Sequential Ring Expansion and Ketene Elimination Reactions in the Novel Rhodium(I)-Catalyzed Carbonylation of Thiazolidines

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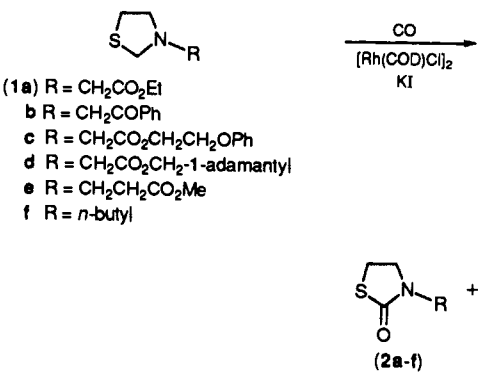
Abstract: 1,3-Thiazolidines react with carbon monoxide, in the presence of catalytic quantities of chloro(1,5-cyclooctadiene)rhodium(I) dimer and potassium iodide, to give thiazolidinones in 56–88% yields. Reaction in the absence of KI afforded the six-membered ring thiazin-3-one. The rhodium(I) complex can catalyze the quantitative conversion of the thiazin-3-one to the thiazolidinone under carbon monoxide, with ketene as the reaction by-product. The conversion of thiazolidines to thiazolidinones involves a novel regiospecific insertion of carbon monoxide into one of two ring carbon–nitrogen bonds, as well as a metal-catalyzed ketene elimination process.

Transition metal catalyzed reactions of heterocyclic compounds with carbon monoxide constitute an important area of organometallic catalysis.[1] Reactions of this type provide direct access to a large variety of organic compounds including lactams, lactones, and thiolactones. While the transition metal catalyzed carbonylation and ring expansion of three- and four-membered-ring heterocycles has been shown to be reasonably facile,[2,3] there have been only a few reports of the carbonylation of five-membered-ring heterocyclic compounds. One of us recently reported the first example of the transition metal catalyzed insertion of carbon monoxide into a pyrrolidine to produce a δ-lactam. Depending on the nature of the N-substituent, an unusual carbonyl transposition reaction was also observed.[4] The rhodium(I)-catalyzed carbonylation of tetrahydrofuran affords tetrahydropyran-2-one and/or α-methylene-γ-butyrolactone in 48–62% yield depending on the promoters.[5] Copper-catalyzed carbonyl insertion into 1,3-dioxolane affords 1,4-dioxan-2-one.[6]

While the carbonylation of heterocycles containing one heteroatom (N, O, or S) has been investigated in considerable detail, there are no examples, to our knowledge, of the carbonylation and ring expansion of a heterocycle containing two different heteroatoms. The question arises as to what degree of selectivity of carbon monoxide insertion occurs into rings containing two heteroatoms. In particular, the regioselectivity of the ring expansion reaction (insertion into carbon–nitrogen vs carbon–sulfur bonds of an N,S-containing heterocycle) is a matter of considerable interest. To this end, we have examined the carbonylation of 1,3-thiazolidines. While the anticipated carbonylation does occur, the reaction proceeds in a novel manner, affording thiazolidinones in high yield. An unusual ketene elimination step is part of the overall process. We now describe these synthetically useful results.

Results and Discussion

The carbonylation of a series of N-substituted thiazolidine derivatives (**1a–f**) was carried out in dry benzene, at 65 atm of carbon monoxide and 180 °C for 48 h (96 h for **1f**) using chloro(1,5-cyclooctadiene)rhodium(I) dimer as the catalyst precursor and potassium iodide as the promoter.[7] Under these conditions, complete conversion of **1** occurred and thiazolidinones **2a–f** were obtained as the only products in good to excellent yields (eq 1).



The results are presented in Table 1. Only 1% $[Rh(COD)Cl]_2$ is needed to catalyze the carbonylation, as well as 1 equiv of KI per rhodium atom. Lower product yields resulted in the absence of the iodide promoter (as in **1a** and **1b**), and in some cases (e.g. **1c**, **1d**) the reaction is completely inhibited. More importantly, in the case of **1a**, a key intermediate in the thiazolidinone synthesis can be isolated when KI is not present (*vide infra*).

Table 1. Rhodium(I)-Catalyzed Carbonylation of 1,3-Thiazolidines[a]

reactant	reaction time, h	product	% yield[b]
1a	48	**2a**	80 (58)[c,d]
1b	48	**2b**	82 (65)[c]
1c	48	**2c**	70
1d	48	**2d**	68
1e	48	**2e**	(56)[c]
1f	96	**2f**	88
7a	48	**2a**	83
7b	48	**2b**	72

[a] Reaction conditions: 5 mmol of **1**, 0.05 mmol of $[Rh(1,5\text{-}COD)Cl]_2$, 0.10 mmol of KI, 10 mL of benzene, 65 atm of CO, 180 °C. [b] Yield of purified product. [c] The yields in parentheses were obtained by running the reaction in the absence of KI. [d] Total yield of 58% without KI: 30% **2a**, 28% **5a**.

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(1) Colquhoun, H. M.; Thompson, D. G.; Twigg, M. V. *Carbonylation*; Plenum Press: New York, 1991; pp 191–203.
(2) Calet, S.; Urso, F.; Alper, H. *J. Am. Chem. Soc.* **1989**, *111*, 931.
(3) Roberto, D.; Alper, H. *J. Am. Chem. Soc.* **1989**, *111*, 7539.
(4) Wang, M. D.; Alper, H. *J. Am. Chem. Soc.* **1992**, *114*, 7018.
(5) Jenner, G.; Kheradmand, H.; Kiennemann, A. *J. Organomet. Chem.* **1984**, *277*, 427.
(6) Soma, Y.; Yamamoto, N.; Sano, H.; Yamauchi, K.; Tamaoki, K.; Tanaka, K.; Yabushita, T. (Agency of Ind. Sci. Tech. and Kyowa Co.) Jpn. Kokai Tokkyo Koho 89 299 285; *Chem. Abstr.* **1990**, *112*, 216979.
(7) Alper, H.; Hamel, N.; Smith, D. J. H.; Woell, J. B. *Tetrahedron Lett.* **1985**, *26*, 2273.

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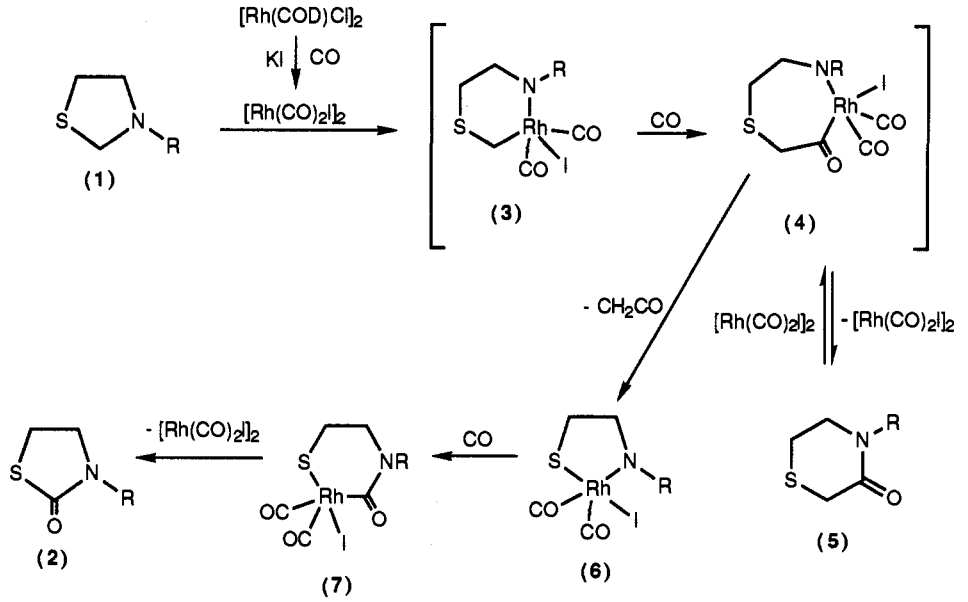
Scheme 1

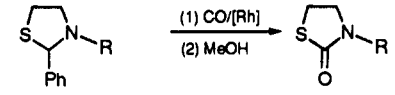


Some thiazolidinones are of commercial value; for example, **2f** possesses fungicidal activity.[8] Surprisingly, cobalt carbonyl, a useful catalyst for the ring expansion of pyrrolidines to piperidinones,[4] is ineffective in the case of thiazolidines. It is also interesting to note that under conditions where the corresponding pyrrolidines underwent the carbonyl transposition reaction the starting thiazolidines were recovered unchanged (e.g. **1a**, **1b**).

The structures of (**2a–e**) were assigned on the basis of spectral data (see Experimental Section). The ^{1}H NMR spectra show that the singlet for the methylene protons in between the sulfur and nitrogen atoms disappear, and the two triplets due to CH_2S and CH_2N in the thiazolidine ring are shifted downfield by approximately 1 ppm. The ^{13}C NMR spectra display a signal for the thiazolidinone carbonyl carbon at δ 172.70–173.05 ppm. Molecular ion peaks consistent with the structures **2a–e** are observed in the mass spectra. The structure of **2b** was also confirmed by X-ray crystallography.[9]

The conversion of **1** to **2** appears, on first consideration, to be an oxidation of a methylene to a carbonyl group. While pursuing information about the mechanism of this formal oxidation, we made some intriguing and quite unexpected observations. Most importantly, the anticipated ring expansion of the 1,3-thiazolidine to a thiazinone *does* occur. Specifically, when **1a** was treated with carbon monoxide and $[Rh(COD)Cl]_2$ in the absence of potassium iodide, the six-membered-ring heterocycle **5a** was isolated in 28% yield together with 30% of **2a**, 10% of unreacted **1a**, and the remainder being unidentified decomposition products (reactions followed by TLC and NMR of crude reaction mixtures). The structure of **5a** was identified by spectral data (see Experimental Section). The isolation of **5a** from the reaction mixture demonstrates that the ring expansion is regiospecific, with exclusive carbon monoxide insertion into the nitrogen–C2 bond of **2a** and no insertion into the other ring carbon–nitrogen bond or into either carbon–sulfur bond.

After isolating **5a** and **2a** in the absence of KI, the question arose as to whether **5a** was involved in the conversion of **1** to **2**. When **5a** was subjected to the standard reaction conditions ([Rh(COD)Cl]$_2$, KI, CO, C_6H_6, 65 atm), **2a** was obtained in quantitative yield. Note that repetition of the experiment in the absence of KI afforded **2a** in only 19% yield. In addition, simply heating **5a** in the absence of the rhodium catalyst gave only starting material and some decomposition. Given these results, it is clear that rhodium(I) not only catalyzes the ring *expansion* but also the subsequent ring *contraction*. This sequence of events (Scheme 1)[10] requires an unusual ketene elimination from the rhodacycle **4**, generated by oxidative addition of rhodium(I) to **1** and migratory insertion of CO into the Rh–C bond of **3**. Competitive with ketene elimination of **4** to **6** is reductive elimination of **4** to the thiazin-3-one **5** (a reversible process). Subsequent carbonyl insertion into the Rh–N bond of **6** to give **7**, followed by reductive elimination, would form **2** and regenerate the catalyst. In order to determine whether or not ketene was produced, the rhodium-(I)-catalyzed reaction of **8a** was worked up with methanol. This afforded not only **2a** in 72% yield but also methyl phenylacetate (8–10%). The latter is derived from the addition of methanol to phenyl ketene (eq 2). Methyl phenylacetate is also produced (10%



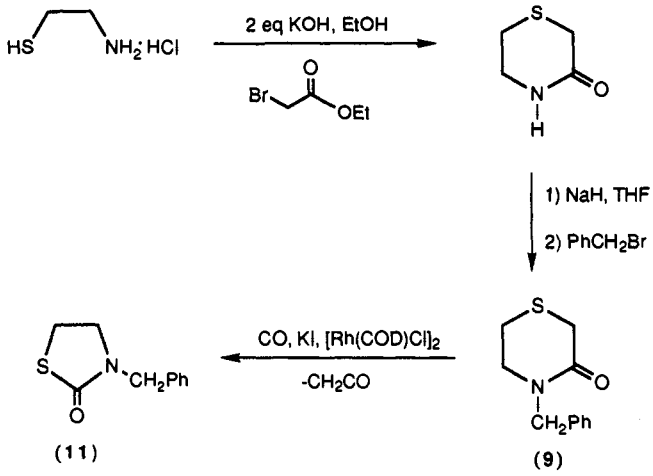
(**8a**) R = CH_2COOEt
(**8b**) R = CH_2COPh (2)

yield) in the reaction of substrate **8b** along with thiazolidinone **2b** (83% yield). The lower yield of methyl phenylacetate is likely due to the instability of the ketene under the reaction conditions. Note that an infrared spectrum of the reaction mixture prior to workup with methanol showed an absorption band due to ketene stretching at 2163 cm^{-1}.[11]

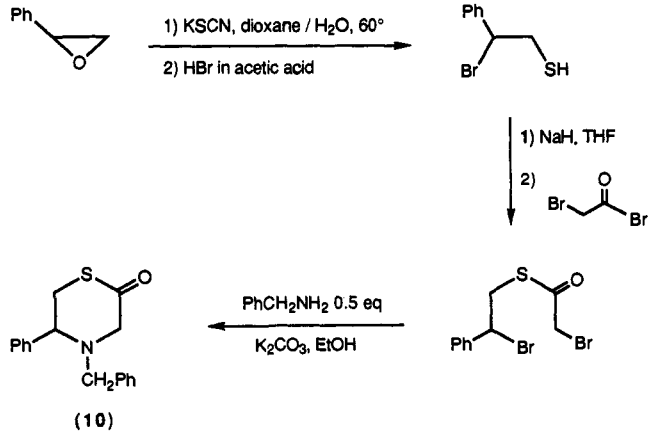
These results, especially the isolation of **5a** from the reaction mixture, demonstrate the regiospecificity of the carbonylation into the nitrogen–C2 bond. In an attempt to direct CO insertion into the C–S bond, in accord with previous results,[3,12] substrate **1g**, containing a benzylic C–S bond, was prepared and subjected to the standard reaction conditions. In acyclic systems containing an aliphatic or benzylic amine and a benzylic sulfide, the carbonylation occurs exclusively at the C–S bond.[13] However, substrate **1g** surprisingly underwent carbonylation exclusively at

(8) Montedison, S. p. A. Jpn. Kokai Tokkyo Koho 81 87 574; *Chem. Abstr.* **1981**, *95*, 187236h.
(9) The X-ray data for **2b** will be reported separately by C. Bensimon.
(10) We are indebted to a referee for suggesting the pathway for the conversion of **4** to **2** and **5**.
(11) Patai, S., Ed. *The Chemistry of Ketenes, Allenes and Related Compounds*; John Wiley & Sons: Norwich, 1980; pp 165–188.
(12) Wang, M. D.; Calet, S.; Alper, H. *J. Org. Chem.* **1989**, *54*, 20.
(13) Khumtaveeporn, K.; Alper, H. *J. Org. Chem.* **1994**, *59*, 1414.
(14) Giordano, G.; Crabtree, R. H. *Inorg. Synth.* **1979**, *19*, 218.

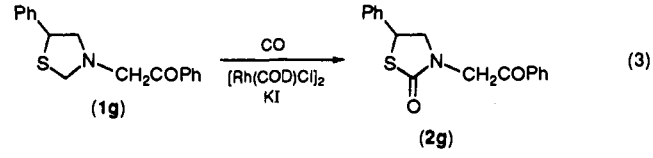
Scheme 2



Scheme 3



the C–N bond, affording **2g** in 72% yield (eq 3). The regio-



(3)

chemistry of the carbon monoxide insertion is therefore completely opposite in cyclic and acyclic systems, with the presence of a phenyl group at the 4-position of a thiazolidine ring having no influence on the course of the reaction.

In order to prove that the carbonylation reaction proceeded by CO insertion into the C–N, not the C–S, bond, compounds **9** and **10** were synthesized by alternative methods (Schemes 2 and 3). Under the standard carbonylation conditions (Rh(I) catalyst, KI, CO (65 atm), C_6H_6), compound **9** was converted cleanly to **11** in 86% yield, while compound **10** was recovered unchanged. The formation of **11** from **9** is in accord with the conversion of **5a** to **2a**.

In conclusion, 1,3-thiazolidines are converted to 1,3-thiazolidinones in good to excellent yields by rhodium(I)-catalyzed carbonylation, with ketenes as the accompanying products. The overall process is indeed novel and involves the insertion of two molecules of carbon monoxide, two ring expansion steps as well as a ring contraction, and a completely regiospecific carbonyl insertion into one of the two ring carbon–nitrogen bonds.

Experimental Section

General. Spectral data were obtained by use of the following instruments: Bomem MB-100 (FT-IR), Bruker AMX-500, Varian XL 300 or Gemini 200 MHz (NMR), VG 7070E (MS). Elemental analyses were carried out by MHW Laboratories, Phoenix, AZ. [Rh(1,5-COD)-Cl]$_2$ was prepared according to the described procedure.[14] The carbonylation reactions were run in 45-mL stainless steel autoclaves, containing a glass liner.

General Procedure for the Preparation of Thiazolidine Derivatives. To a suspension of thiazolidine (0.89 g, 10 mmol) and potassium carbonate (1.52 g, 11 mmol) in ethanol (95%, 10 mL) was added the requisite bromide as a solution in ethanol (10 mmol in 5 mL). After stirring overnight, the cloudy solution was worked up by extraction with CH_2Cl_2 and water. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel, using 15–30% ethyl acetate in hexane as the eluant, to yield the thiazolidine derivatives.

Preparation of the Alkylating Agent, $BrCH_2COOCH_2CH_2OPh$, for 1c. To a solution of 2-phenoxyethan-1-ol (1.38 g, 10 mmol) in dry benzene (10 mL) was added sodium metal (0.23 g, 10 mmol), and the mixture was stirred for 3 h. The sodium salt of 2-phenoxyethan-1-ol was then added dropwise to a benzene solution of bromoacetyl bromide (4.04 g, 20 mmol). After stirring at room temperature for 2 h, the reaction mixture was worked up by extraction with CH_2Cl_2 and water. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo*.

Preparation of the Alkylating Agent, $BrCH_2COOCH_2C_{10}H_{15}$, for 1d. The reaction was carried out with 1-adamantanemethanol using the same procedures as that for **1c**. Generation of the sodium salt required refluxing the alcohol with sodium metal for 2 h.

2-Phenylthiazolidine.[15] A mixture of 2-aminoethanethiol hydrochloride (2.27 g, 20 mmol), benzaldehyde (2.12 g, 20 mmol), and potassium hydroxide (1.12 g, 20 mmol) in 100 mL of benzene was refluxed, and the water was removed with a Dean–Stark apparatus. After the calculated amount of water was removed, the reaction mixture was worked up by removing the solvent and then extracting with CH_2Cl_2 and water. The organic phase was dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to yield 84% of 2-phenylthiazolidine. The product was purified by recrystallization using CH_2Cl_2–hexane. The alkylation was carried out as described above.

5-Phenylthiazolidine (1g).[16,17] An aqueous solution of 1-phenyl-2-amino-1-ethanol (6.85 g, 50 mmol) was neutralized to a methyl red endpoint with 50% aqueous sulfuric acid, followed by addition of an equal volume of acid. Water was removed by heating the solution to 130 °C at 10–15 mmHg. The product was heated at 120–130 °C under reduced pressure to constant weight. The sulfate ester was then added to 300 mL of 2 N NaOH at 0 °C, and the mixture was slowly heated to 90 °C for 2 h. The reaction mixture was then separated from solution by steam distillation to yield 72% of 2-phenylaziridine.

To a solution of 2-phenylaziridine (4.16 g, 35 mmol) in 20 mL of 95% ethanol at 0 °C was added dropwise a 37% formaldehyde solution (1.05 g, 35 mmol). The mixture was then saturated with hydrogen sulfide for 1 h and was left stirring overnight at room temperature. The mixture was worked up by extracting with water and CH_2Cl_2. The organic layer was dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*, affording 5-phenylthiazolidine (37%), which was used in the next step without further purification.

The alkylation was carried out as described above to form **1g**, which was purified by recrystallization in ethanol.

Yields and Characterization Data for Reactants. 3-[(Ethoxycarbonyl)-methyl]thiazolidine (1a): 78% yield; IR (neat) ν (CO) 1738 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15 (t, 3H, CH_3CH_2O), 2.85 (t, 2H, CH_2S), 3.05 (t, 2H, CH_2N), 3.12 (s, 2H, NCH_2CO), 4.10 (s, 2H, SCH_2N), 4.18 (q, 2H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 14.02 (CH_3), 29.29 (CH_2S), 54.04 (CH_2N), 58.04 ($COCH_2N$), 60.29 (SCH_2N), 60.68 (CH_2O), 170.28 (CO); MS (*m/e*) 175 [M$^+$].

3-(Benzoylmethyl)thiazolidine (1b): 82% yield, IR (neat) ν (CO) 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.95 (t, 2H, CH_2S), 3.18 (t, 2H, CH_2N), 3.90 (s, 2H, NCH_2CO), 4.18 (s, 2H, SCH_2N), 7.38–8.00 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 29.64 (CH_2S), 58.30 (CH_2N), 58.90 ($COCH_2N$), 61.38 (SCH_2N), 127.96, 128.66, 133.46, 135.65 (aromatic carbons), 195.90 (CO); MS (*m/e*) 207 [M$^+$].

3-[[(2-Phenoxy)ethoxy]carbonyl]methyl]thiazolidine (1c): 64% yield; IR (neat) ν (CO) 1742 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.80 (t, 2H, CH_2S), 3.05 (t, 2H, CH_2N), 3.20 (s, 2H, NCH_2CO), 4.05 (s, 2H, SCH_2N), 4.10 (t, 2H, CH_2OPh), 4.40 (t, 2H, $COOCH_2$), 6.78–7.30 (m, 5H, aromatic

(15) Terol, A.; Fernandez, S. J. P.; Robbe, Y.; Chapat, J. P.; Granger, R. *Org. Magn. Reson.* **1981**, *17*, 68.
(16) Brois, S. J. *J. Org. Chem.* **1962**, *27*, 3532.
(17) Barbry, D.; Couturier, D. *Chem. Ber.* **1987**, *120*, 1073.

protons); ^{13}C NMR ($CDCl_3$) δ 29.48 (CH_2S), 54.15 (CH_2N), 58.20 ($COCH_2N$), 60.89 (SCH_2N), 63.21 ($PhOCH_2$), 65.57 (CO_2CH_2), 114.51, 121.19, 129.52, 158.30 (aromatic carbons), 170.50 (CO); MS (*m/e*) 267 [M$^+$].

3-[[[(1-Adamantyl)methoxy]carbonyl]methyl]thiazolidine (1d): 68% yield; IR (neat) ν (CO) 1738 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.45–1.95 (m, 15H, protons for 1-adamantyl), 2.85 (t, 2H, CH_2S), 3.12 (t, 2H, CH_2N), 3.22 (s, 2H, NCH_2CO), 3.70 (s, 2H, OCH_2-adamantyl), 4.13 (s, 2H, SCH_2N); ^{13}C NMR ($CDCl_3$) δ 28.00, 28.21 (CH-adamantyl), 29.59 (CH_2S), 33.21 (quaternary C-adamantyl), 36.91, 37.19, 39.05, 39.23 (CH_2-adamantyl), 54.22 (CH_2N), 58.26 ($COCH_2N$), 60.97 (CH_2O), 61.02 (SCH_2N), 170.61 (CO); MS (*m/e*) 295 [M$^+$].

3-[(Methoxycarbonyl)ethyl]thiazolidine (1e): 64% yield; IR (neat) ν (CO) 1731 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.42 (t, 2H, $CH_2CO_2CH_3$), 2.65 (t, 2H, $NCH_2CH_2CO_2CH_3$), 2.85 (t, 2H, CH_2N), 3.03 (t, 2H, CH_2S), 3.68 (s, 3H, OCH_3), 4.25 (s, 2H, SCH_2N); ^{13}C NMR ($CDCl_3$) δ 30.01 (CH_2S), 34.69 ($COCH_2$), 48.96 (CH_2N side chain), 52.18 (CH_2N in ring), 58.59 (OCH_3), 60.87 (SCH_2N), 172.95 (CO); MS (*m/e*) 175 [M$^+$].

3-Butylthiazolidine (1f): 73% yield; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, $CH_3CH_2CH_2CH_2$), 1.20–1.55 (m, 4H, $CH_2CH_2CH_3$), 2.35 (t, 2H, CH_2CH_2N), 2.85 (t, 2H, CH_2S), 3.05 (t, 2H, CH_2N), 4.05 (s, 2H, SCH_2N); ^{13}C NMR ($CDCl_3$) δ 14.57 (CH_3), 21.03 (CH_2CH_3), 30.12 (CH_2S), 31.79 (CH_2CH_2N), 53.09 (CH_2N in ring), 58.59 (CH_2N), 61.60 (SCH_2N); MS (*m/e*) 145 [M$^+$].

3-(Benzoylmethyl)-5-phenylthiazolidine (1g): 77% yield; IR (neat) ν (CO) 1696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.01, 3.04 (dd, J = 12.65, 9.5 Hz, 1H, CH_2N), 3.64 (ddd, J = 12.65, 6.4, 1.9 Hz, 1H, $PhCHCH_2N$), 4.04, 4.22 (AB, J = 17.2 Hz, 2H, NCH_2CO) 4.30 (dd, J = 9.5, 1.9 Hz, 1H, SCH_2N), 4.66 (d, J = 9.5 Hz, 1H, SCH_2N), 4.68, 4.69 (dd, J = 9.5, 6.4 Hz, 1H, PhCHS), 7.23–8.00 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 52.34 (PhCHS), 60.13 (NCH_2CO), 63.38 (SCH_2N), 68.41 ($PhCHCH_2N$), 127.95, 128.47, 128.63, 129.25, 129.33, 134.17, 136.20, 141.26 (aromatic carbons), 196.43 (CO). The structure assignment is also based on HMQC, COSY, TOCSY, and NOESY experiments. MS (*m/e*): 283 [M$^+$].

3-[(Ethoxycarbonyl)methyl]-2-phenylthiazolidine (8a): 57% yield; IR (neat) ν (CO) 1737 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3H, CH_3CH_2O), 2.90–3.50 (m, 6H, CH_2S, CH_2N, NCH_2CO), 4.01 (s, 2H, SCH_2N), 4.25 (q, 2H, OCH_2CH_3), 5.30 (s, 1H, CHPh), 7.20–7.60 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 14.21 (CH_3), 30.66 (CH_2S), 53.42 (CH_2N), 56.08 ($COCH_2N$), 60.72 (CH_2O), 74.75 (SCHN), 127.99, 128.18, 128.28, 140.25 (aromatic carbons), 170.46 (CO); MS (*m/e*) 251 [M$^+$].

3-(Benzoylmethyl)-2-phenylthiazolidine (8b): 65% yield; IR (neat) ν (CO) 1697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.95–3.20 (m, 3H, CH_2S, 1H of CH_2N), 3.30–3.42 (m, 1H of CH_2N), 3.72, 4.05 (AB system, J_{AB} = 20 Hz, 2H, NCH_2CO), 5.29 (s, 1H, CHPh), 7.15–7.85 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 30.86 (CH_2S), 56.13 (CH_2N), 58.63 ($COCH_2N$), 75.92 (SCHN), 128.05, 128.17, 128.32, 128.56, 133.35, 136.56, 140.25 (aromatic carbons), 170.46 (CO); MS (*m/e*) 283 [M$^+$].

General Procedure for the Carbonylation of Thiazolidines. A mixture of the thiazolidine (5 mmol), $[Rh(COD)Cl]_2$ (0.025 g, 0.05 mmol), potassium iodide (if used) (0.017 g, 0.10 mmol), and benzene (10 mL) was placed in an autoclave containing a glass liner and stirring bar. The autoclave was purged several times with carbon monoxide and pressurized to 65 atm. The reaction mixture was stirred at 180 °C for 48 h (96 h for **1f**). The reaction was then cooled to room temperature and filtered through acidic alumina using CH_2Cl_2 and then ethyl acetate as eluant. The more polar fraction (containing the product) was purified by preparative thin-layer chromatography using 30% ethyl acetate in hexane as the developer.

The carbonylation of **5a** was carried out following the general procedure except for a reaction time of 24 h in this case. After work up, **2a** was obtained in quantitative yield.

Yield and Characterization Data for Products. 3-[(Ethoxycarbonyl)-methyl]thiazolidin-2-one (2a): 80% yield (with KI), 58% yield (without KI); IR (neat) ν (CO) 1738, 1671 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3H, CH_3CH_2O, J = 6.3 Hz), 3.25 (t, 2H, CH_2S, J = 9.25 Hz), 3.70 (t, 2H, CH_2N, J = 9.25 Hz), 4.02 (s, 2H, NCH_2CO), 4.15 (q, 2H, OCH_2CH_3, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 14.06 (CH_3), 25.69 (CH_2S), 45.68 (CH_2N), 48.81 ($COCH_2N$), 61.41 (CH_2O), 168.15 (COOEt), 172.93 (SCON); MS (*m/e*) 189 [M$^+$]. Anal. Calcd for $C_7H_{11}NO_3S$: C, 44.44; H, 5.82; N, 7.4. Found: C, 44.71; H, 6.02; N, 7.30.

4-[(Ethoxycarbonyl)methyl]-1,4-thiazin-3-one (5a): 28% yield; IR (neat) ν (CO) 1738, 1653 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3H, CH_3CH_2O, J = 6.9 Hz), 2.89 (t, 2H, CH_2S, J = 7.0 Hz), 3.32 (s, 2H, SCH_2CO), 3.65 (t, 2H, CH_2N, J = 7.0 Hz), 4.12 (s, 2H, NCH_2CO), 4.15 (q, 2H, OCH_2CH_3, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 14.07 (CH_3), 26.07 (CH_2S), 30.11 (SCH_2CO), 49.25 (CH_2N), 50.75 ($COCH_2N$), 61.32 (CH_2O), 166.79 (COOEt), 168.83 (CON); MS (*m/e*) 203 [M$^+$]. Anal. Calcd for $C_8H_{13}NO_3S$: C, 47.29; H, 6.40; N, 6.89. Found: C, 47.57; H, 6.33; N, 6.49.

3-(Benzoylmethyl)thiazolidin-2-one (2b): 82% yield (with KI), 65% yield (without KI); IR (neat) ν (CO) 1696, 1667 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.35 (t, 2H, CH_2S, J = 8.0 Hz), 3.75 (t, 2H, CH_2N, J = 8.0 Hz), 4.75 (s, 2H, NCH_2CO), 7.38–7.95 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 25.93 (CH_2S), 49.01 (CH_2N), 50.72 ($COCH_2N$), 127.98, 128.87, 133.95, 134.63 (aromatic carbons), 173.05 (SCON), 195.90 (CO); MS (*m/e*) 221 [M$^+$]. Anal. Calcd for $C_{11}H_{11}NO_2S$: C, 59.73; H, 4.98; N, 6.33. Found: C, 59.45; H, 5.17; N, 5.99.

3-[[[(2-Phenoxy)ethoxy]carbonyl]methyl]thiazolidin-2-one (2c): 70% yield; IR (neat) ν (CO) 1744, 1667 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.29 (t, 2H, CH_2S, J = 9.3 Hz), 3.71 (t, 2H, CH_2N, J = 9.3 Hz), 4.10 (s, 2H, NCH_2CO), 4.18 (t, 2H, CH_2OPh, J = 4.7 Hz), 4.47 (t, 2H, $COOCH_2$, J = 4.7 Hz), 6.82–7.32 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 25.70 (CH_2S), 45.63 (CH_2N), 48.76 ($COCH_2N$), 63.70 ($PhOCH_2$), 65.45 (CO_2CH_2), 114.51, 121.28, 129.52, 158.23 (aromatic carbons), 168.15 (CO), 173.03 (SCON); MS (*m/e*) 281 [M$^+$]. Anal. Calcd for $C_{13}H_{15}NO_4S$: C, 55.52; H, 5.34; N, 4.98. Found: C, 55.37; H, 5.44; N, 5.03.

3-[[[(1-Adamantyl)methoxy]carbonyl]methyl]thiazolidin-2-one (2d): 68% yield; IR (neat) ν (CO) 1740, 1672 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.50–1.95 (m, 15H, protons for 1-adamantyl), 3.30 (t, 2H, CH_2S, J = 9.3 Hz), 3.70 (s, 2H, OCH_2-adamantyl), 3.72 (t, 2H, CH_2N, J = 9.3 Hz), 4.10 (s, 2H, NCH_2CO); ^{13}C NMR ($CDCl_3$) δ 25.71 (CH_2S), 27.87, 28.11, 28.30 (CH-adamantyl), 33.06 (quaternary C-adamantyl), 36.79, 38.96, 39.10 (CH_2-adamantyl), 45.71 (CH_2N), 48.90 ($COCH_2N$), 73.77 (CH_2O), 168.34 (CO), 172.70 (SCON); MS (*m/e*) 309 [M$^+$]. Anal. Calcd for $C_{16}H_{23}NO_3S$: C, 62.136; H, 7.44; N, 4.53. Found: C, 61.98; H, 7.48; N, 4.27.

3-[(Methoxycarbonyl)ethyl]thiazolidin-2-one (2e): 56% yield (without KI); IR (neat) ν (CO) 1734, 1666 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.60 (t, 2H, $CH_2CO_2CH_3$, J = 5.0 Hz), 3.25 (t, 2H, CH_2S, J = 8.5 Hz), 3.58 (t, 2H, $NCH_2CH_2CO_2CH_3$, J = 5.0 Hz), 3.65 (t, 2H, CH_2N, J = 8.5 Hz), 3.70 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 26.56 (CH_2S), 33.14 (CH_2CO), 41.37 (CH_2N side chain), 49.96 (CH_2N in ring), 52.53 (OCH_3), 172.71 ($COOCH_3$), 172.90 (SCON); MS (*m/e*) 189 [M$^+$]. Anal. Calcd for $C_7H_{11}NO_3S$: C, 44.44; H, 5.82; N, 7.41. Found: C, 44.38; H, 5.85; N, 7.71.

3-Butylthiazolidin-2-one (2f): 88% yield; IR (neat) ν (CO) 1662 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, $CH_3CH_2CH_2CH_2$, J = 7.0 Hz), 1.25–1.60 (m, 4H, $CH_2CH_2CH_3$), 3.25 (m, 4H, CH_2CH_2N and CH_2S), 3.58 (t, 2H, CH_2N, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 13.71 (CH_3), 19.92 (CH_2CH_3), 25.67 (CH_2S), 29.53 (NCH_2CH_2), 44.58 (NCH_2 in ring), 48.51 (NCH_2), 171.68 (CO); MS (*m/e*) 159 [M$^+$].

3-(Benzoylmethyl)-5-phenylthiazolidin-2-one (2g): 72% yield (with KI), 44% yield (without KI); IR (neat) ν (CO) 1738 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.79 (dd, 1H, CH_2N, J = 1.6, 8.0 Hz), 4.01 (dd, 1H, CH_2N, J = 1.6, 8.0 Hz), 4.82 (s, 2H, NCH_2CO), 4.95 (t, 1H, PhCHS, J = 8.0 Hz), 7.15–8.00 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 46.69 (PhCHS), 51.31 ($PhCHCH_2N$), 57.32 (NCH_2CO), 128.22, 128.62, 129.01, 129.53, 129.58, 134.62, 135.23, 139.51 (aromatic carbons), 173.04 (SCON), 193.82 (CO); MS (*m/e*) 297 [M$^+$]. Anal. Calcd for $C_{17}H_{15}NO_2S$: C, 68.69; H, 5.05; N, 4.71. Found: C, 68.71; H, 4.81; N, 4.63.

***N*-Benzyl-1,4-thiazin-3-one (9)**. To a solution of 2-aminoethanethiol hydrochloride (1.13 g, 10 mmol) and potassium hydroxide (1.12 g, 20 mmol) in ethanol (95%, 20 mL) was added ethyl bromoacetate (1.84 g, 11 mmol) in ethanol (10 mL). The solution was left stirring overnight at room temperature. The reaction was then extracted with 2 N HCl and CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield thiazen-3-one (84%). The crude product was used in the next step without further purification.

To the solution of thiazen-3-one (0.59 g, 0.5 mmol) in dry THF (10 mL) was added sodium hydride (80% in oil, 0.01 g, 0.5 mmol). After stirring at room temperature for 0.5 h, benzyl bromide was then added to the solution (0.09 g, 0.5 mmol) in dry THF (5 mL). The mixture was stirred for 3 h. The reaction mixture was then worked up by extraction with CH_2Cl_2 and water. The organic layer was dried and the solvent removed under vacuum. Purification by silica gel column chromatography using 10–30% ethyl acetate in hexane as the eluant yielded **9** in 74% yield: ^{1}H NMR ($CDCl_3$) δ 2.75 (t, 2H, CH_2S, J = 6.5 Hz), 3.37 (s, 2H,

$COCH_2S$), 3.52 (t, 2H, CH_2CH_2N; J = 6.5 Hz), 4.63 (s, 2H, NCH_2Ph), 7.20–7.42 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 26.98 (CH_2S), 31.04 ($COCH_2S$), 49.19 (CH_2N), 51.29 (NCH_2Ph), 128.25, 128.62, 129.33, 137.33 (aromatic carbons); MS (m/e) 207 [M^+]. Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.77; H, 6.28; N, 6.76. Found: C, 63.72; H, 6.44; N, 7.01.

The carbonylation of **9** was carried out and worked up according to the general procedure described above (24-h reaction time), affording **11** in 86% yield.

3-Benzylthiazolidin-2-one (11): 86% yield; IR (neat) ν (CO) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.28 (t, 1H, CH_2S, J = 9.25 Hz), 3.49 (t, 2H, CH_2N, J = 9.25 Hz), 4.45 (s, 2H, NCH_2Ph), 7.28–7.50 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 26.09 (CH_2S), 48.55 (NCH_2), 49.23 (NCH_2Ph), 128.46, 128.71, 129.41, 136.60 (aromatic carbons), 172.81 (CO); MS (m/e) 193 [M^+]. Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.18; H, 5.70; N, 7.25. Found: C, 62.05; H, 6.13; N, 7.31.

4-Benzyl-5-phenyl-1,4-thiazin-2-one (10). 2-Phenylthiirane was prepared as described in the literature.[18] To the solution of 2-phenylthiirane (2.72 g, 20 mmol) in ethanol (95%, 20 mL) was added dropwise HBr in acetic acid (30% wt, 6.5 g, 22 mmol) at 0 °C. After stirring at room temperature for 4 h, the reaction mixture was extracted with CH_2Cl_2, saturated $NaHCO_3$ solution, and then water. The organic layer, after drying ($MgSO_4$) and removing the solvent under vacuum, yielded the crude product (78%). This product was used in the next step without further purification.

To the solution of the bromothiol (2.17 g, 10 mmol) in dry THF (20 mL) was added sodium hydride (80% in oil, 0.2 g, 10 mmol). The reaction mixture was left stirring at room temperature for 1 h. To the solution of bromoacetyl bromide (4.02 g, 20 mmol) in dry benzene (10 mL) was added dropwise the sodium thiolate. The reaction was stirred for 3 h and then worked up by extraction with CH_2Cl_2 and saturated $NaHCO_3$ solution followed by water. After drying ($MgSO_4$) and removing the solvent, the dibromo compound was obtained in 55% yield: ^1H NMR ($CDCl_3$) δ 3.75–3.90 (m, 2H, CH_2S), 4.02 (s, 2H, $COCH_2Br$), 5.10 (dd, 1H, PhCHBr), 7.28–7.55 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 33.96 (CH_2S), 39.17 ($COCH_2Br$), 51.73 (PhCHBr), 128.18, 129.52, 129.71, 140.26 (aromatic carbons), 192.11 (CO).

To the mixture of the dibromo compound (0.68 g, 2 mmol) and potassium carbonate (0.28 g, 2 mmol) in ethanol (10 mL) was added benzylamine (0.11 g, 1 mmol) in 5 mL of ethanol. The reaction mixture was stirred at room temperature overnight and then worked up by extraction with CH_2Cl_2 and water. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo* to form **10**: ^1H NMR ($CDCl_3$) δ 2.72, 2.85 (AB, 2H, CH_2S), 3.32 (s, 2H, $COCH_2N$), 3.85 (s, 2H, NCH_2Ph), 4.45 (m, 1H, PhCHBr), 7.15–7.45 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 33.86 (CH_2S), 40.19 (NCH_2Ph), 43.89 (NCH_2CO), 59.98 (PhCHN), 128.96, 129.08, 129.11, 129.18, 129.40, 129.51, 130.05, 130.19, 139.18 (aromatic carbons), 201.55 (CO); MS (m/e) 283 [M^+]. Anal. Calcd for $C_{17}H_{17}NOS$: C, 72.08; H, 6.01; N, 4.95. Found: C, 72.40; H, 5.75; N, 4.59.

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