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Synthesis of 2(3*H*)-Furanones via Electrophilic Cyclization

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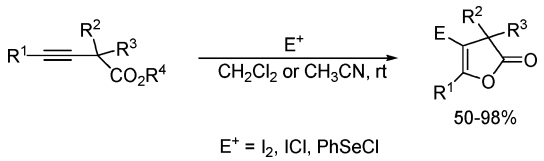


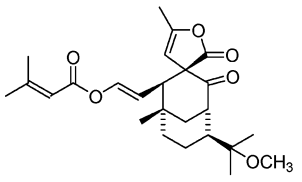
A variety of highly substituted 2(3*H*)-furanones are readily prepared from 3-alkynoate esters and the corresponding acids via electrophilic cyclization. Successful electrophiles in this process include I_2, ICl, and PhSeCl. This highly efficient process proceeds under mild conditions, tolerates various functional groups, and generally provides substituted 2(3*H*)-furanones in good to excellent yields.

Introduction

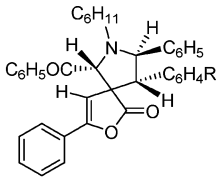
2(3*H*)-Furanone derivatives[1] constitute an important group of natural products and possess a wide range of biological activities. For example, the dihydro-2(3*H*)-furanone moiety is abundant in a large variety of natural and synthetic compounds used as agrochemicals, pharmaceuticals, and in the food industry.[2] Recently, several highly substituted, unsaturated 2(3*H*)-furanones have been discovered, attracting great interest due to their biological activities. For example, the naturally occurring compound Spirovibsanin A (I) has been isolated from the plant *Viburnum awabuki*.[3] Some other highly substituted 2(3*H*)-furanones, such as spiro[butenolide]pyrrolidines (II), have been studied for their antibacterial and antifungal activity against human pathogenic bacteria and dermatophytic fungi (Scheme 1).[4]

The electrophilic cyclization of functionally substituted alkynes has attracted much attention due to its wide utility in the preparation of a range of useful, functionally substituted heterocycles and carbocycles,[5] including quinolines,[6] isoxazoles,[7] isoindolin-1-ones,[8] benzo[*b*]thiophenes,[9] bicyclic β-lactams,[10] indoles,[11] chromones,[12] pyrilium salts and isochromenes,[13] 2-naphthols,[14] benzofurans,[15] cyclic carbonates,[16]

SCHEME 1



Spirovibsanin A (I)



Spiro[butenolide]pyrrolidines (II)

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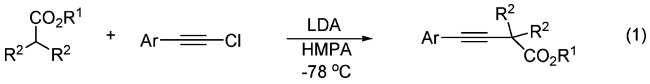
pyrroles,[17] furans,[18] isocoumarins and α-pyrones,[19] isoquinolines and naphthyridines,[20] polycyclic aromatics,[14,21] benzo[*b*]selenophenes,[22] and furopyridines.[23] Herein, we report an efficient approach to various highly substituted 2(3*H*)-furanones by the electrophilic cyclization of 3-alkynoate esters and acids. The resulting iodine-containing products can be further elaborated to a wide range of functionally substituted furanones using subsequent palladium-catalyzed processes.

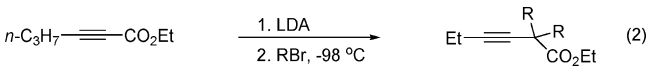
Results and Discussion

The 3-alkynoate esters required for our studies have typically been prepared in two or three steps. The 4-aryl-2,2-dialkylbut-3-ynoates have been synthesized by the reaction of alkyl-substituted ester enolates with the corresponding 2-aryl-1-chloroethynes at −78 °C (eq 1).[24]



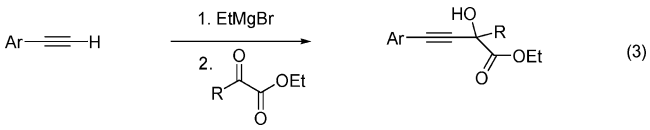
(1)

The 2,2-dialkyl-3-hexynoate esters have been synthesized by a one-pot reaction of ethyl 2-hexynoate with excess LDA at −98 °C, followed by the addition of an excess of the appropriate alkyl bromide (eq 2).[25]



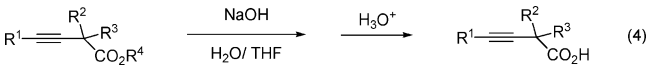
(2)

Various methods have been utilized to prepare the remaining esters. For example, the 2-alkyl-4-aryl-2-hydroxybut-3-ynoate esters were prepared by reacting a terminal aryl acetylene with EtMgBr, followed by the appropiate ethyl 2-oxoalkanoate ester (eq 3).[26]



(3)

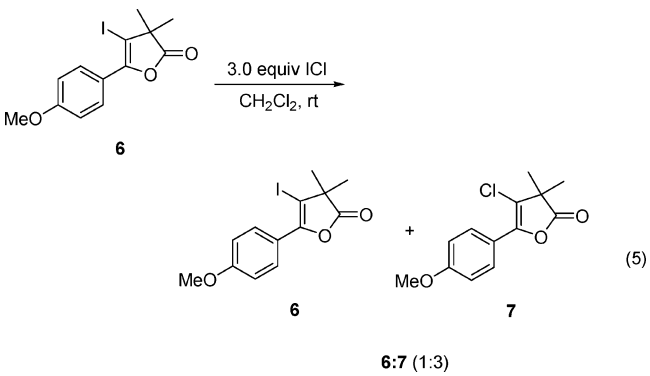
All of the 3-alkynoic acids were prepared from the corresponding esters by alkaline hydrolysis (eq 4).[27] The detailed syntheses of all of the starting materials are provided in the experimental section.



(4)

To examine the reactivity of the 3-alkynoate esters, we first explored the reaction of the 3-alkynoate ester **1** with 1.5 equiv of I_2 in dichloromethane under our previously established reaction conditions for the synthesis of benzo[*b*]thiophenes[9b] and indoles.[11d] The reaction proceeded smoothly and reached completion in 1.5 h, affording an 87% yield of the iodolactone **2** (Table 1, entry 1). We have also examined the reaction of ester **1** with the readily available electrophiles ICl and PhSeCl. ICl gave the fastest reaction and reached completion in 1 h (Table 1, entry 2). However, ICl afforded a 1:1 inseparable mixture of the corresponding 4-iodo- and 4-chloro-2(3*H*)-furanones in a 70% total yield. PhSeCl has also been successfully employed in this electrophilic cyclization, providing a 70% yield of the desired selenium cyclization product **4** in 1 h (Table 1, entry 3).

We next employed this chemistry on various substituted 3-alkynyl esters (Table 1, entries 4−37). 4-Aryl-2,2-dimethylbut-3-ynoate esters bearing an electron-rich aromatic ring, such as **5**, and an electron-deficient aromatic ring, such as **8**, reacted smoothly with I_2, affording the corresponding lactones **6** and **9** in 78% (Table 1, entry 4) and 67% (Table 1, entry 8) yields, respectively. However, when ICl was used in place of I_2, these esters afforded mixtures of the 4-iodo- and 4-chloro-2(3*H*)-furanones. The ratio of these two products depends on the amount of ICl employed. When we utilized 1.1 equiv of ICl in the cyclization of **5**, the iodo-substituted product **6** was dominant. Lactones **6** and **7** were formed in an 11:1 ratio (Table 1, entry 5). As we increased the amount of ICl to 1.5 equiv, the ratio of the iodo-substituted product **6** to the chloro-substituted product **7** decreased to 2:1 (Table 1, entry 6). When we employed 3.0 equiv of ICl in the reaction of **5**, the ratio of **6** to **7** changed to 1:3 and the overall yield dropped to 40% (Table 1, entry 7). Furthermore, when ICl was allowed to react directly with the pure iodo-substituted product **6**, a mixture of **6** and **7** was obtained after 24 h (eq 5). For substrate **8**, cyclization using 1.5 equiv of ICl also gave a mixture of the iodo-substituted lactone **9** and the chloro-substituted lactone **10** in a 1:1 ratio (Table 1, entry 9). Although it is very interesting that two different halogenated products can be obtained in this process, the mechanism for this formation is unclear.



(5)

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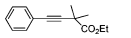
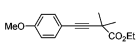
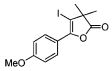
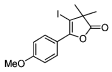
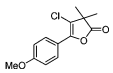
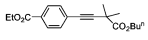
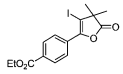
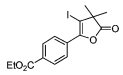
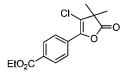
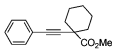
TABLE 1. Synthesis of Substituted 2(3*H*)-Furanones by the Electrophilic Cyclization of 3-Alkynoate Esters[a]

entry	3-alkynoate ester		electrophile	time (h)	product(s)		yield (%)[b] (ratio)[c]
1		**1**	I_2	1.5		**2**	87
2		**1**	ICl	1		**2**	70 (1:1)[c]
						**3**	
3		**1**	PhSeCl	1		**4**	70
4		**5**	I_2	5		**6**	78
5		**5**	ICl[d]	4		**6**	77 (11:1)[c]
						**7**	
6		**5**	ICl	4		**6**+**7**	68 (2:1)[c]
7		**5**	ICl[e]	4		**6**+**7**	40 (1:3)[c]
8		**8**	I_2	2		**9**	67
9		**8**	ICl	2		**9**	70 (1:1)[c]
						**10**	
10		**11**	I_2	24		**12**	89
11		**11**	ICl	1		**12**	89
12		**11**	PhSeCl	1.5		**13**	73
13		**14**	I_2	9		**15**	80
14		**16**	I_2	1		**17**	86
15		**16**	ICl	1		**17**	50
16		**18**	I_2	6		**19**	78
17		**18**	ICl	1		**19**	60
18		**20**	I_2	2		**21**	84
19		**22**	I_2	1		**23**	97
20		**22**	ICl	0.5		**23**	86
21		**24**	I_2	1		**25**	96
22		**26**	I_2	24		**27**	62
23		**28**	I_2	48		**29**	0[f]
24		**30**	I_2	3		**31**	0
25		**32**	I_2	5		**33**	0[f]
26		**34**	I_2	3		**35**	0
27		**36**	I_2	1.5		**37**	0[g]
28		**36**	ICl	1.5		**37**	0[g]
29		**38**	I_2	1.5		**39**	0[g]
30		**40**	I_2	2		**41**	66
31		**40**	ICl	1.5		**41**	0[g]
32		**42**	I_2	24		**43**	0
33		**42**	ICl	24		**43**	-[h]
34		**44**	I_2	24		**45**	0[f]
35		**44**	ICl	2		**45**	0[f]
36		**46**	I_2	1		**47**	0[f]
37		**46**	ICl	1		**47**	0

[a] All reactions were conducted on a 0.25 mmol scale using 1.5 equiv of electrophile in 4 mL of CH_2Cl_2 at room temperature unless otherwise indicated. [b] All yields are isolated yields. [c] Yield is the combined yields of the iodo-substituted and chloro-substituted products. The ratio of these products, as determined by ^1H NMR spectroscopy, is reported in parentheses. [d] Employing 1.1 equiv of ICl. [e] Employing 3.0 equiv of ICl. [f] Only the product of addition of the electrophile across the carbon−carbon triple bond was obtained. Some addition product was not stable and reverted to the starting material upon column chromatography. [g] Only unidentified products, which are not 2-furanones, were obtained. [h] An inseparable mixture was obtained.

When there is a six-membered ring present next to the ester moiety, the reaction proceeds more slowly than the 2,2-dimethyl counterpart. Cyclization of the 3-alkynoate ester **11** with I_2 reached completion in 24 h and resulted in an 89% yield (Table 1, entry 10). The reaction of **11** with ICl and PhSeCl gave the desired 2-furanone products in 89% and 73% yields, respectively (Table 1, entries 11 and 12). The chloro-substituted product was not observed in the ICl cyclization of **11**. The I_2 cyclization of

the 3-alkynoate ester **14** bearing β-ketoester functionality proceeded smoothly and resulted in an 80% yield of the spirocyclic product **15** (Table 1, entry 13). Although the oxygens of both of the carbonyl groups could potentially attack the presumed iodonium intermediate (see the later mechanistic discussion), only the ester oxygen reacted to give the lactone **15** as the exclusive product. Previous work on the electrophilic cyclization of acetylenic ketones and aldehydes has been reported by others and our group.[13,18] This chemoselectivity may be explained by the closer proximity of the ester oxygen to the hypothetical iodonium intermediate.

When we introduced an alkyl group instead of an aryl group into the 4-position of the 3-alkynoate ester, the reaction was somewhat faster (Table 1, entries 14−20). The cyclization of 3-alkynoate ester **16** proceeded cleanly in 1 h using I_2 and afforded an 86% yield of the iodolactone **17** (Table 1, entry 14). The yield for the analogous ICl cyclization was significantly lower (Table 1, entry 15). However, none of the corresponding chlorolactone was observed. For the 3-alkynoate ester **18** bearing a cyclohexane moiety, the reaction proceeded more slowly than that of **16**, when employing I_2 (Table 1, entry 16). However, we still obtained a 78% yield of the corresponding iodolactone **19**. Here ICl cyclization of **18** gave exclusively iodolactone **19** in 1 h, but in only a 60% yield (Table 1, entry 17). When we employed I_2 in the cyclization of the 2,2-diallyl-3-alkynoate ester **20**, the reaction proceeded smoothly affording an 84% yield of iodolactone **21** (Table 1, entry 18). Thus, neighboring carbon−carbon double bonds are not problem. However, the terminal double bonds of **20** were vulnerable to ICl and the reaction with this reagent was messy. In the case of the cyclopentane-containing ester **22**, the yield of the corresponding iodolactone **23** was almost quantitative when using I_2 (Table 1, entry 19). The ICl cyclization of **22** gave exclusively iodolactone **23** in only 0.5 h in an 86% yield (Table 1, entry 20).

We next considered the possibility of preparing 2-furanones by the cyclization of 3-alkynoate esters bearing one or no α-substituents. Since mono-α-substituted alkynoate esters are not very stable and can be easily isomerized to the corresponding allenic esters in the presence of a base,[28] we chose to explore instead the cyclization of the allenic ester **24**, rather than a monosubstituted 3-alkynoate ester. This cyclization resulted in a 96% yield of the lactone **25**, bearing the more stable conjugated 2-furanone ring (Table 1, entry 21). Similar allenic ester and acid electrophilic cyclizations with different electrophiles have been explored by others under different reaction conditions.[29] Thus, we chose not to examine any additional allenic esters.

When we explored the α-unsubstituted 3-alkynoate ester **26**, extensive isomerization occurred, affording the conjugated 2-furanone **27** in a 62% yield (Table 1, entry 22). Substrate **28** with a terminal alkyne failed to give the desired cyclization product **29** even after 2 days (Table 1, entry 23). Some starting material reacted with I_2 to form a product resulting from addition of the I_2 across the acetylene moiety. Introducing two methyl groups in the 2 position did nothing to improve the situation (Table 1, entry 24). Introduction of a trimethylsilyl group on the acetylene failed to afford any of the desired lactone using either I_2 or ICl (Table 1, entry 25). This ester only gave products of addition of the I_2 across the carbon−carbon triple bond, which decomposed back to the starting material **32** upon column chromatography. The α-unsubstituted substrate **34** also failed to provide any iodolactone; only starting material was recovered after aqueous work up and neither the desired conjugated cyclization product **35** nor the corresponding 2(3*H*)-furanone was observed (Table 1, entry 26). Comparing entries 1 and 26, the Thorpe-Ingold effect of the gem-dimethyl group clearly benefits the cyclization.[30] When we attempted to cyclize the α-hydroxy substrate **36**, where the oxygen from the OH group and the oxygen of the carbonyl group can both serve as nucleophiles, we obtained an unidentified compound, which was not the desired lactone (Table 1, entries 27 and 28). Even after we protected the OH group with a TBS group, the desired I_2 cyclization product was not formed (Table 1, entry 29). Surprisingly, however, the TMS-protected compound **40** afforded the desired 2-furanone **41** in a 66% yield (Table 1, entry 30). However, the ICl cyclization of **40** did not give the desired product (Table 1, entry 31). We also examined substrate **42**, which has an sp^2 carbon center in the α position. No reaction took place using I_2. With ICl, we obtained a mixture of the desired cyclization product and an acetylene addition product, which were hard to separate (Table 1, entry 33). When we introduced a carbonyl group into the α position (**44**), we only observed acetylene addition products when employing either I_2 or ICl (Table 1, entries 34 and 35).

In conclusion, the substitution and the hybridization of the α position of the 3-alkynoate ester are crucial for the electrophilic cyclization to take place successfully. If there is an sp^2 carbon center present on the α carbon, cyclization is difficult, apparently due to the wider angle between the alkyne and the ester groups. The nucleophilic oxygen of the ester group is apparently simply too far away for the iodonium intermediate to undergo cyclization. For similar reasons, the 3-alkynoate ester bearing a cyclopropane ring in the α position also failed to cyclize when allowed to react with I_2 and only the product of addition to the alkyne was observed (Table 1, entry 36). The addition product was not stable and quickly reverted back to starting material upon aqueous work up. Due to the strained, rather reactive cyclopropane ring system, a ring opened product was observed in the crude ^1H NMR spectrum of the corresponding ICl reaction (Table 1, entry 37).

In an attempt to overcome some of the limitations encountered in the electrophilic cyclization of the 3-alkynoate esters, we have examined the cyclization of the corresponding alkynoic acids. We hydrolyzed our previous best substrate **22** to the corresponding 3-alkynoic acid **48**. This 3-alkynoic acid reacted with both I_2 and ICl in the presence of 3 equiv of $NaHCO_3$ in CH_3CN in slightly better yields than the corresponding ester (Table 2, entries 1 and 2), suggesting that an acid group or rather the corresponding carboxylate is a better nucleophile than the ester in these cyclization reactions. PhSeCl was also a good electrophile and gave the desired product **49** in an 85% yield (Table 2, entry 3). Next, we transformed an unsuccessful 3-alkynoate ester **46** to the corresponding acid **50** and conducted the same cyclization reaction. As we desired, the acid **50** gave the cyclization product **47** using either I_2 or ICl (Table 2, entries 4 and 5). Under the basic conditions, the acidic hydrogen is removed and the anionic carboxylate becomes a better nucleo-

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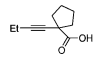
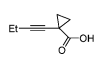
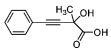
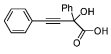
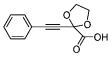
TABLE 2. Synthesis of Substituted 2(3*H*)-Furanones by the Electrophilic Cyclization of Alkynoic Acids[a]

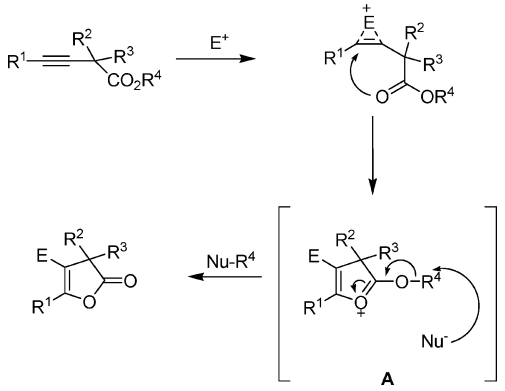
entry	alkynoic acid		electrophile	time (h)	product		yield (%)[b]
1		**48**	I_2	3		**23**	98
2		**48**	ICl	3		**23**	92
3		**48**	PhSeCl	2		**49**	85
4		**50**	I_2	20		**47**	78
5		**50**	ICl	20		**47**	78
6		**51**	I_2	20		**37**	75
7		**51**	ICl	2		**37**	80
8		**51**	PhSeCl	2		**52**	72
9		**53**	I_2	24		**54**	60
10		**53**	ICl	2		**54**	82
11		**53**	PhSeCl	3		**55**	87
12		**56**	I_2	24		**45**	0[c]
13		**57**	I_2	24		**58**	67
14		**57**	ICl	4		**58**	96

[a] All reactions employing carboxylic acids were conducted on a 0.25 mmol scale, using 1.5 equiv of I_2 and 3.0 equiv of $NaHCO_3$ in 4 mL of CH_3CN at room temperature. [b] All yields are isolated yields. [c] Only the product of addition of the electrophile across the carbon−carbon triple bond was obtained.

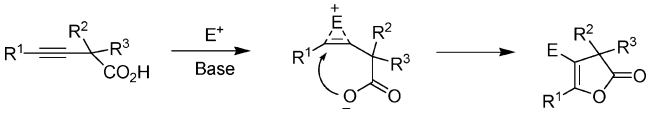
phile than the ester group (see the later mechanistic discussion). Encouraged by these results, we next prepared acid **51** from the unsuccessful substrate **36**. As expected, the desired lactone **37** was obtained upon I_2 cyclization (Table 2, entry 6). Reactions employing ICl and PhSeCl also afforded high yields of the anticipated products (Table 2, entries 7 and 8). The hydroxy acid **53** also gave good to excellent yields with all of these electrophiles (Table 2, entries 9−11). When we introduced a carbonyl group into the α position, none of the desired furanone product was observed using either I_2 or ICl (Table 2, entry 12). Thus, the presence of an sp^2 carbon in the α position is still a problem even with carboxylic acid substrates. To solve this problem, we protected the α carbonyl group as an acetal and the cyclization of acetal **57** proceeded smoothly using either I_2 or ICl to afford 67% and 96% yields of the anticipated lactone (Table 2, entries 13 and 14).

Mechanistically, we believe that the cyclizations of the 3-alkynoate esters proceed by coordination of the carbon−carbon triple bond to the electrophile, followed by nucleophilic attack by the oxygen of the carbonyl group of the ester to produce an intermediate A, which undergoes removal of the alkyl group of the ester group via S_N2 displacement by nucleophiles present in the reaction mixture (Scheme 2). For

SCHEME 2. Mechanism of the Electrophilic Cyclization of 3-Alkynoate Esters



SCHEME 3. Mechanism of the Electrophilic Cyclization of 3-Alkynoic Acids



the 3-alkynoic acids, the acidic hydrogen is removed under the basic reaction conditions and the anionic oxygen of the carboxylate serves as a better nucleophile. In this case, after the electrophile coordinates to the carbon−carbon triple bond, the anionic oxygen attacks the intermediate to form the 4-iodo-2(3*H*)-furanone directly (Scheme 3). For both the 3-alkynoate esters and the 3-alkynoic acids, the hybridization of the carbon in the α position is crucial for the cyclization to take place. The presence of an sp^2 carbon center in the α position of either the 3-alkynoate ester or the 3-alkynoic acid produced unsuccessful cyclizations. Overall, 3-alkynoic acids provide better results in these electrophilic cyclizations than the corresponding 3-alkynoate esters.

This approach to 4-iodo-2(3*H*)-furanones provides a very useful synthesis of various substituted 2(3*H*)-furanones via elaboration of the resulting iodide functionality into other substituents. For instance, the resulting iodolactones are particularly useful intermediates in many palladium-catalyzed processes, such as Sonogashira, Suzuki, and Heck cross-couplings. For instance, compound **23** can be treated under standard Heck,[31] Sonogashira,[32] Suzuki,[33] and carbonylation[34] conditions, providing the corresponding coupling products **59**−**62**, respectively (Scheme 4).

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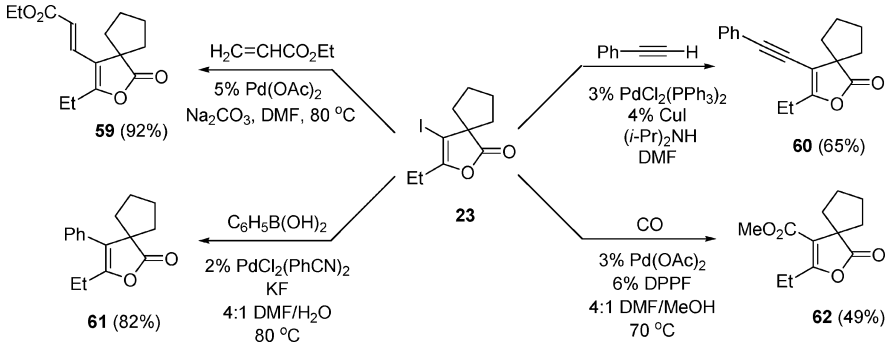
SCHEME 4. Pd-Catalyzed Diversification of 4-Iodo-2(3*H*)-furanone Derivatives



Conclusions

In conclusion, we have developed a simple, highly efficient approach to various highly functionalized, unsaturated 2(3*H*)-furanones via electrophilic cyclization of acetylenic esters and acids. We have shown that the electrophiles I_2, ICl, and PhSeCl can be used in this chemistry. In most cases, the I_2 cyclization gave one pure product in a high yield. The use of ICl as an electrophile occasionally gave more than one product. These reactions are run under mild conditions, tolerate a number of functional groups, and generally provide the highly substituted 2(3*H*)-furanones in good to excellent yields. The resulting iodolactones are readily elaborated to more complex compounds by using known organopalladium chemistry.

Experimental Section

General Procedure for Preparation of 4-Iodo-2(3*H*)-furanones from Alkynoate Esters (Table 1). To a vial of the corresponding alkynoate ester (0.25 mmol) in 1 mL of CH_2Cl_2 under Ar was added dropwise a solution of I_2 or ICl (0.375 mmol) dissolved in 3 mL of CH_2Cl_2. The reaction was stirred at room temperature for the indicated time. The reaction mixture was then quenched with 20 mL of saturated aqueous $Na_2S_2O_3$ solution and extracted three times with ethyl ether (20 mL each). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The product was purified by chromatography on a silica gel column.

3-Ethyl-4-iodo-2-oxaspiro[4.4]non-3-en-1-one (23). Light yellow solid, mp 52−53 °C; ^{1}H NMR ($CDCl_3$) δ 1.13 (t, J = 7.5 Hz, 3H), 1.88−1.93 (m, 8H), 2.40 (q, J = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 11.0, 22.4, 26.7, 37.4, 56.7, 76.1, 155.2, 181.4; IR (CH_2Cl_2) 2959, 2871, 1779, 1663, 1460, 1442, 1278 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{13}O_2I$ 292.9960, found 292.9965.

General Procedure for Preparation of 4-Iodo-2(3*H*)-furanones from Alkynoic Acids (Table 2). To a vial of the corresponding alkynoic acid (0.25 mmol) in 1 mL of CH_3CN was added $NaHCO_3$ (0.75 mmol). The mixture was stirred for 5 min under Ar. Then I_2 or ICl (0.375 mmol) in 3 mL of CH_3CN was added dropwise to the above solution. The reaction was stirred at room temperature for the indicated time. The mixture was then quenched with 20 mL of saturated aqueous $Na_2S_2O_3$ solution and extracted three times with ethyl ether (20 mL each). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The product was purified by chromatography on a silica gel column.

3-Ethyl-4-iodo-2-oxaspiro[4.2]hept-3-en-1-one (47). Light yellow solid, mp 29−30 °C; ^{1}H NMR ($CDCl_3$) δ 1.18 (t, J = 7.5 Hz, 3H), 1.33−1.48 (m, 4H), 2.50 (q, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 11.2, 17.4, 22.7, 31.2, 68.2, 156.3, 177.6; IR (CH_2Cl_2) 2977, 2939, 1790, 1650, 1284 cm^{-1}; HRMS (EI) calcd for $C_8H_9O_2I$ 263.9647, found 263.9652.

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Supporting Information Available: Detailed experimental procedures and characterization data for all previously unknown products. This material is available free of charge via the Internet at http://pubs.acs.org.

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