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Synthesis of 4-Iodo-3-furanones Utilizing Electrophile-Induced Tandem Cyclization/ 1,2-Migration Reactions

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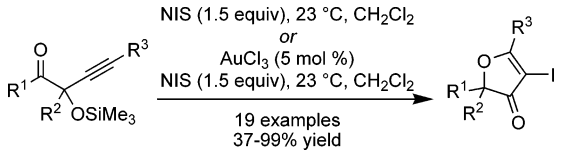
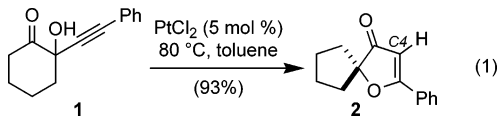


Two protocols for the construction of 4-iodo-3-furanones through a sequence consisting of cyclization and 1,2-migration of 2-alkynyl-2-silyloxy carbonyl compounds were developed. In one, electrophilic cyclization is directly induced by *N*-iodosuccinimide (NIS). In the second less limited variant, $AuCl_3$ catalyzes the tandem reaction in the presence of NIS to provide highly substituted heterocycles in moderate to excellent yields.

Polysubstituted 3(2*H*)-furanones are key structural elements in many naturally occurring compounds such as geiparvarin,[1] eremantholide A,[2] and jatrophone.[3] Moreover, a variety of 3(2*H*)-furanones are known to have pharmaceutical activity[4] (e.g., inhibitory activity on COX-2,[5] inhibitory activity on MAO,[6] and cytotoxic activity[7] against tumor cells). Strategies toward 3(2*H*)-furanones mainly utilize classical condensation methods such as the acid-catalyzed cyclocondensation of substituted α′-hydroxy 1,3-diketones,[8] as pioneered by the work of Smith and co-workers.[9] While there are numerous alternative strategies for 3(2*H*)-furanone synthesis,[10] a particularly effective approach is through transition metal-catalyzed 5-*endo* heterocyclization of an alkenyl alcohol.[11] In 2006, we reported the construction of 3(2*H*)-furanones from 2-alkynyl-2-hydroxy carbonyl compounds[12] using catalytic amounts of $PtCl_2$ as a proton equivalent.[13,14] This tandem reaction consisting of heterocyclization and 1,2-migration is believed to proceed via a cyclic oxonium ion intermediate.[15] For example, reaction of alkynyl carbonyl compound **1** with 5 mol % of $PtCl_2$ in toluene at 80 °C produced the 3(2*H*)-furanone **2** in good yield (93%) (eq 1). Despite the synthetic value of this reaction, 3(2*H*)-



(1)

furanones bearing an additional substituent at C4 are not accessible. A novel electrophile-induced tandem cyclization/ 1,2-migration reaction of 2-alkynyl-2-silyloxy carbonyl compounds is disclosed herein, which produces fully substituted 3(2*H*)-furanones containing an iodo substituent at C4. We also report a $AuCl_3$-catalyzed modification to enhance the scope of accessible 4-iodo-3-furanones.

As an alternative to transition metal-catalyzed cyclizations of unsaturated frameworks,[16] electrophilic cyclizations have been frequently utilized to construct a wide range of carbocycles and

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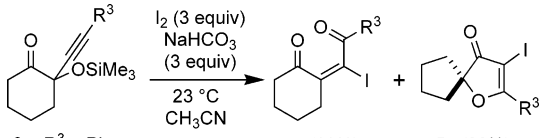
SCHEME 1. Synthesis of 1,3-Diones 4 from Alkynyl Carbonyl Compound 3

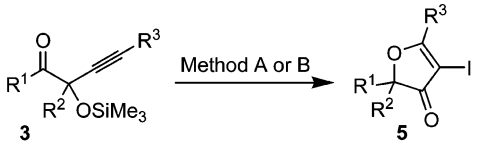


heterocycles.[17] Thus, the reaction of trimethylsilyl ether **3a** was initially examined with use of 3 equiv of I_2 as the electrophile in the presence of $NaHCO_3$ in CH_3CN at room temperature. Under these conditions, the attempted rearrangement of alkynyl carbonyl compound **3a** afforded at most small amounts of 4-iodo-3-furanone **5a**. The major product, isolated in 68% yield, was the unexpected enedione **4a** resulting from a formal Meyer−Schuster rearrangement (Scheme 1).[18,19] The presence of the $NaHCO_3$ proved to be important for the reaction as the yield for the formation of **4a** was significantly lowered without the base.

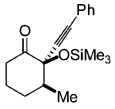
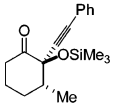
Rearrangement of alkynyl carbonyl compound **3a** to 4-iodo-3-furanone **5a** was achieved in the presence of *N*-iodosuccinimide (NIS) as a stronger electrophile.[20] From a preliminary survey, two particular useful reaction conditions were identified: 1.5 equiv of NIS, CH_2Cl_2 (0.1 M), 23 °C (Method A); and 5 mol % of $AuCl_3$, 1.5 equiv of NIS, CH_2Cl_2 (0.1 M), 23 °C (Method B). For example, exposure of trimethylsilyl ether **3a** to 1.5 equiv of NIS at room temperature in CH_2Cl_2 provided furanone **5a** in 88% yield after 2 h (Table 1, entry 1).[21] In the presence of 5 mol % of $AuCl_3$ under identical conditions, a significant increase in reaction rate was observed with only a marginal increase in yield (Table 1, entry 2).

As summarized in Table 1, spirocyclic compounds **5** were obtained in high yields by using NIS in CH_2Cl_2 in the absence of $AuCl_3$ (Method A). The reaction tolerated substitution on the alkyne with R^3 being both aryl, alkenyl, and alkyl groups. However, the conversion of acyclic substrates into the desired 4-iodo-3-furanones was sluggish under these conditions. While substrate **3i** underwent phenyl migration in poor yield (Table 1, entry 14), the reaction of substrates with R^1 = Et failed to give furanone formation, providing instead a mixture of unidentified products (Table 1, entries 16 and 18). As observed without $AuCl_3$, a broad variety of trimethylsilyl ethers **3** were effectively converted into the corresponding spirocyclic 4-iodo-3-furanones **5a**−**h** (Table 1, entries 1−13) utilizing both NIS and catalytic amounts of $AuCl_3$ (Method B). Of primary importance, acyclic substrates such as **3j** and **3k** also underwent formation of the desired rearrangement products in the presence of $AuCl_3$, albeit in low yields (Table 1, entries 17 and 19). Since 4-iodo-3-furanones **5a**−**h** are prone to slow decomposition at room temperature, extensive storage should occur at −20 °C.[22]

TABLE 1. Formation of 4-Iodo-3-furanones 5 from Alkynyl Carbonyl Compounds 3[a]



Method A: NIS (1.5 equiv), 23 °C, CH_2Cl_2 (0.1 M)
Method B: $AuCl_3$ (5 mol %), NIS (1.5 equiv), 23 °C, CH_2Cl_2 (0.1 M)

	3					time	yield **5**
entry	R^1	R^2	R^3	no.	method	[min]	[%][a]
1	-$(CH_2)_4$-		Ph	**a**	A	120	88
2					B	20	93
3	-$(CH_2)_4$-		2-thienyl	**b**	A	120	90
4					B	30	99
5	-$(CH_2)_4$-		1-cyclohexenyl	**c**	A	180	88
6					B	30	85
7	-$(CH_2)_4$-		*n*Pent	**d**	A	220	79
8					B	30	90
9	-$(CH_2)_4$-		CH_2OCH_2Ph	**e**	A	120	83
10					B	30	65
11	-$(CH_2)_5$-		Ph	**f**	B	35	60
12[b]				**g**	B	30	68
13[b]				**h**	B	30	73
14	Ph	Ph	Ph	**i**	A	300	37
15					B	30	91
16[c]	Et	Et	Ph	**j**	A	120	0
17					B	150	27
18[c]	Et	Et	*n*Pent	**k**	A	120	0
19					B	30	43

[a] Yield of pure product after column chromatography. [b] **3g** and **3h** are racemic. [c] After complete consumption of **3**, formation of **5** was not observed by ^1H NMR.

A plausible mechanism is shown in Scheme 2. Coordination of the iodine electrophile to the triple bond produces iodonium intermediate **A** (Method A), which after nucleophilic attack of the carbonyl oxygen generates oxonium ion **B**. Subsequent 1,2-shift gives 4-iodo-3-furanone **5** through a formal α-ketol rearrangement.[23] For the gold-catalyzed conversion (Method B),[24] a mechanism was envisaged that proceeds through coordination of the soft cation to the alkynyl functionality (**C**) followed by 1,2-migration of the resulting oxonium ion **D**.

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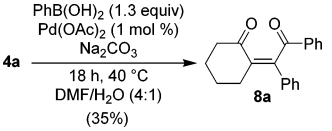
(19) Since the double bond geometry of **4a** could not be determined unequivocally, **4a** was transformed into **8a**. The double bond configuration of **8a** was assigned by ^1H NMR NOE studies



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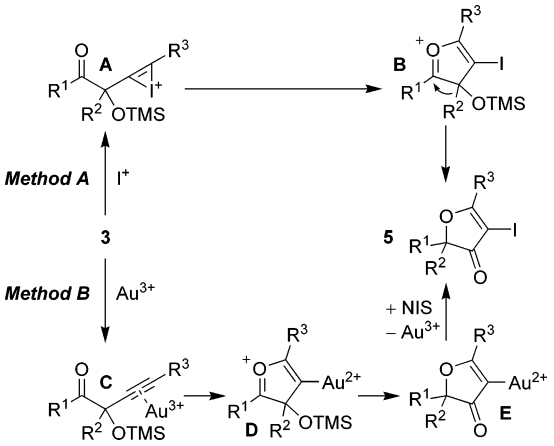
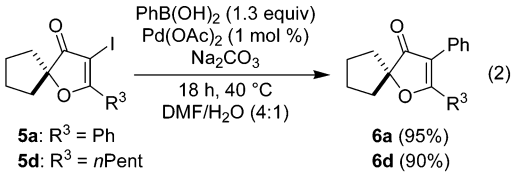
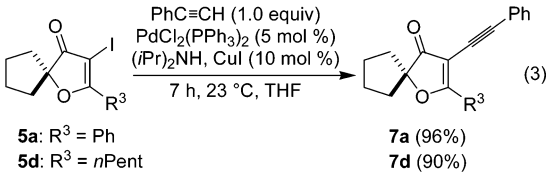
SCHEME 2. Plausible Mechanism



Unlike substrates containing free hydroxy groups (e.g., **1**), the silylated counterparts **3** lack the proton source required for protodemetalation of organogold intermediate **E**. Thus, a rapid iododemetalation[25] in the presence of external NIS might lead to the formation of 3-furanone **5** containing the iodo substituent at C4.

Further transformations of the 4-iodo-3-furanone products using known chemistry were also investigated. For example, Suzuki coupling[5,26] (eq 2) and Sonogashira reaction[27] (eq 3) afforded the anticipated products in good yields, thus accomplishing the synthesis of fully substituted 3(2*H*)-furanones.





In conclusion, two protocols for the synthesis of 4-iodo-3-furanones starting from 2-alkynyl-2-silyloxy carbonyl compounds are described that combine a heterocyclization with a 1,2-alkyl shift. In combination with a subsequent cross-coupling reaction, this transformation provides a convenient and flexible approach to fully substituted 3(2*H*)-furanones.

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Experimental Section

General Experimental Details. All commercially available chemicals were used without further purification. The 2-alkynyl-2-silyloxy carbonyl compounds (**3a**−**k**) were synthesized as previously reported.[13b]

3-Iodo-2-phenyl-1-oxaspiro[4.4]non-2-en-4-one (5a). General Procedure for the 4-Iodo-3-furanone Formation Starting from 2-Alkynyl-2-silyloxy Carbonyl Compounds: Method A. *N*-Iodosuccinimide (59 mg, 0.262 mmol) was added to a solution of **3a** (50 mg, 0.175 mmol) in CH_2Cl_2 (2.5 mL). The reaction vial was sealed and protected from light. The resulting slightly red solution was stirred at room temperature for 120 min (until TLC analysis indicated complete conversion). The mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$ (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica (P/EtOAc = 95/05) gave 4-iodo-3-furanone **5a** as a colorless solid (52 mg, 0.153 mmol, 88%).

Method B. A solution of $AuCl_3$ (5 mol %, 10.6 mg) in MeCN (0.05 mL) was added to a solution of **3a** (200 mg, 0.699 mmol) and *N*-iodosuccinimide (236 mg, 1.049 mmol) in CH_2Cl_2 (13 mL). The reaction vial was sealed and protected from light. The resulting solution was stirred at room temperature for 20 min (until TLC analysis indicated complete conversion). The mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$ (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica (P/EtOAc = 95/05) gave 4-iodo-3-furanon **5a** as a colorless solid (220 mg, 0.647 mmol, 93%). ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.98−2.02 (m, 6 H), 2.08−2.14 (m, 2 H), 7.50−7.53 (m, 2 H), 7.59 (tt, J = 7.0, 1.6 Hz, 1 H), 8.18−8.20 (m, 2 H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 25.9, 38.0, 65.4, 97.2, 128.8, 129.2, 129.9, 132.9, 180.2, 203.3; LRMS (EI) 340 (55) [M^+], 299 (69), 129 (100), 105 (22); HRMS 339.9963 [339.9960 calcd for $C_{14}H_{13}O_2I$ (M^+)].

2,3-Diphenyl-1-oxaspiro[4.4]non-2-en-4-one (6a). General Procedure for the Suzuki-Coupling of 4-Iodo-3-furanones. A solution of Na_2CO_3 (97 mg, 0.915 mmol) in water (0.25 mL) was added to a solution of 4-iodo-3-furanone **5a** (100 mg, 0.294 mmol) and phenylboronic acid (47 mg, 0.382 mmol) in DMF (1 mL). The reaction mixture was degassed with argon for 10 min. After addition of $Pd(OAc)_2$ (0.6 mg, 1 mol %) the reaction mixture was stirred at 40 °C for 18 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl (10 mL) and diluted with Et_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica (P/EtOAc = 98/02) gave furanone **6a** as a colorless solid (81 mg, 0.279 mmol, 95%). ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.95−2.07 (m, 6 H), 2.13−2.20 (m, 2 H), 7.27−7.38 (m, 7 H), 7.46 (tt, J = 7.5, 1.8 Hz, 1 H), 7.63−7.65 (m, 2 H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 26.1, 37.9, 97.4, 115.3, 127.8, 128.7, 128.9, 129.9, 130.4, 130.5, 132.0, 178.8, 205.0; LRMS (EI) 290 (54) [M^+], 249 (100), 178 (48), 105 (35); HRMS 290.1304 [290.1307 calcd for $C_{20}H_{18}O_2$ (M^+)].

2-Phenyl-3-phenylethynyl-1-oxaspiro[4.4]non-2-en-4-one (7a). General Procedure for the Sonogashira-Coupling of 4-Iodo-3-furanones. 4-Iodo-3-Furanone **5a** (96 mg, 0.282 mmol), $PdCl_2(PPh_3)_2$ (11 mg, 0.05 equiv), phenylacetylene (29 mg, 1.0 equiv), and CuI (6 mg, 0.1 equiv) were taken up in THF (2 mL) at 0 °C. Diisoproylamine (91 mg, 3.0 equiv) was added, and the resulting mixture was stirred at 23 °C for 7 h. The reaction mixture was diluted with Et_2O (20 mL) and washed with aqueous HCl (1 M, 20 mL). The layers were separated and the aqueous layer was

extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica (P/EtOAc = 98/02) gave furanone **7a** as a colorless solid (85 mg, 0.271 mmol, 96%). ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.96−2.04 (m, 6 H), 2.12−2.20 (m, 2 H), 7.33−7.39 (m, 3 H), 7.51−7.61 (m, 5 H), 8.36−8.39 (m, 2 H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 26.0, 37.9, 79.5, 98.4, 98.5, 99.5, 123.7, 128.4, 128.6, 128.7, 129.0, 129.8, 131.9, 133.2, 181.5, 203.8; LRMS (EI) 314 (100) [M^+], 286 (27), 202 (18), 105 (63); HRMS 314.1307 [314.1307 calcd for $C_{22}H_{18}O_2$ (M^+)].

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Supporting Information Available: Representative experimental procedures for Method A and Method B, and copies of ^{1}H and ^{13}C NMR of **5**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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