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Remarkable Synthesis of 2-(*Z*)-6-(*E*)-4*H*-[1,4]-Thiazepin-5-ones by Zwitterionic Rhodium-Catalyzed Chemo- and Regioselective Cyclohydrocarbonylative Ring Expansion of Acetylenic Thiazoles

Bernard G. Van den Hoven and Howard Alper*

Contribution from the Centre for Catalysis Research and Innovation, Department of Chemistry, University of Ottawa, 10 Marie Curie St., Ottawa, Ontario, Canada K1N 6N5

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Abstract: Cyclohydrocarbonylative ring expansion of acetylenic thiazoles in the presence of CO, H_2, and catalytic quantities of the zwitterionic rhodium complex (η^6-$C_6H_5BPh_3$)$^-$Rh$^+$(1,5-COD) and triphenyl phosphite affords thiazepinones in 61 to 90% yields. This novel transformation of a 5- to a 7-membered heterocycle is readily applied to acetylenic thiazoles containing hydro, alkyl, alkyl halide, vinyl, and benzo substitutents in positions 4 and 5 of the thiazole ring in addition to alkyl-, ether-, ester-, vinyl-, and aryl-substituted alkynes at position 2.

Introduction

Thiazepinones are pharmacologically important compounds for the treatment of cancer, heart, and inflammatory diseases. These heterocycles aid in treating disease by acting as inhibitors to angitensin converting enzyme (ACE), neutral endopeptidase (NEP),[1] leukocyte adherence,[2] and the inhibition of calcium release in heart mitochondria.[3] These seven-membered heterocycles have been prepared by incorporating addition,[4] condensation,[5] coupling,[6] rearrangement,[7] and thermolysis[8] methodologies in multistep syntheses. In these examples, chirality is introduced prior to or during these transformations. The preparation of a completely unsaturated thiazepinone ring has not been described in the literature. This material would have the potential to be modified and chirality introduced by asymmetric hydrogenation, dihydroxylation,[9] aminohydroxylation,[10] and selenomethoxylation[11] of one of its double bonds.

Transition metal complexes have been advantageously used as catalysts for ring-expansion reactions,[12] and a number of synthetic applications have been simplified due to the availability of these materials. Rhodium complexes have been used for the

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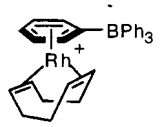
catalytic synthesis of dithionanenones,[13] dioxacycloalkenones,[14] thiazolidines,[15] and diazepinediones.[16] Palladium reagents have provided the means to build isoquinolones,[17] tricyclic compounds,[18] pentadieneamides,[19] thiazenimines,[20] and iminocyclobutanes[21] by catalyzed reactions from appropriate reactants. Piperidinones,[22] mono-cyclic-β-lactams and trans bicyclic-β-lactams,[23] and isoquinoline[24] were obtained by cobalt complexes. Metathesis catalysts were incorporated in the synthesis of bicyclic-β-lactams[25] as well as oxocene derivatives.[26]

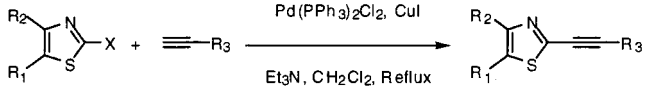
Recently, we reported that the zwitterionic rhodium complex, (η^6-$C_6H_5BPh_3$)$^-$Rh$^+$(1,5-COD) (**1**), with added triphenyl phosphite is an excellent catalytic system for some interesting hydroformylation reactions of α-functionalized alkynes. Treatment of conjugated enynes with CO/H_2 and $(PhO)_3P$ afforded branched formyl dienes,[27] while acetylenic thiophenes preferentially formed unsaturated aldehydes branched to the thiophene ring.[28] Furanones were the dominant products from the cyclohydrocarbonylation of α-ketoalkynes.[29] The functional group adjacent to the triple bond controls the overall chemo- and regioselectivities for these reactions. We reasoned that utilizing the noted catalytic system on conjugated thiazolynes would result in a combination of the chemistry just described. Acetylenic thiazoles incorporate the aromatic sulfur component of a thiophene ring, as well as an imine-like fragment that would compare to a conjugated alkynone. Consequently, it was anticipated that the resulting product would embody an unsaturated thiolactam. We now describe the novel zwitterionic rhodium-catalyzed reaction of simple and functionalized acetylenic thiazoles with carbon monoxide and hydrogen to form 2-(*Z*)-6-(*E*)-4*H*-[1,4]-thiazepin-5-ones in 61 to 90% yields, and in good to excellent chemo- and regioselectivities.



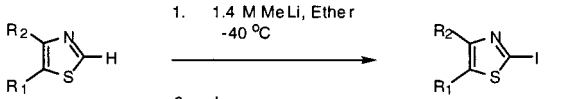
1

Results and Discussion

The requisite acetylenic thiazoles (eq 1) are readily obtained in 56 to 95% yields by the cross-coupling reaction of commercial 2-bromothiazole or presynthesized 2-iodothiazoles with terminal alkynes using catalytic quantities of $Pd(PPh_3)_2Cl_2$ and CuI under basic conditions (Table S1).[30] 2-Iodothiazoles were prepared by subsequent lithiation and iodination of both 4- and 4,5-substituted thiazoles (eq 2) (Table S2).[31] In this manner, 2-acetylenic thiazoles were prepared which contained alkyl-, vinyl-, aryl-, ether-, chloroalkyl-, and ester-substituted groups attached to the heterocyclic ring or the acetylenic unit.

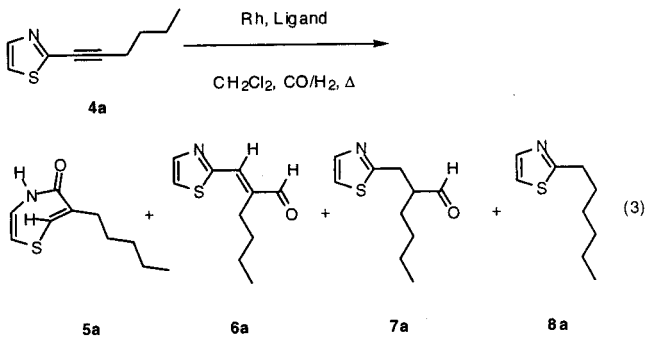


2 **3** **4**



2

Reaction of an acetylenic thiazole **4** (1.5−3.0 mmol) with carbon monoxide (10.5−17.5 atm) and hydrogen (3.5−10.5 atm), in the presence of the zwitterionic rhodium complex **1** (2 mol %) and triphenyl phosphite (8 mol %), at 70−110 °C for 18 to 36 h, afforded the unexpected 2-(*Z*)-6-(*E*)-4*H*-[1,4]-thiazepin-5-ones as the major product with the anticipated unsaturated aldehyde (**6**) and the saturated aldehyde analogue (**7**) as byproducts.



4a **5a** **6a** **7a** **8a**

Given the novel results, the cyclohydrocarbonylation and ring expansion of 2-acetylenic thiazoles was optimized by using 2-hex-1-ynylthiazole (**4a**) as a model substrate. Treating 1.5 mmol of **4a** with 2 mol % **1**, 8 mol % $(PhO)_3P$, 10 mL of CH_2Cl_2, 14 atm of CO, 7 atm of H_2 in a 45 mL autoclave from 70 to 110 °C resulted in a preference for **5a** ranging from 50 to 85% after 20 h and the remainder consisting of a mixture of **6a** and **7a** (Table 1; entries 1, 2, 4, and 6). Changing the pressure to 17.5 atm of CO and 3.5 atm of H_2 from 90 to 110 °C afforded a mixture of **5a** and **6a** in which the selectivity of **5a** was 77 to

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Table 1. Reaction Optimization Using **4a**[a]

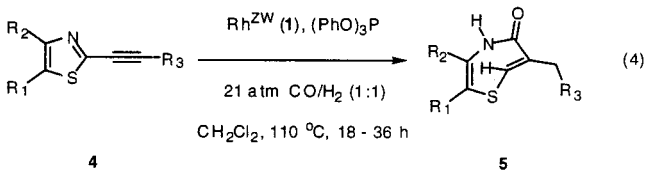
entry	**4a** (mmol)	pressure (atm)	$CO:H_2$	*T* (°C)	conv[b] (%)	**5**:**6**:**7**[c]	% of **5a**[d]
1	1.5	21	2:1	70	90	1:1:t	50
2		21	2:1	90	100	3:1:t	75
3		21	5:1	90	95	3.3:1:t	77
4		21	2:1	100	100	3.3:1:t	77
5		21	5:1	100	95	3.8:1:t	79
6		21	2:1	110	100	11:1:1	85
7		21	5:1	110	100	6.8:1:t	87
8		21	1:1	110	100	9.1:t:1	90
9		14	1:1	110	100	16:1:1	89
10	3.0	21	2:1	110	90	4.9:1:t	83
11		21	1:1	110	95	15:1:1	88

[a] Reaction conditions: **4a**, 1.5−3.0 mmol; **1**, 0.03 mmol (entries 1−9) or 0.06 mmol (entries 10,11) (2 mol %); $(PhO)_3P$, 0.12 mmol (entries 1−9) or 0.24 mmol (entries 10,11) (8 mol %); CH_2Cl_2, 10 mL (entries 1−9) or 20 mL (entries 10,11); 70−110 °C, 20 h. [b] The percent conversion was determined by ^1H NMR. [c] The ratio of **5**:**6**:**7** was determined by ^1H NMR. [d] The percentage of **5a** is based on the ratios of **5**:**6**:**7**.

87% (Table 1; entries 3, 5, and 7). Applying a temperature of 110 °C and a 1:1 ratio of CO/H_2 at a total pressure of 14 and 21 atm resulted in a selectivity for **5a** of 89 and 90%, respectively (Table 1, entries 8 and 9). Increasing the substrate (**4**) from 1.5 to 3.0 mmol and the total volume from 10 to 20 mL of CH_2Cl_2 at 110 °C affords **5a** in 83% selectivity using 21 atm of CO/H_2 in a 2:1 ratio (Table 1, entry 10) and **5a** in 88% selectivity (86% isolated yield) with use of a 1:1 ratio of CO/H_2 (Table 1, entry 11). The latter entry demonstrates thiazepinone production is readily achieved in a reasonable time frame using moderate temperatures and mild CO/H_2 pressures.

Additional ligands and rhodium complexes were examined to determine the uniqueness of the present catalytic system incorporating the conditons of Table 1, entry 8. No reaction takes place with the zwitterionic rhodium complex **1** in the absence of an added ligand. Changing the ligand from $(PhO)_3P$ to $(^iPrO)_3P$, Ph_3P, and dppb gives **5a** in low selectivity and conversion with the addition of the hydrogenated thiazolyne **8a**. The rhodium complexes $Rh(CO)_2acac$, $[Cl(C_2H_4)_2Rh]_2$, and $[Cl(CO)_2Rh]_2$ favor **5a** in lower selectivity along with a mixture of the hydroformylated products **6a** and **7a**. No reaction occurred using catalytic quantities of $RhCl_3$ and $(PhO)_3P$. The catalytic system comprised of the zwitterionic rhodium complex (**1**) and triphenyl phosphite is preferred for obtaining thiazepin-5(4*H*)-one in excellent chemo- and regioselectivity, compared with other rhodium complexes and phosphorus ligands.

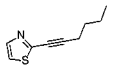
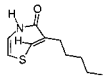
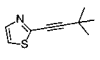
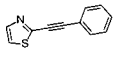
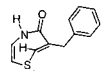
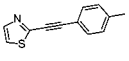
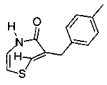
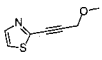
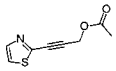
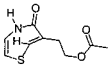
The scope of the acetylenic thiazole/thiazepin-5-one reaction was investigated using thiazolynes with modified alkyne components (Table 2) and altered thiazole rings (Table 3), and imploying the reaction conditions described in Table 1, entry 11 (eq 4). Thiazolynes **4**, unsubstituted at the 4- and 5-positions



(4)

of the heterocycle (i.e. $R_1 = R_2 = H$), and where the acetylenic unit contains an alkyl or aryl substituent (i.e. R_3), react under the noted conditions affording **5a**−**d** in 86 to 90% isolated yields of pure thiazepin-5-ones (Table 2, entries 1 to 4). The 2-(*Z*)-6-(*E*)-4*H*-[1,4]-thiazepin-5-ones, **5e**−**g**, were obtained in 61 to 74% isolated yields when the R_3 group of the alkyne unit was

Table 2. Cyclohydrocarbonylation of Acetylenic Thiazoles with Different Substituents in the Acetylenic Unit[a]

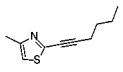
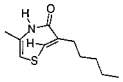
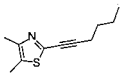
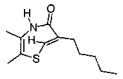
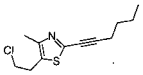
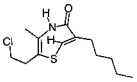
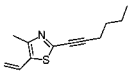
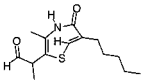
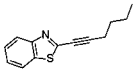
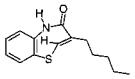
Entry	**4**	t (h)	**5**	Isolated Yield (%)[b]
1	 **4a**	24	 **5a**	86
2	 **4b**	36	 **5b**	89
3	 **4c**	18	 **5c**	90
4	 **4d**	18	 **5d**	87
5[c]	 **4e**	24	 **5e**	72
6[c]	 **4f**	24	 **5f**	74
7[c]	 **4g**	24	 **5g**	61

[a] Reaction conditions: **4**, 3.0 mmol; **1**, 0.06 mmol (2 mol %); $(PhO)_3P$, 0.24 mmol (8 mol %); CH_2Cl_2, 20 mL; CO, 10.5 atm; H_2, 10.5 atm; 110 °C. [b] The reactions proceeded to full conversion (obtained by NMR), and products were isolated by silica gel chromatography with 0:100 to 5:95 $MeOH:CH_2Cl_2$. [c] 70 °C.

an alkyl ether, alkyl ester, or vinyl substituent (Table 2, entries 5 to 7). Note that 2-(3-methylbut-3-en-1-ynyl)thiazole (**4e**) afforded only one thiazepinone in 72% yield (Table 2. entry 5). Effecting reactions of **4e**−**f** at 110 °C instead of 70 °C reduced the yields of **5e**−**g** and substantially increased the proportions of **6** and **7**. Therefore, these substrates react in a significantly temperature-dependent fashion. The occurrence of more **6** and **7** using **4e**−**g** may be explained by the ability of the rhodium catalyst to coordinate with ether, ester, and vinyl functionalities prior to the intramolecular insertion of the catalyst to the triple bond of the thiazolyne. Prior coordination stimulates rhodium insertion to occur on either side of the triple bond near a functionality, as observed in previous studies.[27−29] At lower temperature coordination of the metal to the thiazole ring is preferred to coordination of the metal to the competing functionality.

The conversion of acetylenic thiazoles to 2-(*Z*)-6-(*E*)-4*H*-[1,4]-thiazepin-5-ones also proceeds nicely using substrates substituted at the 4- or 4,5-positions of the reactant. The thiazepin-5-one, **5h**, was isolated in 83% yield using **4h** (R_1 = H, R_2 = Me, and R_3 = n-Bu; Table 3, entry 1). Changing R_1 from H to methyl, chloroethyl, or vinyl afforded the thiazepin-5-ones in 78−81% yields (Table 3, entries 2−4). While the chloroethyl substituent is completely inert under the reaction conditions, the vinyl group reacts in a completely regioselective manner to form the branched chain aldehydic thiazepin-5-one. Finally, the cyclohydrocarbonylation/ring expansion process is applicable to a benzothiazole, i.e., **4l** gave the benzothiazepin-4(5*H*)-one (**5l**) in 76% isolated yield (Table 3, entry 5). This is a particularly impressive result for the cyclohydrocarbonylative

Table 3. Cyclohydrocarbonylation of Acetylenic Thiazoles Containing Substituents at the 4- and 4,5-Positions[a]

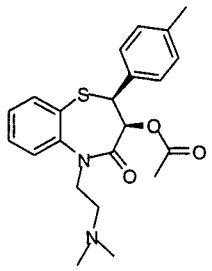
Entry	4	t (h)	5	Isolated Yield (%) [b]
1	 **4h**	24	 **5h**	83
2	 **4i**	18	 **5i**	78
3	 **4j**	18	 **5j**	79
4	 **4k**	18	 **5k**	81
5	 **4l**	18	 **5l**	76

[a] Reaction conditions: **4**, 3.0 mmol; **1**, 0.06 mmol (2 mol %); $(PhO)_3P$, 0.24 mmol (8 mol %); CH_2Cl_2, 20 mL; CO, 10.5 atm; H_2, 10.5 atm; 110 °C. [b] The reactions proceeded to full conversion (obtained by NMR), and products were isolated by silica gel chromatography with 0:100 to 5:95 MeOH:CH_2Cl_2.

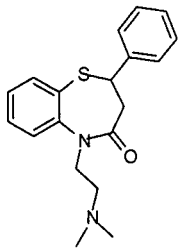
ring expansion reaction, as benzothiazepinones are excellent candidates for evaluation as pharmacologically active compounds.

A possible mechanism for the conversion of acetylenic thiazoles to the thiazepin-5-ones is outlined in Scheme 1. The active rhodium complex (**9**), formed from complex **1**, binds to the thiazolyne via the triple bond and a heteroatom (**10**) or possibly by H-bonding to the thiazole ring (**11**). Depending on the equilibrium between **10** and **11** two products will result. If **11** is favored, subsequent intramolecular insertion of the H−Rh bond to the alkyne would generate **12**. Carbonylation (**13**) of the latter and subsequent addition of hydrogen would give the hydroformylation product **6**. However, if **10** is favored, the intramolecular hydrorhodation would proceed in the opposite manner to form **14**, carbonylation of which would give **15**, coordination with the heterocyclic nitrogen could then afford **16**. Intermediate **16** can undergo intramolecular cyclization resulting in the formation of a β-lactam with allyl-type bonding to Rh (**17**). Hydrogen addition to **17** may afford a strained azetinone-Rh hydride (**18**). Hydrogen transfer with ring opening would form **19** as the *E*-isomer with nitrogen coordinated to the rhodium. Addition of hydrogen completes the thiazepinone ring (**5**) and regenerates the rhodium complex **9**.

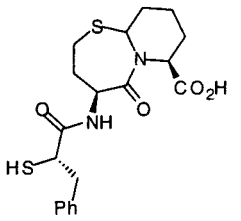
In conclusion, a remarkable synthesis of 2-(*Z*)-6-(*E*)-[1,4]-thiazepin-5-ones was discovered by the reaction of acetylenic thiazoles with CO/H_2 in the presence of catalytic amounts of **1** and triphenyl phosphite. The process is general, and tolerates the presence of functional groups including ether, ester, and chloro. The reactions are simple in execution and workup, and while the thiazepin-5(4*H*)-ones are of significant intrinsic interest, modification of the heterocycles may lead to valuable pharmaceuticals such as diltiazem, BMS-186716, and their analogues.



Diltiazem



Thiazesim



BMS-186716

[Commercial Thiazepinones]

Experimental Section

Materials. 2-Bromothiazole, all thiazoles, and terminal alkynes were purchased from commercial sources. The rhodium complexes chlorobis(ethylene)rhodium(I) dimer, chlorodicarbonylrhodium(I) dimer, dicarbonylrhodium(I) acetoacetonate, and rhodium(III) chloride were purchased from Strem. The zwitterionic rhodium complex (η^6-C_6H_5B-$Ph_3)^-Rh^+$(1,5-COD) (**1**) was prepared according to the procedure of Schrock and Osborn.[32] All solvents were dried and distilled under N_2 prior to use.

General Procedure for the Pd/CuI Coupling of 2-Halothiazoles to Terminal Alkynes. To a 100-mL round-bottom flask purged with N_2 was added triethylamine (20 mL), the terminal alkyne (**3**) (25−30 mmol), CH_2Cl_2 (40 mL), the 2-halothiazole (**2**) (20 mmol), $Pd(PPh_3)_2Cl_2$ (0.2 mmol), and CuI (0.2 mmol), and the mixture was heated to reflux (65 °C) for 6−18 h. Ether (50 mL) was added to the reaction mixture leading to the precipitation of $Et_3NH^+X^-$. The resulting mixture was filtered, evaporated, isolated by silica gel chromatography using a MeOH:CH_2Cl_2 gradient ranging from 0:100 to 5:95, and further purified if necessary by Kugelrohr distillation to give **4** (Table S1).[33]

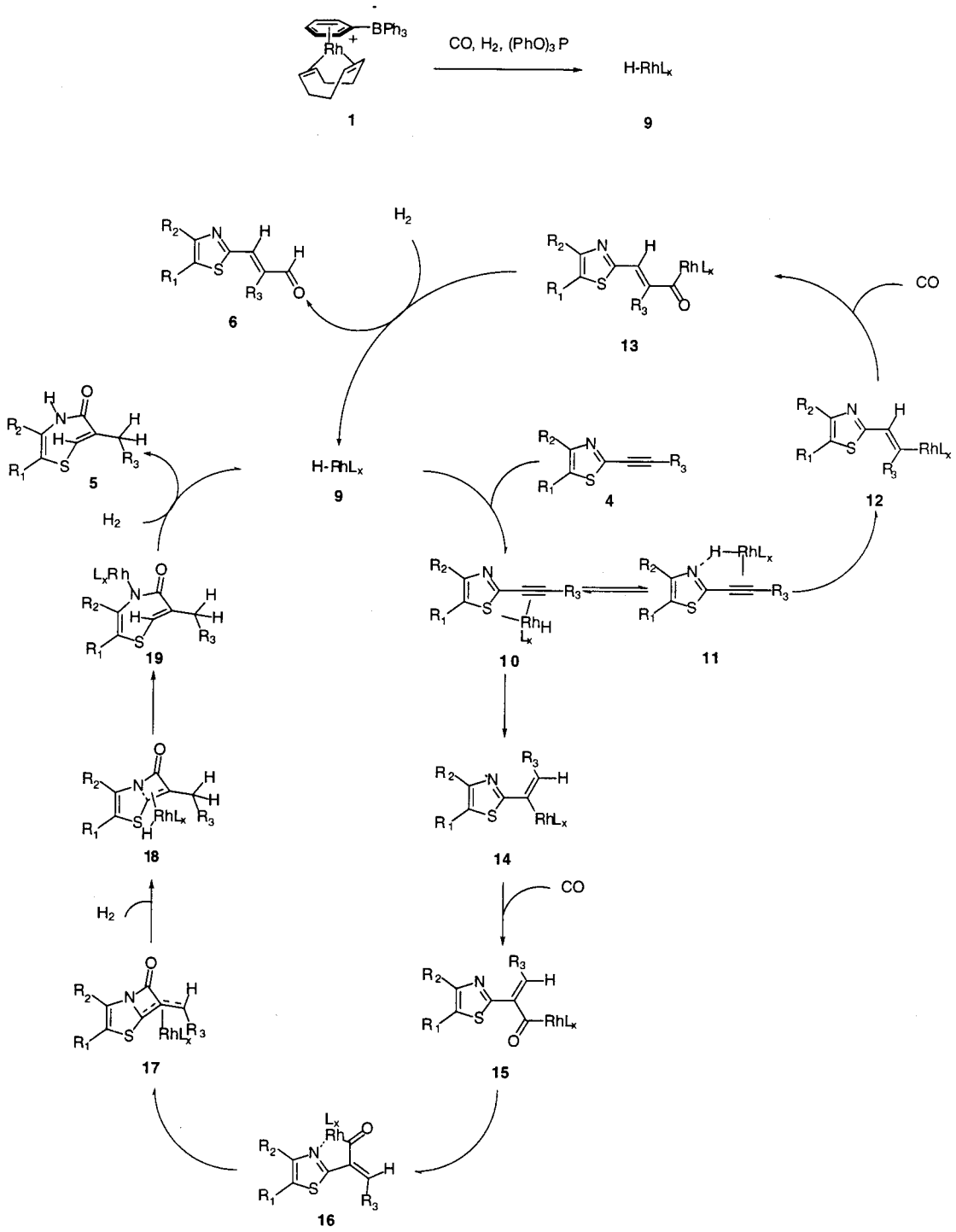
General Procedure for the Preparation of Substituted 2-Iodothiazoles. To a 250-mL round-bottom flask purged with N_2 was added ether (100 mL) and the thiazole (50 mmol), and the mixture was cooled in a dry ice/MeOH bath. An excess amount of 1.4 M MeLi (40 mL) was added over a 15 min time period followed by I_2 (60 mmol), and the reaction mixture was allowed to warm to room temperatue. The reaction mixture was transferred to a separatory funnel, ether (300 mL) was added, and then the organic layer was washed with water (100 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, and evaporated. The product (**2**) was isolated by silica gel chromatography with CH_2Cl_2 as eluant, and further purified by sublimation (Table S2).[33]

General Procedure for the Cyclohydrocarbonylative Ring Expansion of Conjugated Thiazolynes. To a 45-mL autoclave containing a glass liner and stirring bar was placed the zwitterionic rhodium complex **1** (0.06 mmol), triphenyl phosphite (0.24 mmol), acetylenic thiazole **4** (3 mmol), and CH_2Cl_2 (20 mL). The autoclave was flushed three times with carbon monoxide and pressurized to 10.5 atm followed by the introduction of hydrogen to a total pressure of 21 atm. The autoclave was placed in an oil bath at 110 °C for 18 to 36 h, and then

(32) Schrock, P. R.; Osborn, J. A. *Inorg. Chem.* **1970**, *9*, 2339.

(33) Please see the Supporting Information for additional information on the preparation of acetylenic thiazoles (**4**) and iodothiazoles (**2**).

Scheme 1. Proposed Mechanism



allowed to cool to room temperature. The autoclave was depressurized, the reaction mixture was filtered through Celite, and the solvent was removed by rotary evaporation. The resulting residue was purified by silica gel chromatography with use of a MeOH:CH_2Cl_2 gradient ranging from 0:100 to 5:95 as the eluant to afford product **5** (Tables 2 and 3).

2-(*Z*)-6-(*E*)-6-Pentyl-4*H*-[1,4]-thiazepin-5-one (5a): colorless liquid; IR ν(C=O) 1626 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 12.61 (s, 1H), 7.66 (d, 1H, J = 3.4 Hz), 7.03 (d, 1H, J = 3.6 Hz), 6.87 (s, 1H), 2.27 (t, 2H, J = 6.8 Hz), 1.47−1.60 (m, 2H), 1.26−1.36 (m, 4H), 0.87 (t, 3H, J = 7.0 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 170.8, 149.9, 144.4, 114.4, 107.1, 31.5, 30.5, 28.7, 28.7, 22.4, 14.0; EI MS (*m*/*z*) 197 [M$^+$]; HRMS calculated for $C_{10}H_{15}NOS$ [M$^+$] 197.08743, found 197.08876.

(*E*)-2-Butyl-3-thiazol-2-ylpropenal (6a): colorless liquid; IR ν(C=O) 1685 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.99 (d, 1H, J = 3.2 Hz), 7.55 (d, 1H, J = 3.2 Hz), 7.39 (s, 1H), 2.72 (t, 2H, J = 7.4 Hz), 1.36−1.45 (m, 4H), 0.89 (t, 3H, J = 7.2 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 194.5, 162.0, 145.1, 144.6, 139.5, 122.6, 29.7, 25.2, 23.0, 13.8; EI MS (*m*/*z*) 195 [M$^+$]; HRMS calculated for $C_{10}H_{13}NOS$ [M$^+$] 195.07178, found 195.07199.

2-(*Z*)-6-(*E*)-6-(2,2-Dimethylpropyl)-4*H*-[1,4]-thiazepin-5-one (5b): colorless liquid; IR ν(C=O) 1619 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 13.01 (br, 1H), 7.61 (d, 1H, J = 3.2 Hz), 7.03 (d, 1H, J = 3.2 Hz), 6.89 (s, 1H), 2.20 (s, 2H), 0.90 (s, 9H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 172.4, 152.9, 139.8, 113.9, 104.3, 44.2, 32.4, 29.6; EI MS (*m*/*z*) 197 [M$^+$]; HRMS calculated for $C_{10}H_{15}NOS$ [M$^+$] 197.08743, found 197.08783.

2-(*Z*)-6-(*E*)-6-Benzyl-4*H*-[1,4]-thiazepin-5-one (5c): yellow liquid; IR ν(C=O) 1627 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 12.91 (br, 1H), 7.72 (d, 1H, J = 3.4 Hz), 7.30−7.37 (m, 5H), 7.08 (d, 1H, J = 3.6

Hz), 7.07 (s, 1H), 3.71 (s, 2H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 170.6, 151.6, 140.0, 138.7, 128.5, 128.3, 126.5, 114.9, 106.2, 36.4; EI MS (*m*/*z*) 217 [M^+]; HRMS calculated for $C_{12}H_{11}NOS$ [M^+] 217.05613, found 217.05522.

2-(*Z*)-6-(*E*)-6-(4-Methylbenzyl)-4*H*-[1,4]-thiazepin-5-one (5d): yellow liquid; IR ν(C═O) 1627 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 12.80 (br, 1H), 7.72 (d, 1H, J = 3.4 Hz), 7.28 (d, 2H, J = 8.0 Hz), 7.18 (d, 2H, J = 8.2 Hz), 7.09 (s, 1H), 7.08 (d, 1H, J = 3.6 Hz), 3.68 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 170.0, 151.4, 139.9, 136.0, 135.6, 129.0, 128.4, 114.8, 106.3, 35.9, 20.9; EI MS (*m*/*z*) 231 [M^+]; HRMS calculated for $C_{13}H_{13}NOS$ [M^+] 231.07178, found 231.07116.

2-(*Z*)-6-(*E*)-6-(2-Methylpropenyl)-4*H*-[1,4]-thiazepin-5-one (5e): yellow liquid; IR ν(C═O) 1614 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 12.43 (br, 1H), 7.64 (d, 1H, J = 3.4 Hz), 7.03 (d, 1H, J = 3.4 Hz), 6.89 (s, 1H), 5.74 (s, 1H), 1.82 (s, 3H), 1.72 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 170.9, 152.1, 140.2, 138.6, 117.9, 114.8, 106.1, 25.6, 19.4; EI MS (*m*/*z*) 181 [M^+]; HRMS calculated for $C_9H_{11}NOS$ [M^+] 181.05613, found 181.05572.

2-(*Z*)-6-(*E*)-6-(2-Methoxyethyl)-4*H*-[1,4]-thiazepin-5-one (5f): colorless liquid; IR ν(C═O) 1626 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 12.75 (br, 1H), 7.67 (d, 1H, J = 3.4 Hz), 7.10 (d, 1H, J = 3.6 Hz), 6.95 (s, 1H), 3.63 (t, 2H, J = 7.2 Hz), 3.33 (s, 3H), 2.56 (t, 2H, J = 7.0 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 170.5, 151.6, 140.4, 114.4, 103.8, 71.7, 58.6, 30.9; EI MS (*m*/*z*) 185 [M^+]; HRMS calculated for $C_8H_{11}NO_2S$ [M^+] 185.05105, found 185.05066.

2-(*Z*)-6-(*E*)-6-(2-Acetylethoxy)-4*H*-[1,4]-thiazepin-5-one (5f): colorless liquid; IR ν_1(C═O) 1739 cm^{-1}, ν_2(C═O) 1627 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 12.82 (br, 1H), 7.70 (d, 1H, J = 3.6 Hz), 7.14 (d, 1H, J = 3.4 Hz), 6.99 (s, 1H), 4.23 (f, 2H, J = 6.8 Hz), 2.64 (t, 2H, J = 7.0 Hz), 2.05 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 170.9, 169.9, 152.0, 143.8, 140.4, 114.5, 102.9, 63.0, 29.9, 20.9; EI MS (*m*/*z*) 213 [M^+]; HRMS calculated for $C_9H_{11}NO_3S$ [M^+] 213.04596, found 213.04697.

2-(*Z*)-6-(*E*)-3-Methyl-6-pentyl-4*H*-[1,4]-thiazepin-5-one (5h): colorless liquid; IR ν(C═O) 1627 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 12.78 (br, 1H), 6.88 (s, 1H), 6.63 (s, 1H), 2.39 (s, 3H), 2.24 (t, 2H, J = 7.4 Hz), 1.51−1.58 (m, 2H), 1.27−1.34 (m, 4H), 0.88 (t, 3H, J = 6.8 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 170.0, 150.5, 150.0, 108.9, 107.0, 31.4, 30.2, 28.8, 22.4, 16.7, 14.0; EI MS (*m*/*z*) 211 [M^+]; HRMS calculated for $C_{11}H_{17}NOS$ [M^+] 211.10308, found 211.10110.

2-(*Z*)-6-(*E*)-2,3-Dimethyl-6-pentyl-4*H*-[1,4]-thiazepin-5-one (5i): colorless liquid; IR ν(C═O) 1628 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 12.78 (br, 1H), 6.90 (s, 1H), 2.36 (s, 3H), 2.31 (s, 3H), 2.23 (t, 2H, J = 7.0 Hz), 1.59−1.63 (m, 2H), 1.32−1.39 (m, 4H), 0.95 (t, 3H, J = 6.6 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 166.0, 149.5, 145.3, 121.5, 106.6, 31.3, 30.1, 28.8, 22.3, 14.1, 13.9, 10.9; EI MS (*m*/*z*) 225 [M^+]; HRMS calculated for $C_{12}H_{19}NOS$ [M^+] 225.11873, found 225.12050.

2-(*Z*)-6-(*E*)−(2-Chloroethyl)-3-methyl-6-pentyl-4*H*-[1,4]-thiazepin-5-one (5j): yellow oil; IR ν(C═O) 1626 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 12.60 (br, 1H), 6.85 (s, 1H), 3.64 (t, 2H, J = 7.4 Hz), 3.15 (t, 2H, J = 7.2 Hz), 2.30 (s, 3H), 2.20 (t, 2H, J = 7.2 Hz), 1.49−1.60 (m, 2H), 1.25−1.32 (m, 4H), 0.87 (t, 3H, J = 6.8 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 167.6, 150.1, 147.0, 122.7, 106.8, 44.3, 31.4, 30.2, 29.6, 28.8, 22.4, 14.6, 14.0; EI MS (*m*/*z*) 273 [M^+]; HRMS calculated for $C_{13}H_{20}NOClS$ [M^+] 273.09541, found 273.09470.

2-(2-(*Z*)-6-(*E*)-3-Methyl-5-oxo-6-pentyl-4,5-dihydro-[1,4]-thiazepin-2-yl)propanal (5k): yellow oil; IR ν_1(C═O) 1731 cm^{-1}, ν_2(C═O) 1625 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 12.58 (br, 1H), 9.62 (d, 1H, J = 1.4 Hz), 6.90 (s, 1H), 3.93 (qd, 1H, J = 7.2, 1.6 Hz), 2.38 (s, 3H), 2.26 (t, 2H, J = 7.0 Hz), 1.48−1.61 (m, 2H), 1.50 (d, 3H, J = 7.0 Hz), 1.30−1.39 (m, 4H), 0.92 (t, 3H, J = 6.8 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 198.8, 169.2, 150.6, 148.0, 123.9, 107.5, 45.7, 32.0, 30.9, 29.4, 23.0, 16.3, 15.5, 14.6; EI MS (*m*/*z*) 267 [M^+]; HRMS calculated for $C_{14}H_{21}NO_2S$ [M^+] 267.12930, found 267.13017.

2-(*E*)-3-Pentyl-5*H*-[1,4]-benzothiazepin-4-one (5l): yellow oil; IR ν(C═O) 1621 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 13.25 (s, 1H), 7.74 (d, 2H, J = 8.2 Hz), 7.43−7.51 (m, 1H), 7.27−7.34 (m, 1H), 7.23 (s, 1H), 2.37 (t, 2H, J = 7.6 Hz), 1.62−1.73 (m, 2H), 1.36−1.45 (m, 4H), 0.97 (t, 3H, J = 6.6 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 171.0, 155.6, 151.4, 131.8, 127.0, 124.7, 122.0, 120.9, 107.6, 32.0, 30.9, 29.8, 23.1, 14.7; EI MS (*m*/*z*) 247 [M^+]; HRMS calculated for $C_{14}H_{17}NOS$ [M^+] 247.10308, found 247.10076. Anal. Calcd for $C_{14}H_{17}NOS$: C, 67.98; H, 6.93; N, 5.66. Found: C, 68.25; H, 6.95; N, 5.84.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada for support of this research.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **2b**−**2f**, **4a**−**4l**, **5a**−**5l**, and **6a** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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