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Highly Regioselective Synthesis of Tetrahydro-2*H*-1,3-thiazin-2-ones via Rhodium-Catalyzed Carbonylation of *N*-Alkylisothiazolidines

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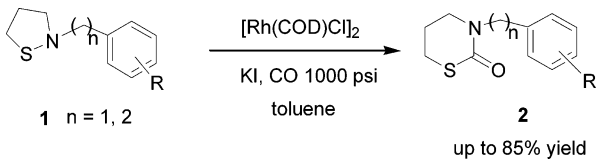
ABSTRACT



The [Rh(COD)Cl]$_2$- and KI-catalyzed carbonylation of functionalized *N*-alkylisothiazolidines in toluene gives the corresponding tetrahydro-2*H*-1,3-thiazin-2-ones in good yield. The carbonylation reaction occurred site-selectively at the S–N bond of the isothiazolidine ring. The reaction is believed to proceed via oxidative addition, followed by CO insertion and reductive elimination to form the tetrahydro-2*H*-1,3-thiazin-2-one derivatives.

The transition-metal-catalyzed carbonylation of heterocycles is an attractive method in organic synthesis. In most cases, the carbonylation reaction provides a very convenient and effective one-step procedure for ring homologation and gives rise to heterocyclic derivatives that are not readily accessible or are unavailable through conventional methods. A number of valuable carbonyl-containing compounds can be prepared in this way from the corresponding simple heterocyclic substrates.[1] Most examples of this type of reaction have involved the ring-expanding or ring-opening carbonylation of substrates with considerable ring strain.[2−9] Although the carbonylation of heterocycles containing one heteroatom has been investigated in considerable detail, few examples have been reported so far using heterocycles with two or more heteroatoms. During the course of our studies of the development of transition-metal-catalyzed carbonylation methods,[9−12] we recently reported that the carbonylation of isoxazolidines proceeded with insertion of CO into the N−O

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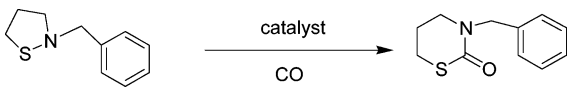
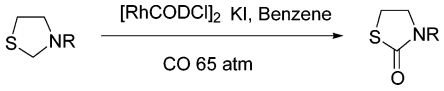
Table 1. Carbonylation of N−Benzylisothiazolidine to 2*H*-1,3-Thiazin-2-one, Tetrahydro-3-(phenyl methyl)[a]



entry	catalyst (%)	solvent	CO (psi)	temp (°C)	yield (%)[b]
1	$[RhCODCl]_2$ (5)	benzene	1000	130	70[c]
2	$Co_2(CO)_8$ (5)	benzene	1000	130	30
3	$[RhCODCl]_2$ (5)	benzene	1000	130	58
4	$[RhCODCl]_2$ (2.5)	benzene	1000	130	45[c]
5	$[RhCODCl]_2$ (5)	benzene	800	130	66[c]
6	$[RhCODCl]_2$ (5)	benzene	600	100	
7	$[RhCODCl]_2$ (5)	toluene	600	130	65[c]
8	$[RhCODCl]_2$ (5)	toluene	1000	130	75[c]
9	$[RhCODCl]_2$ (5)	CH_2Cl_2	1000	130	35
10	$Pd(OAc)_2$ (5)	benzene	1000	130	10
11	$RuCl_2(PPh_3)_2$ (5)	benzene	1000	130	
12	$Pd(OAc)_2$ (5) PPh_3 (20)	benzene	1000	130	
13	$Pd_2(dba)_3$ (5)	benzene	1000	120	

[a] Reaction conditions: *N*-benzylisothiazolidine (0.5 mmol), catalyst, CO for 24 h. [b] Isolated yield. [c] 5 mol % KI was added.

bond, affording tetrahydro-1,3-oxazin-2-ones in 20−82% yield with $[Rh(COD)Cl]_2$ as the catalyst.[13] Also, an unusual regiospecific insertion of carbon monoxide and ketene elimination were observed for the rhodium-catalyzed carbonylation of thiazolidines, with thiazolidinones formed in good yield (eq 1).[14] However, quite drastic reaction conditions (e.g., high temperature) are required for these transformations, presumably because the five-membered ring compounds lack strain energy and are quite stable.



(1)

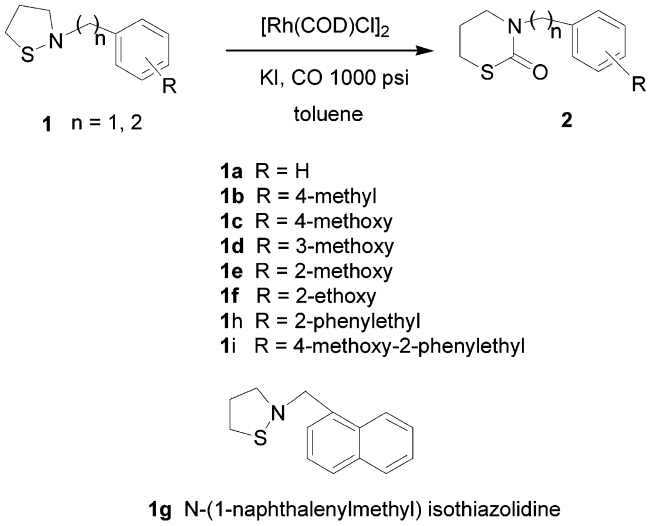
In contrast, to our knowledge there is no report on the effective carbonylation of isothiazolidines. It was anticipated that should such a reaction take place, it would lead to the formation of tetrahydro-2*H*-1,3-thiazin-2-ones, which are important building blocks for the synthesis of some natural and biologically active compounds.[15] In particular, the regioselectivity of the ring-expansion reaction of N−S containing five-membered ring heterocycles is a matter of considerable interest. Herein, we describe the first rhodium-catalyzed site-selective carbonylation reaction of *N*-alkylisothiazolidines for the synthesis of tetrahydro-2*H*-1,3-thiazin-2-ones in good yield under relatively mild reaction conditions.

The reaction of *N*-benzylisothiazolidine (**1a**) with carbon monoxide was first investigated under different reaction conditions (Table 1). When *N*-benzylisothiazolidine was reacted with 5 mol % (1,5-cyclooctadiene)rhodium(I) dimer as the catalyst in benzene, at 130 °C and 1000 psi of carbon monoxide for 24 h, the corresponding 2*H*-1,3-thiazin-2-one, tetrahydro-3-(phenylmethyl) was obtained in 58% yield (entry 3, Table 1). In the presence of 5 mol % of potassium iodide, carbonylation proceeded very well, forming the thiazin-2-one as the major product in 70% yield under the same reaction conditions (entry 1, Table 1). In all reactions investigated, the carbonylation reaction occurred selectively at the N−S bond of the isothiazolidine. No product of insertion into the C−N or C−S bond was detected. In the ^1H NMR spectra of the product, the signals for the proton attached to the carbon next to the N atom are shifted downfield by approximately 1 ppm on introduction of a CO unit. The ^{13}C NMR spectra display the carbonyl signal in the expected chemical shift region of 165 ppm.

Other catalysts were employed for the carbonylation reaction of **1a**. Whereas cobalt carbonyl gave **2a** in 30% yield (entry 2, Table 1), no carbonylation occurred when $Pd(OAc)_2$, $RuCl_2(PPh_3)_2$, $Pd_2(dba)_3$, or $Pd(OAc)_2/PPh_3$ were used as catalysts (entries 10−13). The solvent was next examined. When toluene was used for the reaction of **1a**, **2a** was formed in 75% yield (entry 8, Table 1), whereas the yield was 35% using CH_2Cl_2 (entry 9, Table 1). When the reaction of **1a** was conducted using 600 psi of carbon monoxide (i.e., at lower CO pressure) and 5 mol % $[Rh(COD)Cl]_2$ at 100 °C, *N*-benzylisothiazolidine was recovered unchanged (entry 6, Table 1).

On the basis of these results, we concluded that the catalytic system consisting of 5 mol % $[Rh(COD)Cl]_2$ and KI under 1000 psi CO in toluene is the best for this carbonylation reaction. The scope of the reaction was investigated with a variety of isothiazolidines (Scheme 1), and the results are summarized in Table 2. The reactant isothiazolidines (**1a**−**i**) were prepared according to the literature by [2,3]-sigmatropic rearrangement of allyl-3-alkylaminopropyl sulfoxide to the sulfenates, followed by

Scheme 1



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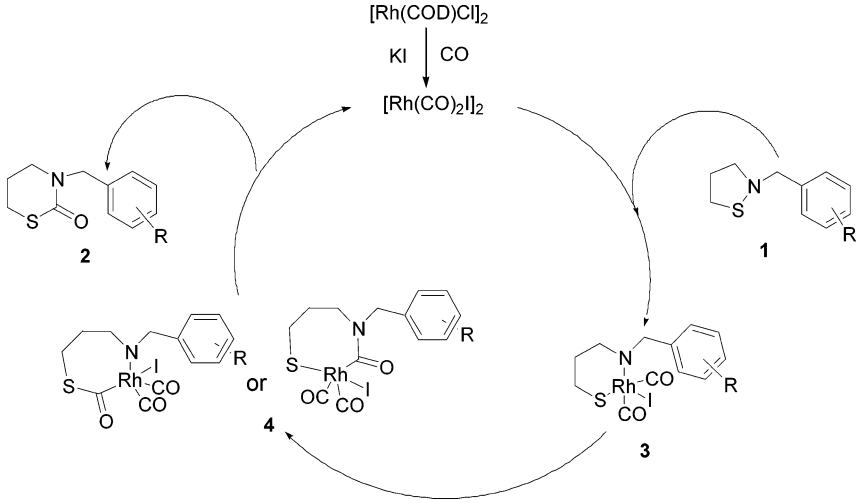
Scheme 2. Proposed Mechanism for Rhodium-Catalyzed Carbonylation of *N*-Alkylisothiazolidines



intramolecular thiophilic substitution of *N*-alkylamino moieties.[16] The carbonylation reactions of *N*-alkylisothiazolidines **1a**−**i** were efficient, and the products were formed in reasonable yields. Furthermore, this reaction tolerates various substituents such as methyl (**1b**), methoxy (**1c**, **1d**, **1e**, and **1g**), and ethoxy (**1f**), affording the corresponding 2*H*-1,3-thiazin-2-ones in 35−85% yield. In the case of *N*-(4-methylbenzyl) isothiazolidine (**1b**), 2*H*-1,3-thiazin-2-one, tetrahydro-3-[(4-methylphenyl) methyl] (**2b**) was obtained in 80% yield (entry 2, Table 2). Moreover, in the reaction

Table 2. Rhodium-Catalyzed Carbonylation of Isothiazolidines[a]

entry	reactants	products	yield (%)[b]
1	**1a**	**2a**	75
2	**1b**	**2b**	80
3	**1c**	**2c**	72
4	**1d**	**2d**	50
5	**1e**	**2e**	35
6	**1f**	**2f**	48
7	**1g**	**2g**	65
8	**1h**	**2h**	85
9	**1i**	**2i**	80

[a] Reaction conditions: (1.0 mmol) of *N*-alkylisothiazolidine, (0.05 mmol) of $[Rh(COD)Cl]_2$, (0.05 mmol) of KI, 6 mL of toluene, CO 1000 psi, 24 h. [b] Yield of purified product.

of **1c**, **1d**, and **1e**, the position of the methoxyl substituent on the phenyl ring has an obvious effect on the product. The reaction of *N*-(4-methoxylbenzyl) isothiazolidine (**1c)** gave **2c** as major product in 72% yield, and **1d** gave the product in 50% yield, whereas in the case of **1e**, 2*H*-1,3-thiazin-2-one, tetrahydro-3-[(2-methoxyphenyl) methyl] was formed in a low yield of 35% (entries 3−5, Table 2), perhaps as a result of the steric hindrance of the methoxy functionality. Carbonylation of *N*-[(1-naphthalenyl)methyl)isothiazolidine (**1g**) afforded 2*H*-1,3-thiazin-2-one, tetrahydro-3-[(1-naphthalenyl) methyl] (**2g**) in 65% yield (entry 7, Table 2). The structure of **2c** was unambiguously confirmed by X-ray crystallographic analyses as shown in Figure 1. We also

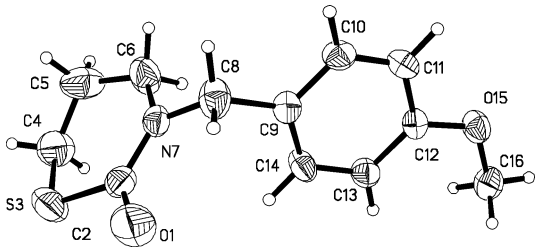


Figure 1. ORTEP view of compound **2c**.

considered the isothiazolidines which contain one more CH_2 unit between the N atom and the phenyl ring. For example, the reaction of *N*-(2-phenylethyl) isothiazolidine **1h** provided **2h** in 85% yield (entry 7, Table 2). The methoxyl substituent isothiazolidine **1i** gave 2*H*-1,3-thiazin-2-one, tetrahydro-3-[2-(4-methoxyphenyl)ethyl] (**2i**) in 80% yield (entry 8, Table 2).

A proposed mechanism for the carbonylation reaction of *N*-alkylisothiazolidines is outlined in Scheme 2. First, oxidative addition of the rhodium(I) complex to the S−N bond of substrate **1** gives intermediate **3**. Subsequent insertion of carbon monoxide into the S−Rh bond or N−Rh bond of **3** would generate **4**. Finally, reductive elimination affords the tetrahydro-2*H*-1,3-thiazin-2-ones and regenerates the catalyst.

In conclusion, we have demonstrated for the first time that tetrahydro-2*H*-1,3-thiazin-2-one derivatives can be easily synthesized in good yield by reaction of *N*-alkylisothiazo-

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lidines with carbon monoxide in the presence of a rhodium catalyst and potassium iodide. The present method provides a novel approach for the synthesis of tetrahydro-2*H*-1,3-thiazin-2-one derivatives in one step.

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Supporting Information Available: General experimental procedures for the carbonylation of isothiazolidines, spectral data of compound **2a**−**i**, ^{1}H and ^{13}C NMR spectra of compounds **2b** and **2c**, and X-ray crystallographic data for **2c** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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