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Electrophile-Induced Cyclization/Migration Reaction for the Synthesis of 2,3-Dihydro-5-iodopyran-4-one

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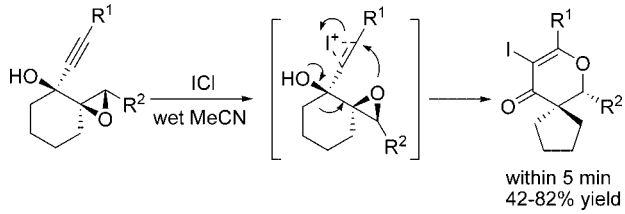
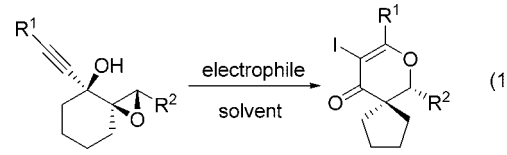


A novel method for the construction of 2,3-dihydro-5-iodopyran-4-one through a domino cyclization/migration reaction of 1-alkynyl-2,3-epoxy alcohol was developed. Wet solvent is essential for this reaction. The resulting iodine-containing product can be readily elaborated to more complex products by using known organopalladium chemistry.

Semipinacol rearrangement is a powerful means of creating a new carbon−carbon bond, frequently with high stereocontrol.[1] It has found wide application in the construct of various structures, such as stereodefined mono- and disubstituted aldol adducts,[2] diols,[3] ketones,[4] ring-expanded[5] and ring-contracted[6] products, β-amino ketones,[7] and β-halo ketones.[8] Furthermore, some more complex structures could be synthesized through the application in a tandem reaction.[9] Despite this, most of these reactions are catalyzed by Lewis acid and the reaction induced by a π-activator is rare.



Electrophilic cyclization has emerged as an important topic in organic chemistry.[10] Many kinds of heterocycles and carbocycles can be constructed by this method. The electrophile has been proven to be very reactive to the unsaturated bond. Recently Kirsch has reported an interesting tandem reaction for the synthesis of 4-iodo-3-furanone from 2-alkynyl-2-silyloxy carbonyl compounds.[11] This reaction was believed to combine the process of a heterocyclization with a 1,2-alkyl shift. As part of our program of electrophile induced reaction,[12] we envisioned that 2,3-dihydro-5-iodopyran-4-one would be produced from the iodo-induced semipinacol reaction of 1-alkynyl-2,3-epoxy alcohol (eq 1). In this paper, we will report our results.

The epoxide alcohol **1a** was synthesized and the reaction was examined under various conditions (Table 1). The reaction was initially examined with 3 equiv of I_2 as the electrophile in the presence of 3 equiv of $NaHCO_3$ in CH_3CN at 0 °C for 12 h (entry 1). The expected rearrangement product **2a** was produced in 60% yield and the enone **3a** was isolated in 23% yield.[13] No reaction was detected with NIS as the reagent. Then ICl was tested in dry CH_3CN and no reaction occurred. However, the

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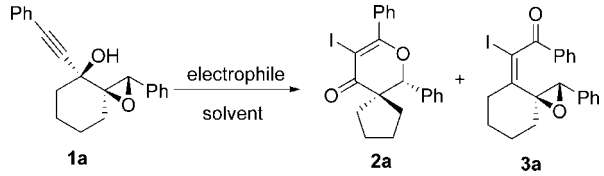
TABLE 1. Optimization of Electrophile Induced Tandem Reaction Conditions[a]



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

				yield (%)	
entry	[I] (equiv)	additives	solvent	**2a**	**3a**
1[b]	I_2 (3.0)	$NaHCO_3$	CH_3CN	60	23
2	ICl (3.0)	$NaHCO_3$	CH_3CN	64 (1:0.24)[c]	
3	ICl (3.0)	Na_2CO_3	CH_3CN	67 (1:0.29)[c]	
4	ICl (3.0)	HOAc	CH_3CN	60 (1:0.35)[c]	
5	ICl (3.0)	H_2O	CH_3CN	71	0
7	ICl (3.0)	H_2O	CH_3OH	66	0
8	ICl (3.0)	H_2O	THF	30[d]	0
9	ICl (3.0)	H_2O	CH_3NO_2	decomposed	
10	ICl (3.0)	H_2O	dioxane	decomposed	
11	ICl (1.5)	H_2O	CH_3CN	40	0

[a] All the reactions were run with 0.1 mmol **1a**, 3 equiv of electrophile, 3 equiv of additive in 1 mL of solvent at 15 °C for 5 min unless otherwise specified; water was used in the ratio of 1/40 of the solvent. [b] The reaction was run for 12 h. [c] The ratio (**2a**:**3a**) was determined by ^1H NMR. [d] About 14% of **1a** was recovered.

reaction could be completed in 5 min after the addition of $NaHCO_3$ (entry 2). Total yield of 64% (**2a**:**3a** = 1:0.24) was achieved with 0.10 mmol of **1a**, 3 equiv of $NaHCO_3$, and 3 equiv of ICl in 1 mL of CH_3CN at 15 °C. Similar results were obtained with other additives such as Na_2CO_3 and HOAc (entries 3 and 4). To our surprise, the addition of water could give the product **2a** exclusively in 71% yield. This result makes the workup process easier. Other solvents, such as MeOH and THF, resulted in lower yields. The substrate decomposed in the solvent dioxane or CH_3NO_2.

With the optimized conditions in hand, various substrates were investigated and the results are summerized in Table 2. The aryl alkynes bearing different functional groups, such as acetyl, methyl, methoxy, chloro, and bromo groups, are readily accommodated under the standard conditions (entries 2−6). Although the reactive acetyl group is contained, **2b** was still obtained in 44% yield. The reaction also tolerated substitution on the alkyne with the alkyl group and a yield of 55% was achieved (entry 7). The substrates with different groups on the oxirane were also investigated: **2h** and **2i** were obtained in 42% and 70% yield. When R^2 = *i*-Pr, **2j** was isolated in 53% yield. Substitution on the cycle also facilitated this process and moderate yields were achieved (entries 11 and 12). By protecting the hydroxy group with TMS, **2a** was isolated in 49% yield. The acyclic compound 2-(phenylethynyl)-7-oxabicyclo[4.1.0]heptan-2-ol was also investigated but it decomposed quickly under the standard conditions.

The utility of 2,3-dihydro-5-iodopyran-4-ones produced by this chemistry as useful synthetic intermediates for further elaboration was briefly investigated by the palladium-catalyzed reaction. The Sonogashira reaction[14] (eq 2) and Suzuki coupling[15] (eq 3) of **2a** afforded the anticipated products in good

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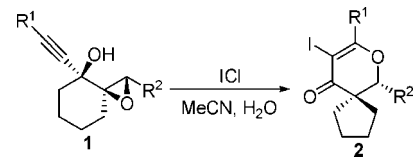
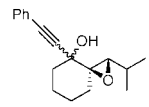
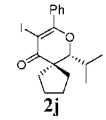
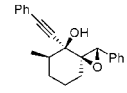
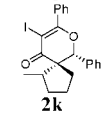
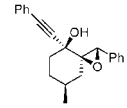
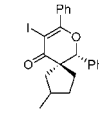
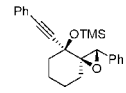
TABLE 2. Synthesis of 2,3-Dihydro-5-iodopyran-4-one from 1-Alkynyl-2,3-epoxy Alcohol[a]

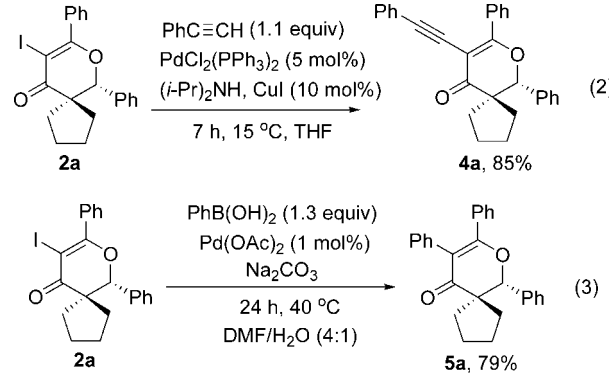


1 **2**

Entry	Substrate			Product	Yield (%)[b]
	R^1	R^2	No.		
1	Ph	Ph	**1a**	**2a**	71
2	p-AcPh	Ph	**1b**	**2b**	44
3	p-MePh	Ph	**1c**	**2c**	77
4	p-MeOPh	Ph	**1d**	**2d**	57
5	p-ClPh	Ph	**1e**	**2e**	82
6	p-BrPh	Ph	**1f**	**2f**	45
7	*n*Pent	Ph	**1g**	**2g**	55
8	Ph	p-MePh	**1h**	**2h**	42
9	Ph	p-ClPh	**1i**	**2i**	70
10			**1j**[c]	 **2j**	53
11			**1k**	 **2k**	62
12			**1l**	 **2l**	50
13			**1m**	**2a**	49

[a] All the reactions were run with 0.2 mmol **1a**, 3 equiv of ICl in 2 mL of wet CH_3CN at 15 °C for 5 min; water was used in the ratio of 1/40 of CH_3CN. [b] Isolated yield. [c] The mixture of diastereoisomers was used.

yields, thus accomplishing the synthesis of fully substituted 2,3-dihydropyran-4-one.



Although the NMR spectroscopic data support the formation of 2,3-dihydro-5-iodopyran-4-one (**2**), the structure was unambiguously secured by an X-ray crystal structure analysis of compound **2a** (Figure 1).

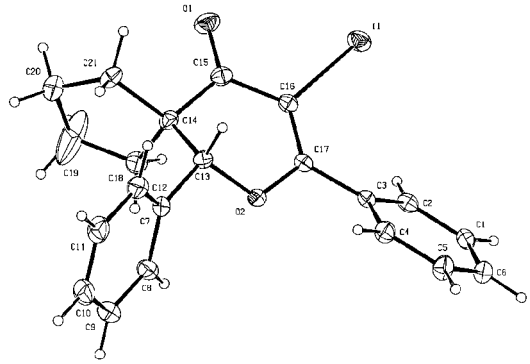
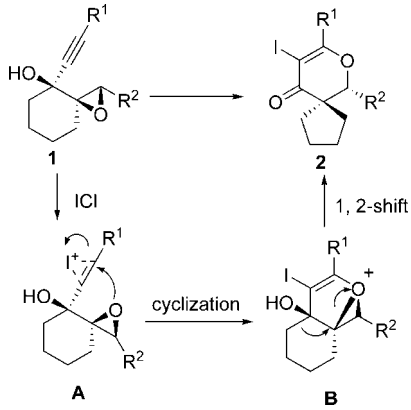


FIGURE 1. X-ray data for **2a**.

SCHEME 1. Plausible Mechanism



An electrophile-induced cyclization/migration mechanism was proposed for this reaction (Scheme 1). Coordination of the iodine electrophile to the triple bond produces iodonium intermediate **A**, which after nucleophilic attack of the oxygen generates oxonium ion **B**. Subsequent 1,2-shift gives 2,3-dihydro-5-iodopyran-4-one through a formal semipinacol rearrangement.[6,16]

In conclusion, an efficient synthesis of highly substituted 2,3-dihydro-5-iodopyran-4-one starting from 1-alkynyl-2,3-epoxy alcohol has been developed that contains a tandem heterocyclization and a 1,2-alkyl shift process. An iodide is readily introduced into the 5-position by using ICl as the electrophile. The resulting iodine-containing products can be readily elaborated to more complex products by using known organopalladium chemistry.

Experiment Section

General Experimental Details. All commercially available chemicals were used without further purification. The 1-alkynyl-2,3-epoxy alcohol compounds (**1a**−**l**) were synthesized as previously reported.[17]

General Procedure for the 2,3-Dihydro-5-iodopyran-4-one Formation. To a solution of **1a** (61 mg, 0.20 mmol) in 2 mL of CH_3CN/H_2O (40:1) was added ICl (97 mg, 0.60 mmol). The mixture was stirred at 15 °C for 5 min. The solution was quenched with aq $Na_2S_2O_3$ (5 mL) and extracted with Et_2O (2 × 10 mL). The combined organic phases were washed with saturated NaCl, dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography on silica (P/EtOAc = 95/05) to give 2,3-dihydro-5-iodopyran-4-one (**2a**) as a light yellow solid (61 mg, 71%): mp 128−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66−7.64 (m, 2H), 7.48−7.36 (m, 8H), 5.49 (s, 1H), 2.31−2.17 (m, 1H), 1.94−1.84 (m, 2H), 1.78−1.53 (m, 3H), 1.40−1.30 (m, 1H), 1.27−1.15 (m, 1H); ^{13}C NMR (75 MHz) δ 193.2, 170.3, 135.5 135.3, 131.1, 129.7, 128.9, 128.4, 128.3, 127.9, 87.3, 55.7, 32.9, 30.5, 25.7; IR (neat, cm^{-1}) 2952, 2868, 1668, 1552, 1447, 1280, 1049, 698. Anal. Calcd for $C_{21}H_{19}IO_2$: C, 58.62; H, 4.45. Found: C, 58.67; H, 4.72.

General Procedure for the Sonogashira Coupling of 2,3-Dihydro-5-iodopyran-4-one (2a). 2,3-Dihydro-5-iodopyran-4-one (**2a**; 86 mg, 0.200 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.05 equiv), phenylacetylene (22 mg, 1.0 equiv), and CuI (4 mg, 0.1 equiv) were taken up in THF (2 mL) at 0 °C. Diisopropylamine (60 mg, 3.0 equiv) was added, and the resulting mixture was stirred at 23 °C for 6 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 2,3-dihydropyran-4-one (**4a**) as a yellow solid (68 mg, 0.168 mmol, 84%): mp 178−180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12−8.09 (m, 2H), 7.52−7.39 (m, 10H), 7.32−7.25 (m, 3H), 5.49 (s, 1H), 2.36−2.26 (m, 1H), 1.93−1.88 (m, 2H), 1.76−1.59 (m, 3H), 1.40−1.29 (m, 1H), 1.23−1.17 (m, 1H); ^{13}C NMR (75 MHz): δ 196.1, 171.2, 135.4, 133.0, 131.7, 131.2, 129.4, 128.8, 128.4, 128.3, 128.1, 128.0, 127.8, 123.7, 99.7, 94.8, 86.9, 83.4, 55.0, 32.0, 30.0, 25.9, 25.8; IR (neat, cm^{-1}) 2954, 2867, 1660, 1552, 1384, 1269, 1140, 751, 693. Anal. Calcd for $C_{29}H_{24}O_2$: C, 86.11; H, 5.98. Found: C, 86.32; H, 5.77.

General Procedure for the Suzuki Coupling of 2,3-Dihydro-5-iodopyran-4-one (2a). A solution of Na_2CO_3 (38 mg, 0.364 mmol) in water (0.10 mL) was added to a solution of 2,3-dihydro-5-iodopyran-4-one (**2a**; 51 mg, 0.117 mmol) and phenylboronic acid (19 mg, 0.152 mmol) in DMF (0.40 mL). The reaction mixture was degassed with argon for 10 min. After addition of $Pd(OAc)_2$ (0.3 mg, 1 mol %) the reaction mixture was stirred at 40 °C for 24 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 2,3-dihydropyran-4-one (**5a**) as a colorless solid (35 mg, 0.092 mmol, 79%): mp 126−128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51−7.49 (m, 2H), 7.44−7.39 (m, 3H), 7.27−7.20 (m, 6H), 7.19−7.11 (m, 2H), 7.08−7.05 (m, 2H), 5.54 (s, 1H), 2.32−2.26 (m, 1H), 1.98−1.94 (m, 2H), 1.75−1.58 (m, 3H), 1.38−1.34 (m, 1H), 1.25−1.16 (m, 1H); ^{13}C NMR (75 MHz) δ 197.1, 166.3, 136.2, 134.5, 133.9, 131.6, 130.1, 129.9, 128.6, 128.5, 128.2, 128.0, 127.7, 126.8, 115.7, 86.3, 54.6, 31.9, 30.0, 25.9; IR (neat, cm^{-1}) 2954, 2868, 1661, 1591, 1566, 1367, 1230, 734, 698. Anal. Calcd for $C_{27}H_{24}O_2$: C, 85.23; H, 6.36. Found: C, 85.48; H, 6.16.

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Supporting Information Available: Experimental details and characterization data for all new compounds and X-ray data of **2a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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