Pergamon

Bioorganic & Medicinal Chemistry 10 (2002) 1137–1142

BIOORGANIC &
MEDICINAL
CHEMISTRY

A Facile One-Pot Synthesis of 4,5-Diaryl-2,2-dimethyl-3(*2H*)-furanones

Ki-Wha Lee, Young Hoon Choi, Yung Hyup Joo, Jin Kwan Kim, Song Seok Shin, Young Joo Byun, Yeonjoon Kim and Shin Chung*

Drug Discovery, Pacific Corporation R&D Center, 314-1 Bora-ri, Kiheung-eup, Yongin-si, Kyounggi-do 449-729, South Korea

Received 3 September 2001; accepted 23 October 2001

Abstract—An efficient and practical one-pot synthesis of 4,5-diaryl-2,2-dimethyl-3(*2H*)-furanones has been achieved from 1,2-diarylethanones and 2-bromoisobutyryl cyanide in the presence of excess base, by employing the 'hard soft acid base' principle. The reaction scope of 2-bromoisobutyryl cyanide could be expanded to prepare a variety of 2,2-dimethyl-3(*2H*)-furanone derivatives other than 4,5-diaryl-2,2-dimethyl-3(*2H*)-furanones. © 2002 Elsevier Science Ltd. All rights reserved.

Introduction

Recently, a novel class of 4,5-diaryl-2,2-dimethyl-3(*2H*)-furanone derivatives **1** has been reported to possess strong oral anti-inflammatory potency originating from their selective inhibition of cyclooxygenase-2 over cyclooxygenase-1.[1] It is notable that 3(*2H*)-furanone derivatives showed extremely high potency in adjuvant arthritis by therapeutic model. In particular, compound **1a** showed an adjuvant arthritis ED_{50} of 0.03 mg/kg/day (daily once and oral). In the same measurement conditions, blockbuster comparator celecoxib showed an adjuvant arthritis ED_{50} of 0.2 mg/kg/day. Such pronounced activities of **1** in adjuvant arthritis would be one of the strongest among the reported cyclooxygease-2 inhibitors of 1,2-diarylalkene type or its structural equivalent.[2] Thus, 3(*2H*)-furanone derivatives **1** could be a promising candidate for clinical evaluation against arthritis (Fig. 1).

Previously, 3(*2H*)-furanone derivatives **1** were prepared as described in Scheme 1,[1] involving Suzuki coupling[3] as a key reaction. Even though the Suzuki coupling reaction played an essential role in generating structural diversity for structure–activity relationship assessment, the coupling reaction may not be appropriate for scale-up synthesis of the specific candidate among **1** due to the following several reasons: (1) Suzuki coupling reaction is not cost-effective due to the expensive nature of palladium reagents, (2) the coupling reaction often requires chromatographic separation for purification of the coupling products, and (3) the purified coupling products are still likely to be contaminated with a significant amount of residual palladium species,[4] which would often make such a scale-up process incompatible with good manufacturing practice (GMP) guidelines. Furthermore, our experience with Scheme 1 suggests that many of the reactions of Scheme 1 require chromatographic purification.[1] Thus, a huge amount of efforts should be needed to solve the issue of purification in order for Scheme 1 to be a cost-effective scale-up process for our development candidate.

In this article, an efficient process will be presented where 4,5-diaryl-2,2-dimethyl-3(*2H*)furanone derivatives **1** can be prepared through a one-pot reaction starting from 1,2-diarylethanones by adopting 'hard soft acid base (HSAB)' principle.[5]

Results and Discussion

In order to prepare **1** by a process compatible with GMP guidelines, a retrosynthetic consideration was applied to the structure of **1** to identify the key synthons of 1,2-diarylethanone **2**[6] and 2-bromoisobutyryl bromide or its structural equivalent (Scheme 2). Scheme 2 is quite simple and straightforward, and may be an attractive option for a scale-up process for 3(*2H*)-furanone derivatives **1**.

---

*Corresponding author. Tel.: +82-31-280-5910; fax: +82-31-281-8391; e-mail: schung@pacific.co.kr

0968-0896/02/$ - see front matter
PII: S0968-0896(01)00388-1

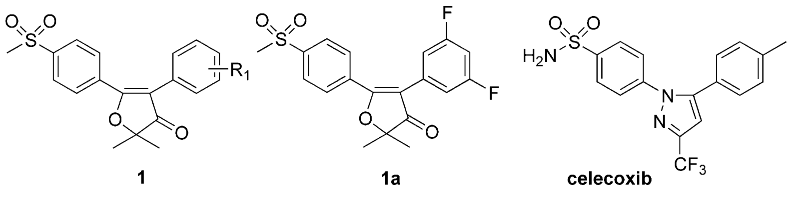
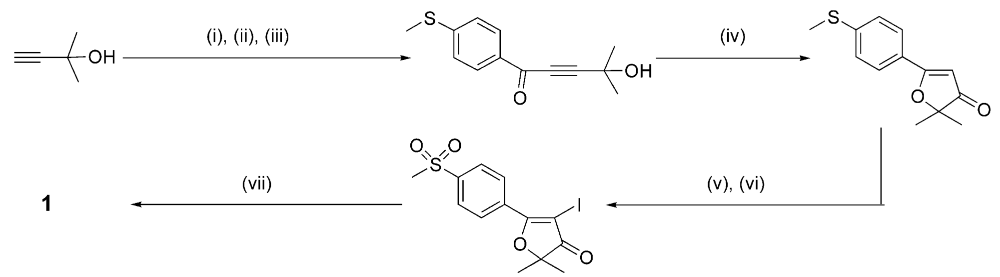
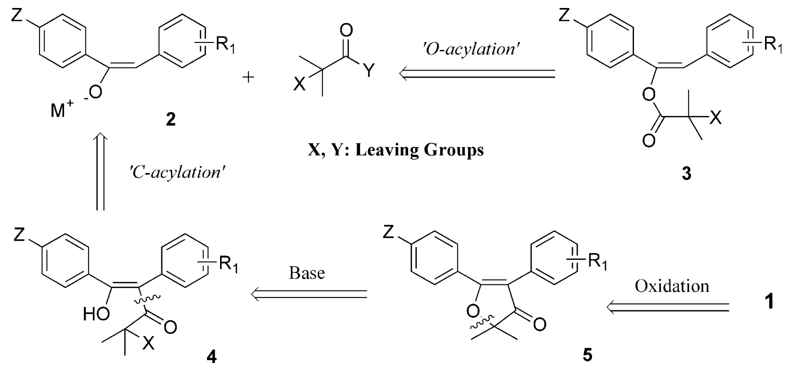


Figure 1.



Scheme 1. (i) *n*-BuLi (2.2 equiv), THF; (ii) 4-(methylthio)benzaldehyde (81% in two steps); (iii) MnO_2, CH_2Cl_2 (81%); (iv) Et_2NH, MeOH (75%); (v) OXONE®, THF/MeOH/H_2O; (vi) bis(trifluoroacetoxy)iodobenzene, I_2, CCl_4 (82% in two steps); (vii) arylboronic acid, $Pd(PPh_3)_4$, aq $NaHCO_3$/toluene/EtOH (40–70%).

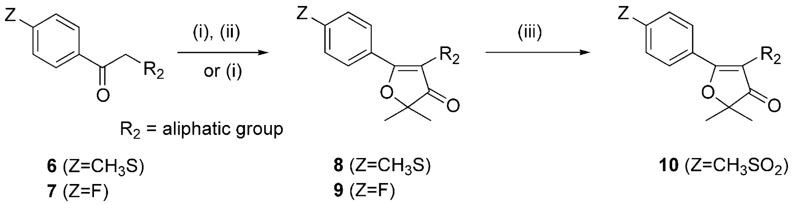


Scheme 2. Retrosynthetic analysis of 4,5-diaryl-2,2-dimethyl-3(*2H*)-furanones **1**.

Scheme 2 addresses a classical issue of '*C*- versus *O*-acylation' to an ambivalent enolate. Learning from ample documented cases for selective *C*-acylation of an enolate, two simple approaches were conceived to effect selective *C*-acylation.[7] Increase of covalency between the enolate oxygen and a counter metal ion tends to make *C*-acylation favorable. On the other hand, by the choice of an appropriate soft electrophile, it is possible to make the balance between *C*- and *O*-acylation shift to the desired *C*-acylation. In this study, both possibilities were examined and the latter approach turned out to be operative significantly better for construction of the 3(*2H*)-furanone derivatives.

When the sodium enolate **2** was reacted with commercially available 2-bromoisobutyryl bromide in THF at 0 °C, mainly *O*-acylation product **3** was isolated (see Experimental for **3c**). Switching the counter ion to magnesium from sodium yielded *C*-acylation product **4** predominant over *O*-acylation product **3** (see Experimental of Method B for **5b**). An attempt to effect the *C*-acylation by using lithium enolate was not successful, suggesting that the lithium enolate might not possess covalency strong enough to screen the oxygen atom of the enolate from reacting with 2-bromoisobutyryl bromide.[8] Usually the reaction of the enolate yielded many products amenable to chromatographic separation, which might not be suitable for scale-up in this specific case of 3(*2H*)-furanones.

In order to solve the '*C*- versus *O*-acylation' issue, we replaced 2-bromoisobutyryl bromide with 2-bromoisobutyryl cyanide,[9] an extreme case of soft electrophile. When the sodium enolate **2** was reacted with 2-bromoisobutyryl cyanide, the *C*-acylation reaction became highly dominant.[10] Interestingly, the *C*-acylation product **4** was further cyclized completely to 3(*2H*)-furanones in the presence of excess base, 'sodium hydride' in this case. In other words, the reaction of 2-bromoisobutyryl cyanide can be further optimized to be a one-pot synthesis of 3(*2H*)-furanone derivatives **5** from appropriate 1,2-diarylethanones. In the one-pot reaction, the cyclization product **5** was isolated as crystals in good to excellent yield in many cases (Table 1).[11] Such generality appears to work for many derivatives of **5**, which makes the 2-bromoisobutyryl cyanide an attractive choice of electrophile for a scale-up process compatible with GMP guidelines.



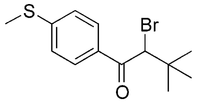
Scheme 3. (i) Sodium bis(trimethylsilyl)amide, 2-bromoisobutyryl cyanide, THF; (ii) NaH, THF; (iii) OXONE®, THF/MeOH/H_2O.

Table 1. One-pot synthesis of 3(*2H*)-furanone 5 from 1,2-diarylethanones[a] and 2-bromoisobutyryl cyanide in the presence of NaH

Entry	R_1	*Z*	Yield of **5** (%)[b]	
1	3-F, 5-F	CH_3S	**5a**	71
2	3-F	CH_3S	**5b**	81
3	H	H	**5c**	65
4	H	CH_3S	**5d**	80
5	3-Cl	CH_3S	**5e**	77
6	4-NO_2	CH_3S	**5f**	57
7	4-CH_3O	CH_3S	**5g**	40

[a] R_1 and *Z* are the same as those of **2** in Scheme 2.

[b] Yields were not optimized and might be subject to improvement.



11

Figure 2.

The following synthetic example demonstrates well the simplicity and efficiency of this one-pot reaction between 2-bromoisobutyryl cyanide and the sodium enolate of 1,2-diarylethanone: To a stirred solution of 2-(3-fluorophenyl)-1-[4-(methylthio)phenyl]ethanone (**2b**, 100 g, 384 mmol) in anhydrous THF (1000 mL) at 0 °C, was added 95% sodium hydride (26 g, 1.03 mol) portionwise. The reaction mixture was stirred for an hour at the same temperature, to which was added drop-wise 2-bromoisobutyryl cyanide (69 g, 392 mmol). Then the mixture was allowed to warm to room temperature, and stirred for another 5 h. The reaction was quenched by slowly adding water drop-wise. The mixture was concentrated under reduced pressure, and then the resulting residue was extracted with ethyl acetate and brine. The organic layer was dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by recrystallization from MeOH to give 102 g of 2,2-dimethyl-4-(3-fluorophenyl)-5-[4-(methylthio)phenyl]-3(*2H*)-furanone (**5b**, 81%; see Experimental for physical data).

Even though the afore-mentioned one-pot synthesis using 2-bromoisobutyryl cyanide was developed primarily for the scale-up synthesis of COX-2 inhibitors **1**, the scope of the reaction can be extended to generate structural diversity of 2,2-dimethyl-3(*2H*)-furanone derivatives. For example, by replacing the 2-position of aromatic group in 1,2-diarylethanone **2** with an aliphatic group, some 4-alkyl-5-aryl-2,2-dimethyl-3(*2H*)-furanone derivatives **8** and **9** could be generated (Scheme 3, Table 2 and Fig. 2).

Table 2. Cyclization of 1-aryl-1-alkanones using 2-bromoisobutyryl cyanide (Scheme 3)

Entry	R_2	*Z*	Yield of **8** or **9** (%)	
1	CH_3	CH_3S	**8a**	66
2	$CH(CH_3)_2$	CH_3S	**8b**	8[a]
3	$C(CH_3)_3$	CH_3S	**8c**	—[a,b]
4	Cyclohexyl	CH_3S	**8d**	—[a]
5	Heptyl	F	**9a**	20
6	Pentyl	F	**9b**	31

[a] Poor reaction yields for these cases might suggest a clue to a potential side reaction.[12]

[b] 2-Bromo-3,3-dimethyl-1-[4-(methylthio)phenyl]-1-butanone (**11**) was obtained as a major product in 37% yield.

Actual synthetic examples are presented in the Experimental to manifest that the reaction of 2-bromoisobutyryl cyanide would find a broad range of application in the construction of 3(*2H*)-furanone derivatives. It is notable that it would be difficult to prepare **8** or **9** through Suzuki coupling reaction as in Scheme 1. Thus, 2-bromoisobutyryl cyanide should be a reagent of choice to prepare 2,2-dimethyl-3(*2H*)-furanone derivatives.

Conclusion

An efficient one-pot synthesis for 4,5-diaryl-2,2-dimethyl-3(*2H*)-furanone derivatives was achieved from 1,2-diarylethanones by applying the HSAB principle. 2-Bromoisobutyryl cyanide turned out to be a preferred choice of soft electrophile for the one-pot-synthesis leading to the novel class of orally active cyclooxygenase-2 inhibitors. The scope of the one-pot reaction can be further extended to 2,2-dialkyl-3(*2H*)-furanones, if an appropriate 2-bromo-2,2-dialkylacetyl cyanide is available.

Experimental

Reagents and solvents were obtained from commercial suppliers and used as received, unless noted otherwise. Dry solvents were purchased from Aldrich and used without further drying manipulation. Column chromatography was performed on silica gel (Merck, grade 60/230–400 mesh). NMR (^1H NMR; 300 MHz) spectra were recorded on a Varian Gemini 2000 FT-NMR spectrometer with TMS as an internal standard. Melting points were measured on a Thomas-Hoover melting point apparatus and are uncorrected. Mass spectral analyses were carried out either in-house on a Hewlett-Packard GC/MS (HP5890-2 GC + HP5971

Series Mass) or at the National Instrumentation Center for Environmental Management (NICEM), Suwon, Korea. High resolution mass spectra were recorded at the Inter-University Center for Natural Science Research Facilities at Seoul National University, Seoul, Korea. Infrared spectra were recorded on a BioRad FT-IR spectrometer (FTS-40).

Typical procedure for the synthesis of 4,5-diaryl-2,2-dimethyl-3(*2H*)-furanones. 4-(3,5-Difluorophenyl)-2,2-dimethyl-5-[4-(methylthio)phenyl]-3(*2H*)-furanone (5a). To a stirred solution of 2-(3,5-difluorophenyl)-1-[4-(methylthio)phenyl]ethanone (**2a**, 5.86 g, 21.05 mmol) in anhydrous THF (50 mL) at 0 °C was added 60% sodium hydride (2.1 g, 52.5 mmol) portion-wise. The reaction mixture was stirred for an hour at the same temperature, to which was added drop-wise 2-bromoisobutyryl cyanide (4.5 g, 25.57 mmol). Then the mixture was allowed to warm to room temperature, and stirred overnight. The reaction was quenched by slowly adding water drop-wise. The mixture was concentrated under reduced pressure, and then the resulting residue was extracted with ethyl acetate and brine. The organic layer was dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by recrystallization from MeOH to give **5a** (5.55 g, 71%) as a solid. Mp 122–123 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.54 (s, 6H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.24–7.37 (m, 6H), 7.58 (d, *J* = 8.7 Hz, 2H); IR (neat, cm^{-1}) 1696 (carbonyl), 1623, 1602, 1390; MS (ESI) *m*/*z* 347 (MH^+); HRMS (CI) calcd for $C_{19}H_{17}F_2O_2S$ 347.0918 (MH^+), found 347.0920.

2,2-Dimethyl-4-(3-fluorophenyl)-5-[4-(methylthio)phenyl]-3(*2H*)-furanone (5b). Method A. The procedure was described in the text. Mp 106–106.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.55 (s, 6H), 2.50 (s, 3H), 6.97–7.11 (m, 3H), 7.18 (d, *J* = 9.0 Hz, 2H), 7.26–7.36 (m, 1H), 7.55 (d, *J* = 9.0 Hz, 2H); IR (neat, cm^{-1}) 1694 (carbonyl), 1617, 1599, 1387; MS (ESI) *m*/*z* 329 (MH^+); HRMS (CI) calcd for $C_{19}H_{17}FO_2S$ 329.1012 (MH^+), found 329.1008.

Method B. To a stirred slurry of bromomagnesium diisopropylamide[13] (8.45 mmol) in anhydrous diethyl ether (50 mL) at −78 °C was added drop-wise a solution of 2-(3-fluorophenyl)-1-(4-methylthiophenyl)ethanone (**2b**, 1.0 g, 3.84 mmol) dissolved in 10 mL anhydrous THF. The reaction solution was stirred at room temperature for an h, to which was added 2-bromoisobutyryl bromide (1.06 g, 4.61 mmol) drop-wise at 0 °C. Then the mixture was allowed to warm to room temperature, and stirred for another 2 h. The reaction was quenched by addition of water. Then the mixture was subjected to extraction with ethyl acetate and brine. The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was dissolved in anhydrous THF (50 mL), to which was added 95% sodium hydride (0.18 g, 7.12 mmol). After the reaction solution was stirred for 2 h at room temperature, the reaction was quenched by drop-wise addition of water. The mixture was concentrated under reduced pressure, and then the resulting residue was subjected to extraction with ethyl acetate and brine. The organic layer was concentrated in vacuo and the resulting residue was purified by column chromatography (EtOAc–hexane = 1:10) to afford **5a** (410 mg, 33%) as a solid.

2,2-Dimethyl-4,5-diphenyl-3(*2H*)-furanone (5c). By a similar method employed for **5a**, deoxybenzoin (**2c**, 200 mg, 1.02 mmol) was converted to **5c** (176 mg, 65%) as an oil after purification by column chromatography (EtOAc–hexane = 1:10), which turned into a solid upon prolonged standing. Mp 76.5–78 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.55 (s, 6 H), 2.51 (s, 3H), 6.71–6.78 (m, 1H), 6.84–6.92 (m, 2H), 7.21 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 8.7 Hz, 2H); IR (neat, cm^{-1}) 1694 (carbonyl), 1623, 1389; MS (EI) *m*/*z* 264 (M^+); HRMS (EI) calcd for $C_{18}H_{16}O_2$ 264.1150 (M^+), found 264.1151.

2,2-Dimethyl-5-[4-(methylthio)phenyl]-4-phenyl-3(*2H*)-furanone (5d). By a similar method employed for **5a**, 1-[4-(methylthio)phenyl]-2-phenylethanone (**2d**, 2.0 g, 8.25 mmol) was converted to **5d** (2.51 g, 80%) as a solid after purification by recrystallization from MeOH. Mp 109–110 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.55 (s, 6H), 2.49 (s, 3H), 77.15–7.22 (m, 3H), 7.27–7.31 (m, 2H), 7.33–7.36 (m, 1H), 7.54 (d, *J* = 8.7 Hz, 2H); IR (neat, cm^{-1}) 1693 (carbonyl), 1623, 1596, 1386; MS (EI) *m*/*z* 310 (M^+); HRMS (EI) calcd for $C_{19}H_{18}O_2S$ 310.1027 (M^+), found 310.1044.

4-(3-Chlorophenyl)-2,2-dimethyl-5-[4-(methylthio)phenyl]-3(*2H*)-furanone (5e). By a similar method employed for **5a**, 2-(3-chlorophenyl)-1-[4-(methylthio)-phenyl]ethanone (**2e**, 11.4 g, 14.24 mmol) was converted to **5e** (10.98 g, 77%) as a solid after purification by recrystallization from MeOH. Mp 85–86.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.55 (s, 6H), 2.51 (s, 3H), 6.71–6.78 (m, 1H), 6.84–6.92 (m, 2H), 7.21 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 8.7 Hz, 2H); IR (neat, cm^{-1}) 1693 (carbonyl), 1609, 1596, 1361; MS (EI) *m*/*z* 344 (M^+); HRMS (EI) calcd for $C_{19}H_{17}ClO_2S$ 344.0638 (M^+), found 344.0627.

2,2-Dimethyl-5-[4-(methylthio)phenyl]-4-(4-nitrophenyl)-3(*2H*)-furanone (5f). By a similar method employed for **5a**, 1-[4-(methylthio)phenyl]-2-(4-nitrophenyl)ethanone (**2f**, 1.0 g, 3.48 mmol) was converted to **5f** (0.70 g, 57%) as an oil after purification by column chromatography (EtOAc–hexane = 1:6), which turned into a solid upon prolonged standing. Mp 90–92 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.57 (s, 6H), 2.51 (s, 3H), 7.21 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 9.0 Hz, 2H), 8.21 (d, *J* = 8.7 Hz, 2H); IR (neat, cm^{-1}) 1692 (carbonyl), 1597, 1514, 1344; MS (EI) *m*/*z* 355 (M^+); HRMS (EI) calcd for $C_{19}H_{17}NO_4S$ 355.0878 (M^+), found 355.0871.

2,2-Dimethyl-4-(4-methoxyphenyl)-5-[4-(methylthio)phenyl]-3(*2H*)furanone)-furanone (5g). By a similar method employed for **5a**, 2-(4-methoxyphenyl)-1-[4-(methylthio)phenyl]ethanone (**2g**, 3.01 g, 11.05 mmol) was converted to **5g** (1.51 g, 40%) as a solid after purification by recrystallization from MeOH. Mp 116–117 °C; ^{1}H

NMR ($CDCl_3$, 300 MHz) δ 1.54 (s, 6H), 2.49 (s, 3H), 3.83 (s, 3H), 6.91 (d, $J=9.0$ Hz, 2H), 7.16 (d, $J=8.7$ Hz, 2H), 7.23 (d, $J=9.0$ Hz, 2H), 7.53 (d, $J=8.7$ Hz, 2H); IR (neat, cm^{-1}) 1693 (carbonyl), 1597, 1512, 1386; MS (EI) *m*/*z* 340 (M^+); HRMS (EI) calcd for $C_{20}H_{20}O_3S$ 340.1133 (M^+), found 340.1131.

Typical procedure for the synthesis of 4-alkyl-5-aryl-2,2-dimethyl-3(*2H*)-furanones. 2,2-Dimethyl-4-methyl-5-[4-(methylsulfonyl)phenyl]-3(*2H*)furanone)-furanone (10a). To a stirred solution of 1-[4-(methylthio)phenyl]-1-propanone (**6a**, 1.0 g, 5.55 mmol) in anhydrous THF (15 mL) at −78 °C was added sodium bis(trimethylsilyl)amide (11.1 mL of 1 M THF solution) drop-wise. The reaction mixture was stirred for an hour at the same temperature, to which was added 2-bromoisobutyryl cyanide (1.46 g, 8.29 mmol) drop-wise at 0 °C. Then the mixture was allowed to warm to room temperature, and stirred for another 7 h. The reaction was quenched by slowly adding water drop-wise. The mixture was concentrated under reduced pressure, and then the resulting residue was extracted with ethyl acetate and brine. The organic layer was dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was dissolved in anhydrous THF (15 mL), to which was added 95% sodium hydride (0.23 g 9.10 mmol) at 0 °C. After the reaction solution was stirred at room temperature overnight, the reaction was quenched by adding water drop-wise. The mixture was concentrated under reduced pressure, and then the resulting residue was subjected to extraction with ethyl acetate and brine. The organic layer was concentrated in vacuo and the resulting residue was purified by column chromatography (EtOAc–hexane = 1:10) to afford 2,2-dimethyl-4-methyl-5-[4-(methylthio)phenyl]-3(*2H*)-furanone (**8a**, 0.91 g, 66%) as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 6H), 1.99 (s, 3H), 2.54 (s, 3H), 7.34 (d, $J=8.4$ Hz, 2H), 7.75 (d, $J=8.4$ Hz, 2H). A solution of **8a** (0.80 g, 3.22 mmol) in tetrahydrofuran (20 mL), MeOH (20 mL), and water (20 mL) was stirred with OXONE® (5.94 g, 9.66 mmol) for 3 h at room temperature. The mixture was concentrated under reduced pressure, and then the resulting residue was subjected to extraction with ethyl acetate and brine. The organic layer was dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by recrystallization from EtOAc/hexane to give **10a** (0.85 g, 94%) as a solid. Mp 135.5–136.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 6H), 2.03 (s, 3H), 3.10 (s, 3H), 8.02 (d, $J=8.4$ Hz, 2H), 8.09 (d, $J=8.4$ Hz, 2H); IR (neat, cm^{-1}) 1694 (carbonyl), 1315; MS (EI) *m*/*z* 280 (M^+); HRMS (EI) calcd for $C_{14}H_{16}O_4S$ 280.0769 (M^+), found 280.0763.

2,2-Dimethyl-4-isopropyl-5-[4-(methylsufonyl)phenyl]-3(*2H*)-furanone (10b). By a similar method employed for **8a**, 3-methyl-1-[4-(methylthio)phenyl]-1-butanone (**6b**, 1.0 g, 4.80 mmol) was converted to 2,2-dimethyl-4-isopropyl-5-[4-(methylthio)phenyl]-3(*2H*)-furanone (**8b**, 102 mg, 8%) as an oil after purification by column chromatography (EtOAc–hexane = 1:10). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (d, $J=6.9$ Hz, 6H), 1.41 (s, 6H), 2.53 (s, 3H), 2.91 (sept, $J=6.9$ Hz, 1H), 7.32 (d, $J=8.7$ Hz, 2H), 7.58 (d, $J=8.4$ Hz, 2H). Then **8b** (80 mg, 0.29 mmol) was oxidized by a similar condition as described for **10a**. The resulting **10b** (85 mg, 95%) was obtained initially as an oil after purification by column chromatography (EtOAc–hexane = 1:6), which turned into a solid upon prolonged standing. Mp 83–85 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (d, $J=6.9$ Hz, 6H), 1.43 (s, 6H), 2.83 (sept, $J=6.9$ Hz, 1H), 3.10 (s, 3H), 7.84 (d, $J=8.4$ Hz, 2H), 8.07 (d, $J=8.7$ Hz, 2H); IR (neat, cm^{-1}) 1694 (carbonyl), 1317; MS (EI) *m*/*z* 308 (M^+); HRMS (CI) calcd for $C_{16}H_{21}O_4S$ 309.1161 (MH^+), found 309.1154.

2,2-Dimethyl-5-(4-fluorophenyl)-4-heptyl-3(*2H*)-furanone (9a). By a similar method employed for **8a**, 1-(4-fluorophenyl)-1-nonanone (**7a**, 350 mg, 1.48 mmol) was converted to **9a** (90 mg, 20%) as an oil after purification by column chromatography (EtOAc–hexane = 1:15): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (m, 3H), 1.29 (m, 8H), 1.43 (s, 6H), 1.49 (m, 2H), 2.39 (dd, $J=7.5$, 8.1 Hz, 2H), 7.19 (m, 2H), 7.79 (m, 2H), IR (neat, cm^{-1}) 2927, 1688, 1587, 1390, 1093, 844, MS (EI) *m*/*z* 304 (M^+); HRMS (EI) calcd for $C_{19}H_{25}FO_2$ 304.1839 (M^+), found 304.1832.

2,2-Dimethyl-5-(4-fluorophenyl)-4-pentyl-3(*2H*)-furanone (9b). To a stirred solution of 1-(4-fluorophenyl)-1-heptanone (**7b**, 410 mg, 1.97 mmol) in anhydrous THF (5 mL) at −78 °C was added sodium bis(trimethylsilyl)amide (12 mL of 1 M THF solution) drop-wise. The reaction mixture was stirred for an hour at the same temperature, to which was added 2-bromoisobutyryl cyanide (500 mg, 2.84 mmol) drop-wise. Then the mixture was allowed to warm to room temperature, and stirred for another 7 h. The reaction was quenched by slowly adding water drop-wise. The mixture was extracted with ethyl acetate and brine. The organic layer was dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography (EtOAc–hexane = 1:15) to afford **9b** (170 mg, 31%) as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (m, 3H), 1.32 (m, 4H), 1.44 (s, 6H), 1.51 (m, 2H), 2.39 (m, 2H), 7.19 (m, 2H), 7.80 (m, 2H), IR (neat, cm^{-1}) 2928, 1690, 1610, 1508, 1390, 1093, 844, MS (EI) *m*/*z* 276 (M^+); HRMS (EI) calcd for $C_{17}H_{21}FO_2$ 276.1526 (M^+), found 276.1540.

Typical procedure for *O*-acylation product. 1,2-Diphenylvinyl 2-bromo-2-methylpropionate (3c). To a stirred solution of deoxybenzoin (**2c**, 500 mg, 2.55 mmol) in anhydrous THF (10 mL) at 0 °C was added portion-wise 95% sodium hydride (193 mg 7.64 mmol). After stirring at the same temperature for 1 h, 2-bromoisobutyryl bromide (700 mg, 3.04 mmol) was added drop-wise. Then the mixture was allowed to warm to room temperature, and stirred for another 5 h. The reaction was quenched by drop-wise addition of water. The mixture was concentrated under reduced pressure, and then the resulting residue was extracted with ethyl acetate and brine. The organic layer was dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by recrystallization from ethyl acetate/hexane to afford **3c** (659 mg, 75%). Mp 42–44 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.01 (s, 6H), 6.73 (s, 1H), 7.27–7.62

(m, 10H); IR (neat, cm^{-1}) 1748 (carbonyl), 1448, 1253, 1136; MS (EI) *m*/*z* 344 and 346 (M$^+$); HRMS (CI) calcd for $C_{18}H_{18}BrO_2$ 345.0490 (MH$^+$), found 345.0500.

Reaction of 3,3-dimethyl-1-[4-(methylthio)phenyl]-1-butanone with 2-bromoisobutyryl cyanide. 3,3-Dimethyl-1-[4-(methylthio)phenyl]-1-butanone (**6c**, 1.0 g, 4.5 mmol) was reacted with 2-bromoisobutyryl cyanide (1.2 g, 6.82 mmol), similarly as described for the preparation of **8a**. Instead of the desired 4-*t*-butyl-2,2-dimethyl-5-[4-(methylthio)phenyl]-3(*2H*)-furanone (**8c**), however, was isolated a major product ascribable to 2-bromo-3,3-dimethyl-1-[4-(methylthio)phenyl]-1-butanone (**11**) in 37.1% yield (0.50 g) after recrystallization from MeOH.[16] Mp 86–88 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (s, 9H), 2.53 (s, 3H), 5.07 (s, 1H), 7.28 (d, $J = 8.4$ Hz, 2H), 7.89 (d, $J = 8.4$ Hz, 2H); IR (neat, cm^{-1}) 1685 (carbonyl), 1585, 1404, 1275; MS (EI) *m*/*z* 300 and 302 (M$^+$); HRMS (CI) calcd for $C_{13}H_{18}BrOS$ 301.0262 (MH$^+$), found 301.0257.

Acknowledgements

We would like to thank Mrs. Hyea-Sook Shin and the Inter-University Center for Natural Science Research Facilities at Seoul National University for HRMS.

References and Notes

1. Shin, S. S.; Noh, M.-S.; Byun, Y. J.; Choi, J. K.; Kim, J. Y.; Lim, K. M.; Ha, J.-Y.; Kim, J. K.; Lee, C. H.; Chung, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 165.
2. (a) Reitz, D. B.; Seibert, K. *Ann. Rep. Med. Chem.* **1995**, *30*, 179. (b) Carter, J. S. *Exp. Opin. Ther. Pat.* **2000**, *10*, 1011.
3. (a) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513. (b) Hoshino, Y.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3008.
4. Zhang, T. Y.; Allen, M. J. *Tetrahedron Lett.* **1999**, *40*, 5813.
5. Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper & Row: New York, 1987; p 318.
6. 1,2-Diarylethanones were prepared by Friedel–Crafts reaction of phenylacetyl chlorides with thioanisole using aluminum chloride in good yield, by using a similar procedure as described in the following literature: Lee, S. H.; Lee, S.-G.; Song, C. E.; Kim, I. O.; Chung, B. Y. *Kor. J. Med. Chem.* **1997**, *7*, 34.
7. March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley & Sons: New York, 1985; p 436 and references therein.
8. The lithium enolates **2**, prepared by treating with LDA or *n*-BuLi at −78 °C, were reacted with 2-bromoisobutyryl bromide similarly as described in the Experimental for **3c**.
9. 2-Bromoisobutyryl cyanide was prepared according to the following literature: Herrmann, K.; Simchen, G. *Synthesis* **1979**, 204.
10. When the acylation reaction was performed below −30 °C, the reaction stopped at the stage of the *C*-acylation product and the cyclization reaction did not proceed. ^{1}H NMR data for **4d** ($Z = CH_3S$, $R_1 = H$): ($CDCl_3$, 300 MHz) δ 1.88 (d, $J = 8.1$ Hz, 6H), 2.48 (s, 3H), 6.57 (s, 1H), 7.19–7.39 (m, 7H), 7.90 (d, $J = 8.7$ Hz, 2H).
11. Some of **5** were isolated initially as an oil after column chromatography, which frequently turned into a solid upon prolonged standing.
12. These results suggest that 2-bromoisobutyryl cyanide, depending on the nature of an enolate, can be a brominating agent reminiscent of cyanogen bromide reaction. Enolates of strong basicity would undergo bromination rather than the desired *C*-acylation. However, the unwanted bromination might be circumvented by switching the bromine of 2-bromoispbutyryl cyanide to chlorine, a harder atom for nucleophilic attack by an enolate.
13. Krafft, M. E.; Holton, R. A. *Tetrahedron Lett.* **1983**, *24*, 1345.