JOC*Note*

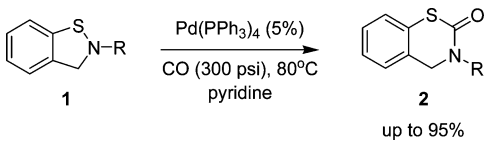
Synthesis of 3-Substituted-3,4-dihydro-2*H*-1,3-benzothiazin-2-ones via a Highly Regioselective Palladium-Catalyzed Carbonylation of 2-Substituted-2,3-dihydro-1,2-benzisothiazoles

Gwenaella Rescourio and Howard Alper*

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

halper@science.uottawa.ca

Received October 3, 2007



A novel synthesis of 3-substituted-3,4-dihydro-2*H*-1,3-benzothiazin-2-ones is described herein. The strategy relies on a highly regioselective palladium-catalyzed carbonylation of 2-substituted-2,3-dihydro-1,2-benzisothiazoles to give the corresponding 3,4-dihydro-2*H*-1,3-benzothiazin-2-one derivatives in good to excellent yields.

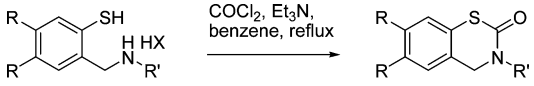
Transition-metal-catalyzed carbonylation reactions have become an invaluable tool in organic synthesis in both industry and academia.[1−4] These reactions provide access to a broad range of structurally diverse organic compounds, including functionalized heterocyclic structures such as lactams, lactones, or thiolactones.[5−7]

From a practical point of view, one of the main advantages of this methodology is the possibility of accessing functionalized heterocycles in a single reaction step. Thus, a number of research groups have demonstrated that the insertion of carbon monoxide into the carbon−heteroatom bond of cyclic compounds containing one heteroatom (usually N, S, or O) can be effectively used to synthesize the aforementioned heterocyclic structures.[8] In contrast with these studies, little attention has been paid to the carbonylative insertion reaction of substrates containing two adjacent heteroatoms.[9]

Our research group has recently reported several examples that illustrate the applicability of this methodology.[10] In particular, we found that the carbonylative ring expansion of *N*-alkylisothiazolidines[10a] and 1,3-thiazolidines[10c] could take place with a rhodium-based catalyst (chloro(1,5-cyclooctadiene)-rhodium(I) dimer) and elevated pressures and temperatures (typically 1000 psi of CO and 130 or 180 °C depending on the substrate used). Despite the severity of the conditions required for this transformation to occur, the corresponding tetrahydro-2*H*-1,3-thiazin-2-ones could be isolated in modest to good yields (35−88% yield).

Due to the intrinsic value of developing alternative strategies for the synthesis of this valuable class of compounds, we decided to expand our studies in this area. We were particularly interested in the possibility of applying a metal-catalyzed carbonylation reaction to benzisothiazole substrates in order to directly access the corresponding benzothiazin-2-ones. We felt that this methodology could be distinctively useful due to the limited availability of synthetic methods to elaborate these structures. To our knowledge, only one example has been reported in the literature thus far for the preparation of this class of functionalized heterocycles (Scheme 1). The strategy relied on the reaction of benzenethiol derivatives **3a**−**d** with phosgene, a transformation that generally proceeds in poor to modest yields (33−62%).[11]

SCHEME 1. Synthetic Approach Followed by Szabó et al.



3a, X = Cl
3b, X = I
3c, X = Br
3d, X = Cl

a R = MeO, R' = H
b R = MeO, R' = Me
c R = MeO, R' = Et
d R = H, R' = H

4a, 33%
4b, 38%
4c, 62%
4d, 36%

To test the viability of utilizing a metal-catalyzed carbonylation approach toward the synthesis of benzothiazin-2-ones, we needed to access precursor **1**. Thus, we envisioned a strategy in which benzisothiazole **1** would be derived from an amino intermediate **5** (Figure 1). This key intermediate would be subjected to a tandem oxidation−[2,3]-sigmatropic rearrangement reaction with concomitant nucleophilic attack to give **1**. The key amino derivative **5** would be obtained via reductive amination of aldehyde **6**, which in turn would be synthesized

(1) (a) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453. (b) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *Curr. Org. Chem.* **2004**, *8*, 919. (c) Vizer, S. A.; Yerzhanov, K. B.; Al Aziz Al Quntar, A.; Dembitsky, V. M. *Tetrahedron* **2004**, *60*, 5499. (d) Morimoto, T.; Kakiuchi, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 5580.

(2) (a) El Ali, B.; Alper, H. *Synlett* **2000**, *2*, 161. (b) Vasapollo, G.; Mele, G. *Targets Heterocycl. Syst.* **2002**, *6*, 197. (c) Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W. *Angew. Chem., Int. Ed.* **2002**, *41*, 2781.

(3) (a) Nagy, E.; Benedek, C.; Heil, B.; Tõrös, S. *Appl. Organomet. Chem.* **2002**, *16*, 628. (b) Tõrös, S.; Gemes-Pecsi, I.; Heil, B.; Mahob, S.; Tuba, Z. *J. Chem. Soc., Chem. Commun.* **1992**, *11*, 859.

(4) (a) Larksarp, C.; Alper, H. *J. Org. Chem.* **2000**, *65*, 2773. (b) Larksarp, C.; Alper, H. *Org. Lett.* **1999**, *1*, 1619. (c) Dhawan, R.; Dghaym, R. D.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2003**, *125*, 1474. (d) Boeckman, R. K., Jr.; Reed, J. E.; Ge, P. *Org. Lett.* **2001**, *3*, 3651. (e) Dghaym, R. D.; Dhawan, R.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3228.

(5) (a) Davoli, P.; Moretti, I.; Prati, F.; Alper, H. *J. Org. Chem.* **1999**, *64*, 518. (b) Van den Hoven, B. G.; Alper, H. *J. Am. Chem. Soc.* **2001**, *123*, 10214.

(6) (a) Van den Hoven, B. G.; El Ali, B.; Alper, H. *J. Org. Chem.* **2000**, *65*, 4131. (b) Yoneda, E.; Kaneko, T.; Zhang, S.-W.; Onitsuka, K.; Takahashi, S. *Org. Lett.* **2000**, *2*, 441. (c) Consorti, C. S.; Ebeling, G.; Dupont, J. *Tetrahedron Lett.* **2002**, *43*, 753.

(7) Wang, M.-D.; Calet, S.; Alper, H. *J. Org. Chem.* **1989**, *54*, 20.

(8) Khumtaveeporn, K.; Alper, H. *Acc. Chem. Res.* **1995**, *28*, 414.

(9) (a) Soma, Y.; Yamamoto, N.; Sano, H.; Yamauchi, K.; Tamaoki, K.; Tanaka, K.; Yabushita, T. Agency of industrial Sciences and Technology. Jpn. Patent 01,299,285; *Chem. Abstr.* **1990**, *112*, 216979e. (b) Souma Y. Agency of industrial Science and Technology. U.S. Patent 4,990,629.

(10) (a) Dong, C.; Alper, H. *Org. Lett.* **2004**, *6*, 3489. (b) Khumtaveeporn, K.; Alper, H. *J. Org. Chem.* **1995**, *60*, 8142. (c) Khumtaveeporn, K.; Alper, H. *J. Am. Chem. Soc.* **1994**, *116*, 5662. (d) Alper, H.; Delledone, D.; Kameyama, M.; Roberto, D. *Organometallics* **1990**, *9*, 762.

(11) Szábo, J.; Varga, I.; Fodor, L.; Bernáth, G.; Sohár, P. *Acta Chim. Hung.* **1984**, *115*, 429.

10.1021/jo702146n CCC: $40.75
Published on Web 01/11/2008

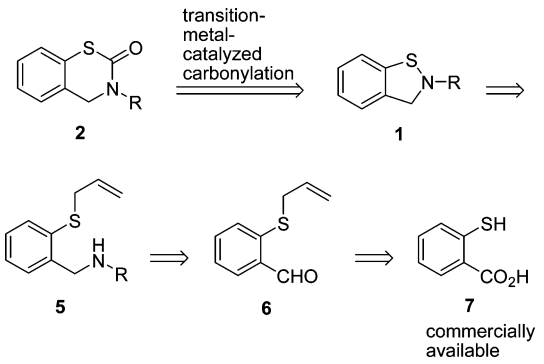
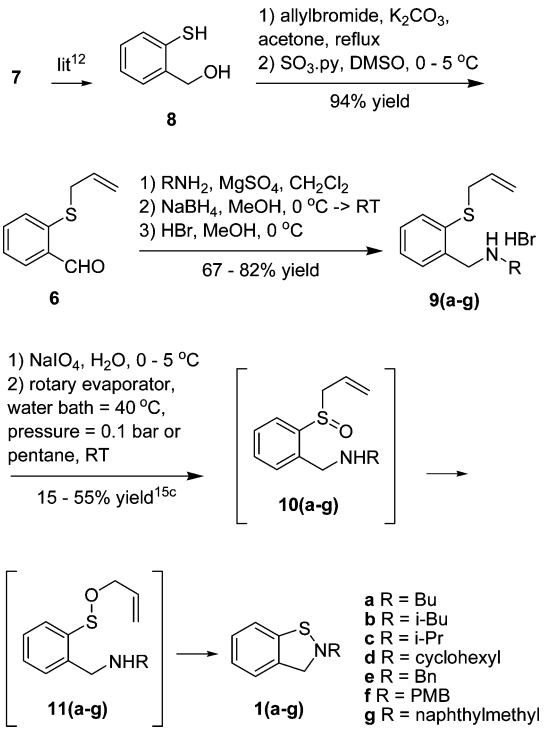


FIGURE 1. Retrosynthetic analysis.

from readily available 2-mercapto benzoic acid **7** via a three-step sequence (reduction−allylation−oxidation).

The synthesis of the benzisothiazole precursor **1** started with the lithium aluminum hydride reduction of commercially available 2-mercapto benzoic acid **7** to give the alcohol **8** (Scheme 2).[12] Allylation of 2-(mercaptophenyl)methanol **8** with allylbromide in the presence of potassium carbonate[13] and subsequent oxidation of the alcohol moiety with sulfur trioxide−pyridine complex[14] afforded the aldehyde **6** in 94% overall yield. At this stage, the amination of **6** was carried out with a number of different amines and the in situ reduction of the corresponding imines was performed with sodium borohydride. The resulting secondary amines were then converted into their hydrobromic salts **9a**−**g** in good yields. The sulfur atom of these last intermediates **9a**−**g** was oxidized with sodium metaperiodate to produce the sulfoxide derivatives **10a**−**g**.[15] The latter spontaneously underwent a [2,3]-sigmatropic rearrangement[16] to form the corresponding sulfenates **11a**−**g** followed by a concomitant intramolecular thiophilic substitution.[15]

SCHEME 2. Synthesis of 2-Substituted-2,3-dihydro-1,2-benzisothiazoles



With these precursors in hand, the carbonylation reaction of a series of 2-substituted-2,3-dihydro-1,2-benzisothiazoles **1a**−**g** was performed using 5% of tetrakis(triphenylphosphine)-palladium(0) in dry pyridine and 300 psi of carbon monoxide at 80 °C for 24 h.[17] Column chromatography of the resulting crude reaction mixture allowed the isolation of the corresponding 3-substituted-3,4-dihydro-2*H*-1,3-benzothiazin-2-ones in good to excellent yields and as the only products. Table 1 summarizes the outcome of this study. The reaction is compatible with a number of substituents, including primary and secondary alkyl groups (entries 1 to 4) and benzylic (entries 5 to 6) and the naphthylmethyl (entry 7) functionalities. Comparison of the first four entries of the table shows that the yield is clearly dependent on the size of the substituent attached to the nitrogen atom. When the steric hindrance decreases (*n*-Bu< *i*-Bu < *i*-Pr ≈ cyclohexyl), the yield of the carbonylation reaction increases (*n*-Bu > *i*-Bu > *i*-Pr ≈ cyclohexyl). Entries 5 and 7 show that both benzylic and naphthylmethyl groups are well tolerated, whereas a diminution of yield is noticed when a methoxy group is introduced in the para position of the aromatic ring. In all the cases, we observed that the conversion is complete and that the carbonylative insertion occurs with complete regioselectivity in the N−S bond under these reactions conditions. In addition, it is worth noting that the conditions are somewhat milder than those used for the carbonylative insertion of other heterocycles such as isoxazolidines and *N*-alkylisothiazolidines.[10a,c]

TABLE 1. Palladium-Catalyzed Carbonylation of 2-Substituted-2,3-dihydro-1,2-benzisothiazoles[a]

entry	reactants	products	yield (%)[b]
1, R = Bu	**1a**	**2a**	92
2, R = *i*-Bu	**1b**	**2b**	82[c]
3, R = *i*-Pr	**1c**	**2c**	56[c]
4, R = cyclohexyl	**1d**	**2d**	62[c]
5, R = Bn	**1e**	**2e**	95
6, R = PMB	**1f**	**2f**	75, 86[d]
7, R = naphthylmethyl	**1g**	**2g**	91

[a] Reaction conditions: **1** (0.5 mmol), $Pd(PPh_3)_4$ (0.025 mmol), pyridine (1 mL), and CO (300 psi) at 80 °C for 24 h. [b] Isolated yield. [c] Reactant not pure, yield calculated as if it was pure. [d] Reaction conditions: **1f** (2 mmol), $Pd(PPh_3)_4$ (0.1 mmol), pyridine (4 mL), and CO (300 psi) at 80 °C for 24 h.

The structures of the products **2a**−**g** were assigned based on analysis of the spectroscopic data (see the Experimental Section).

(12) Roberts, C. F.; Hartley, R. C. *J. Org. Chem.* **2004**, *69*, 6145.
(13) Burkhard, C. A.; Schmitz, J. V.; Burnett, R. E. *J. Am. Chem. Soc.* **1953**, *75*, 5957.
(14) Nicolaou, K. C.; Gray, D. L. F.; Tae, J. *J. Am. Chem. Soc.* **2004**, *126*, 613.
(15) (a) Hoffmann, R. W.; Goldmann, S. *Chem. Ber.* **1978**, *111*, 2716. (b) Antonjuk, D. J.; Ridley, D. D.; Smal, M. A. *Aust. J. Chem.* **1980**, *33*, 2635. (c) It must be noted that the efficiency of this process is highly dependent on the nature of the alkyl amine. With some of the substrates the overall yields were acceptable (48−55%) but with some other alkyl amines, this tandem oxidation−[2,3]-sigmatropic rearrangement−nucleophilic substitution process was low yielding (see the Experimental Section). A possible solution to this problem could be to follow a different approach, see ref 15d. However, we decided to employ this strategy for all our substrates due to the inherent convenience of utilizing the "one-pot" reaction sequence. (d) Kanakarajan, K.; Meier, H. *Angew. Chem.* **1984**, *96*, 220.
(16) (a) Miller, E. G.; Rayner, D. R.; Thomas, H. T.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4861. (b) Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4869. (c) Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 2100. (d) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147.

Thus, we observed that the ^{13}C NMR spectra show a signal at 165.3−166.4 ppm corresponding to the carbonyl group in the benzothiazin-2-one adducts **2a**−**g** and that the infrared spectra display a thiourethane $\gamma_{C=O}$ bond at 1635, 1643, or 1647 cm^{-1}. In addition, the structure of **2e** was also confirmed by X-ray crystallographic analysis (see Figure 2).

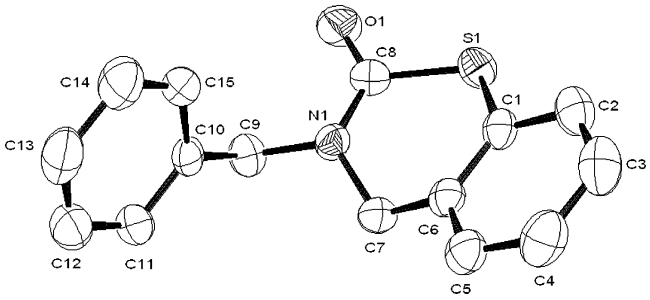
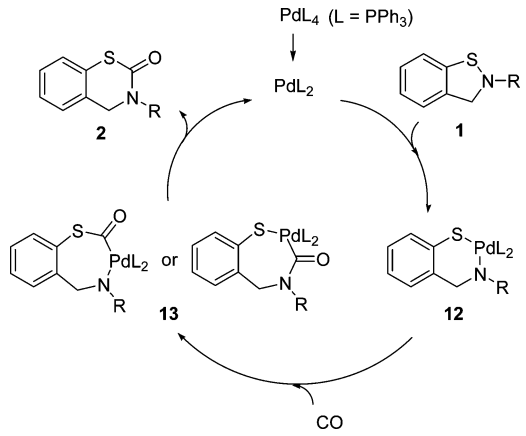


FIGURE 2. ORTEP view of compound **2e**.

A plausible mechanism for the palladium-catalyzed carbonylation of 2-substituted-2,3-dihydro-1,2-benzisothiazoles is proposed in Scheme 3. After the loss of phosphine ligands, the resulting coordinatively unsaturated Pd(0) complex inserts into the N−S bond of **1** via oxidative addition generating a Pd(II) species **12**. Insertion of carbon monoxide into the S−Pd bond or the N−Pd bond in **12** produces a transient palladium−carbonyl intermediate **13**, which affords the desired product **2** and regenerates the catalyst via reductive elimination. This mechanism is also consistent with the trend in yields observed in our experiments, since it is well-known that Pd reactions are particularly sensitive to steric factors.

SCHEME 3. Proposed Mechanism for the Palladium-Catalyzed Carbonylation of 1



In conclusion, we have described a novel approach toward the synthesis of 3-substituted-3,4-dihydro-2*H*-1,3-benzothiazin-2-ones that relies on the palladium-catalyzed carbonylation reaction of 2-substituted-2,3-dihydro-1,2-benzisothiazoles. This carbonylative insertion process occurs in good to excellent yields with total regioselectivity at the N−S bond of the benzisothiazole precursor and the reaction tolerates a number of substituents, including primary and secondary alkyl groups and benzylic and naphthylmethyl functionalities.

Experimental Section

The synthesis and purification of the substrates **1a**−**g** are described in the Supporting Information. Anhydrous pyridine was purchased from Aldrich and was used without further purification. Tetrakis(triphenylphosphine)palladium(0) was purchased from Strem Chemicals.

3-Butyl-3,4-dihydro-2*H*-1,3-benzothiazin-2-one (2a): Typical Procedure for the Palladium-Catalyzed Carbonylation Reaction of 2-Substituted-2,3-dihydro-1,2-benzisothiazoles 1a−g. Based on the method of Kuniyasu et al.,[17] into a 50 mL stainless steel autoclave containing a glass liner and stirring bar were added freshly prepared 2-substituted-2,3-dihydro-1,2-benzisothiazole (**1a**) (97 mg, 0.5 mmol), anydrous pyridine (1 mL), and $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) under an argon atmosphere. The autoclave was then purged three times with carbon monoxide and pressured to 300 psi. The reaction mixture was stirred at 80 °C for 24 h, cooled to room temperature, and diluted with a 1:1 mixture of hexanes−diethyl ether (ca. 25 mL). The precipitate was filtered through Celite and washed several times with hexanes−diethyl ether (1:1). The filtrate was concentrated in vacuo and the crude mixture was purified by flash chromatography on silica using a mixture of hexanes−methylene chloride (polarity increasing from 3.5:1.5 to 1:1) as eluent. **2a** (102 mg, 92%) was isolated as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$ with TMS) δ 7.29−7.22 (m, 4 H), 4.39 (s, 2H), 3.53 (t, J = 6.4 Hz, 2H), 1.64−1.54 (m, 2H), 1.38−1.25 (m, 2H), 0.92 (t, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ with TMS) δ 165.3 (s), 132.9 (s), 131.3 (s), 128.3 (d), 126.6 (d), 126.1 (d), 126.0 (d), 52.8 (t), 49.0 (t), 29.9 (t), 19.9 (t), 13.8 (q); EI-HMRS calcd for $C_{12}H_{15}NOS$ $[M]^+$ 221.0874, found 221.0881.

3-Isobutyl-3,4-dihydro-2*H*-1,3-benzothiazin-2-one (2b): ^1H NMR (300 MHz, $CDCl_3$ with TMS) δ 7.29−7.22 (m, 4H), 4.39 (s, 2H), 3.36 (d, J = 8.7 Hz, 2H), 2.06−1.92 (m, 1H), 0.89 (d, J = 7.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$ with TMS) δ 165.6 (s), 133.0 (s), 131.4 (s), 128.3 (d), 126.6 (d), 126.1 (d), 126.0 (d), 56.5 (t), 53.5 (t), 27.6 (d), 19.9 (2q); EI-HMRS calcd for $C_{12}H_{15}NOS$ $[M]^+$ 221.0874, found 221.0868.

3-Isopropyl-3,4-dihydro-2*H*-1,3-benzothiazin-2-one (2c): ^1H NMR (300 MHz, $CDCl_3$ with TMS) δ 7.30−7.19 (m, 4H), 4.84−4.70 (m, 1H), 4.25 (s, 2H), 1.21 (d, J = 6.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$ with TMS) δ 165.6 (s), 133.2 (s), 132.0 (s), 128.3 (d), 126.6 (d), 126.0 (d), 125.9 (d), 46.8 (d), 45.7 (t), 19.9 (2q); EI-HMRS calcd for $C_{11}H_{13}NOS$ $[M]^+$ 207.0718, found 207.0696.

3-Cyclohexyl-3,4-dihydro-2*H*-1,3-benzothiazin-2-one (2d): ^1H NMR (300 MHz, $CDCl_3$ with TMS) δ 7.30−7.21 (m, 4H), 4.40−4.30 (m, 1H), 4.27 (s, 2H), 1.85−1.67 (m, 5H), 1.55−1.31 (m, 4H), 1.21−1.06 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ with TMS) δ 165.8 (s), 133.3 (s), 132.2 (s), 128.2 (d), 126.6 (d), 126.0 (d), 125.8 (d), 55.0 (d), 46.8 (t), 30.3 (2t), 25.5 (2t), 25.4 (t); EI-HMRS calcd for $C_{14}H_{17}NOS$ $[M]^+$ 247.1031, found 247.1009.

3-Benzyl-3,4-dihydro-2*H*-1,3-benzothiazin-2-one (2e): ^1H NMR (300 MHz, $CDCl_3$ with TMS) δ 7.36−7.26 (m, 7H), 7.20−7.14 (m, 1H), 7.07−7.04 (m, 1H), 4.73 (s, 2H), 4.29 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$ with TMS) δ 166.1 (s), 135.9 (s), 132.4 (s), 130.9 (s), 128.8 (2d), 128.3 (d), 128.0 (2d), 127.8 (d), 126.6 (d), 126.2 (d), 125.9 (d), 51.9 (2t); EI-HMRS calcd for $C_{15}H_{13}NOS$ $[M]^+$ 255.0718, found 255.0739.

3-(4-Methoxybenzyl)-3,4-dihydro-2*H*-1,3-benzothiazin-2-one (2f): ^1H NMR (300 MHz, $CDCl_3$ with TMS) δ 7.25−7.24 (m, 2H), 7.21−7.18 (m, 2H), 7.16−7.12 (m, 1H), 7.06−7.03 (m, 1H), 6.86−6.81 (m, 2H), 4.64 (s, 2H), 4.25 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ with TMS) δ 166.4 (s), 159.7 (s), 132.9 (s), 131.4 (s), 129.9 (2d), 128.7 (d), 128.4 (s), 127.0 (d), 126.7 (d), 126.4 (d), 114.6 (2d), 55.7 (q), 52.1 (t), 51.8 (t); EI-HMRS calcd for $C_{16}H_{15}NO_2S$ $[M]^+$ 285.0823, found 285.0803.

(17) (a) Kuniyasu H.; Hiraike H.; Morita M.; Tanaka A.; Sugoh K.; Kurosawa H. *J. Org. Chem.* **1999**, *64*, 7305. For some other examples on Pd-mediated carbonylation of the N−S bond, see: (b) Knapton, D. J.; Meyer, T. Y. *J. Org. Chem.* **2005**, *70*, 785. (c) Kuniyasu, H.; Kato, T.; Asano, S.; Ye, J. H.; Ohmori, T.; Morita, M.; Hiraike, H.; Fujiwara, S. I.; Terao, J.; Kurosawa, H.; Kambe, N. *Tetrahedron Lett.*, **2006**, *47*, 1141.

3-(1-Naphthylmethyl)-3,4-dihydro-2*H*-1,3-benzothiazin-2-one (2g): ^{1}H NMR (300 MHz, $CDCl_3$ with TMS) δ 7.98−7.95 (m, 1H), 7.83−7.76 (m, 2H), 7.47−7.32 (m, 4H), 7.21−7.14 (m, 2H), 7.03 (td, J = 7.0, 1.9 Hz, 1H), 6.85−6.83 (m, 1H), 5.14 (s, 2H), 4.23 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$ with TMS) δ 165.8 (s), 133.7 (s), 132.2 (s), 131.4 (s), 131.1 (s), 130.8 (s), 128.8 (d), 128.7 (d), 128.2 (d), 126.8 (d), 126.7 (d), 126.5 (d), 126.2 (d), 126.1 (d), 125.8 (d), 125.1 (d), 123.3 (d), 51.2 (t), 49.7 (t); EI-HMRS calcd for $C_{19}H_{15}NOS$ $[M]^+$ 305.0874, found 305.0902.

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

Supporting Information Available: Experimental procedures, full characterization data, and ^{1}H and ^{13}C NMR spectra of all compounds, as well as X-ray crystallographic data of compound **2e**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702146N