47(m, 3H), 7.37−7.35(d, J = 7.2 Hz, 1H), 6.68(d, J = 1.8 Hz,1H), 2.08−2.07(d, J = 1.7 Hz, 3H); EIMS m/z 302[M^+(^{79}Br), 100.00], 304[M^+(^{81}Br), 97.43]; IR(KBr) 1742, 1652 cm^{-1}. Anal. Calcd for $C_{15}H_{11}BrO_2$: C 59.41, H 3.69. Found: C 59.17, H 3.54.

4-Bromo-3-(*n*-propyl)-5-(1-naphthyl)-2(5*H*)-furanone (2fb): starting from **1f** (63 mg, 0.25 mmol) to afford 81 mg (98% yield) of **2fb**; white solid, mp 119−120 °C; ^{1}H NMR(300 MHz, $CDCl_3$) δ 8.13−8.10(d, J = 8.2 Hz,1H), 7.94−7.92(d, J = 8.0 Hz, 2H), 7.64−7.47(m, 3H), 7.36−7.33(d, J = 7.2 Hz, 1H), 6.65(s, 1H), 2.47 (t, J = 7.4 Hz, 2H), 1.78−1.66(m, 2H), 1.03(t, J = 7.4 Hz, 3H); EIMS m/z 330[M^+(^{79}Br), 14.09], 332[M^+(^{81}Br), 12.46], 127-(100.00); IR (KBr) 1748, 1640 cm^{-1}. Anal. Calcd for $C_{17}H_{15}BrO_2$:C 61.65, H 4.57. Found: C 61.52, H 4.61.

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Supporting Information Available: The ^{1}H NMR spectra of compounds **2aa**, **2ba,** and **2da**. This material is available free of charge via the Internet at http://pubs.acs.org.

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