ORGANIC LETTERS

2010
Vol. 12, No. 23
5567−5569

# Palladium-Catalyzed Domino Ring-Opening/Carboxamidation Reactions of *N*-Tosyl Aziridines and 2-Iodothiophenols: A Facile and Efficient Approach to 1,4-Benzothiazepin-5-ones

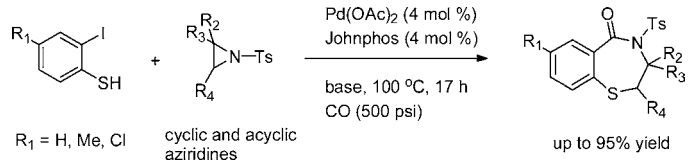
**Fanlong Zeng and Howard Alper***

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

*howard.alper@uottawa.ca*

**Received October 4, 2010**

## ABSTRACT




**A novel and efficient domino procedure has been developed for the synthesis of 1,4-benzothiazepin-5-ones from simple and readily accessible *N*-tosyl aziridines and *o*-iodothiophenols. This process involves aziridines ring-opening with *o*-iodothiophenols, followed by palladium-catalyzed intramolecular carboxamidation. The scope and limitation of this transformation have been investigated in detail by using various aziridines and *o*-iodothiophenols.**

1,4-Thiazepinone moieties represent an important class of heterocyclic compounds with diverse potential biological and pharmacological activities. For example, they can be used as calcium channel blockers,[1] bradykinin agonists,[2] HIV-1 integrase and reverse transcriptase inhibitors,[3] and antitumor,[4] antiplatelet,[5] and antidepressant agents.[6] The traditional methods for the synthesis of 1,4-thiazepinone scaffolds include metal-free reactions, which often afford disulfides as accompanying products, harsh reaction conditions, low regioselectivity, multistep reactions, and low yields.[7] Transition metal-catalyzed synthesis of sulfur-containing compounds has attracted considerable attention in the past decade.[8] Several complexes of transition metals such as palladium,[9] nickel,[10] copper,[11] cobalt,[12] indium,[13] zirconium,[14] rhodium,[15] and iron[16] have been used for this purpose. Nevertheless, these transformations can also result

(1) Floyd, D. M.; Kimball, S. D.; Krapcho, J.; Das, J.; Turk, C. F.; Moquin, R. V.; Lago, M. W.; Duff, K. J.; Lee, V. G.; White, R. E. *J. Med. Chem.* **1992**, *35*, 756.

(2) (a) Amblard, M.; Daffix, I.; Bedos, P.; Bergé, G.; Pruneau, D.; Paquet, J. L.; Luccarini, J. M.; Belichard, P.; Dodey, P.; Martinez, J. *J. Med. Chem.* **1999**, *42*, 4185. (b) Amblard, M.; Daffix, I.; Bergé, G.; Calmès, M.; Dodey, P.; Pruneau, D.; Paquet, J. L.; Luccarini, J. M.; Belichard, P.; Martinez, J. *J. Med. Chem.* **1999**, *42*, 4193.

(3) (a) Neamati, N.; Turpin, J. A.; Winslow, H. E.; Christensen, J. L.; Williamson, K.; Orr, A.; Rice, W. G.; Pommier, Y.; Garofalo, A.; Brizzi, A.; Campiani, G. *J. Med. Chem.* **1999**, *42*, 3334. (b) Maruenda, H.; Johnson, F. *J. Med. Chem.* **1995**, *38*, 2145.

(4) Garofalo, A.; Campiani, G.; Fiorini, I.; Nacci, V. *Farmaco* **1993**, *48*, 275.

(5) Li, R.; Farmer, S. P.; Xie, M.; Quilliam, M. A.; Pleasance, S.; Howlett, S. E.; Yeung, P. K. F. *J. Med. Chem.* **1992**, *35*, 3246.

(6) Krapcho, J.; Turk, C. F. *J. Med. Chem.* **1966**, *9*, 191.

(7) (a) Ilyn, A. P.; Loseva, M. V.; Vvedensky, V. Y.; Putsykina, E. B.; Tkachenko, S. E.; Kravchenko, D. V.; Khvat, A. V.; Krasavin, M. Y.; Ivachtchenko, A. V. *J. Org. Chem.* **2006**, *71*, 2811. (b) Bakthadoss, M.; Murugan, G. *Synth. Commun.* **2008**, *38*, 3406. (c) Smirnov, A. V.; Kalandadze, L. S.; Sakharov, V. N.; Dorogov, M. V.; Ivachtchenko, A. V. *J. Heterocycl. Chem.* **2007**, *44*, 1247. (d) Tu, S.-J.; Cao, X.-D.; Hao, W.-J.; Zhang, X.-H.; Yan, S.; Wu, S.-S.; Han, Z.-G.; Shi, F. *Org. Biomol. Chem.* **2009**, *7*, 557. (e) Crescenza, A.; Botta, M.; Corelli, F.; Santini, A.; Tafi, A. *J. Org. Chem.* **1999**, *64*, 3019.

(8) (a) Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 335. (b) Kondo, T.; Mitsudo, T.-A. *Chem. Rev.* **2000**, *100*, 3205. (c) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.

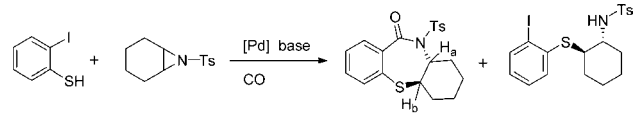
10.1021/ol102394h 
**Published on Web 11/04/2010**

in the deactivation of catalysts by sulfur-containing compounds owing to their strong coordination and absorption properties with transition metals. Hence, exploring new strategies to circumvent these drawbacks is still a highly desirable goal.

Domino reactions are emerging as one of most efficient and powerful tools in generating complex molecular architectures from readily available intermediates.[17] This strategy is characterized by the concomitant formation of multiple new bonds in a single operation, which can minimize the amount of requisite regents, separation processes, chemical waste, energy, time, and cost. Our research focuses on the pursuit of highly efficient and environmentally benign protocols for the synthesis of carbonyl-containing compounds via carbonylation reactions. Recently, we described new domino approaches for the synthesis of quinazolino[3,2-*a*]-quinazolinones,[18] quinazolin-4(3*H*)-ones,[19] isoquinolinones,[20] 1,4-benzo- or pyrido-oxazepinones,[21] 2-acetyl-3,4-dihydronaphthalenones,[22] and 2-carboxyindoles.[23] Herein, we report a highly novel and efficient domino strategy to synthesize 1,4-benzothiazepin-5-ones from readily accessible *N*-tosyl aziridines and *o*-iodothiophenols.

Initially, the reaction of 2-iodothiophenol (**1a**) with the *N*-tosyl aziridine of cyclohexene (**2a**) was selected as the model reaction to investigate the feasibility and efficiency of the new domino protocol (Table 1). Under 500 psi of CO in the presence of 3.0 equiv of $Et_3N$, 4 mol % of $Pd(OAc)_2$, and dppf, at 100 °C for 17 h, the reaction gave only trace amounts of the desired product **3a**, forming the ring-opening product **3a′** in 67% isolated yield (Table 1, entry 1). When xantphos, (±)-binap, and dppb were employed as ligands instead of dppf, the desired 1,4-thiazepinone **3a** was isolated in 41%, 41%, and 83% yield, respectively (Table 1, entries 2, 5, and 6). We were pleased to observe that performing the same reaction but using (2-biphenyl)di-*tert*-butylphosphine (Johnphos) as the ligand increased the yield of **3a** to 93% (Table 1, entry 8). It is noteworthy that using 2.0 equiv of phosphine ligands, i.e., xantphos, afforded the intermediate **3a′** as the main product, which reveals that the ligand/catalyst ratios play a key role in this process (Table 1, entry 3). Running the reaction at lower loading of palladium precursors or at lower pressure of carbon monoxide hampered the reaction efficiency (Table 1, entries 9 and 10). Surprisingly, the inorganic base, $Cs_2CO_3$, is inferior to other bases, such as $K_2CO_3$ and $Et_3N$ (Table 1, entry 13).

**Table 1.** Optimization of the Reaction Conditions Using 2-Iodothiophenol with 7-Tosyl-7-azabicyclo[4.1.0]heptane[a]




1a 2a 3a 3a'

| entry | ligand (L/[Pd]) | solvent | base | **3a** (%)[b] | **3a′** (%)[b] |
|---|---|---|---|---|---|
| 1 | dppf (1.0) | THF | $Et_3N$ | trace | 67 |
| 2 | xantphos (1.0) | THF | $Et_3N$ | 41 | n.d. |
| 3 | xantphos (2.0) | THF | $Et_3N$ | n.d. | 69 |
| 4 | xantphos (1.0) | THF | $Et_3N$ | 36 | trace[c] |
| 5 | (±)-binap (1.0) | THF | $Et_3N$ | 41 | n.d. |
| 6 | dppb (1.0) | THF | $Et_3N$ | 83 | n.d. |
| 7 | Johnphos (2.0) | THF | $Et_3N$ | 67 | 18 |
| 8 | Johnphos (1.0) | THF | $Et_3N$ | 93 | n.d. |
| 9 | Johnphos (1.0) | THF | $Et_3N$ | 80 | trace[d] |
| 10 | Johnphos (1.0) | THF | $Et_3N$ | 80 | 16[e] |
| 11 | Johnphos (1.0) | $CH_3CN$ | $Et_3N$ | 85 | n.d. |
| 12 | Johnphos (1.0) | PhMe | $Et_3N$ | 88 | n.d. |
| 13 | Johnphos (1.0) | THF | $Cs_2CO_3$ | 20 | trace |
| 14 | Johnphos (1.0) | THF | $K_2CO_3$ | 89 | n.d. |
| 15 | Johnphos (1.0) | dioxane | $K_2CO_3$ | 93 | n.d. |

[a] All reactions were carried out with 0.5 mmol of **1a**, 0.55 mmol of **2a**, 0.02 mmol of $Pd(OAc)_2$, 3.0 equiv of base, 6 mL of solvent, 500 psi of CO, 100 °C, 17 h. [b] Isolated yield based on 2-iodothiophenol. [c] [Pd] = $Pd_2(dba)_3{\cdot}CHCl_3$. [d] $P_{CO}$ = 300 psi. [e] [Pd] = 0.01 mmol of $Pd(OAc)_2$.

(9) (a) Fu, C. F.; Liu, Y. H.; Peng, S.-M.; Liu, S.-T. *Tetrahedron* **2010**, *66*, 2119. (b) Fernández-Rodríguez, M. A.; Hartwig, J. F. *Chem.—Eur. J.* **2010**, *16*, 2355. (c) Bryan, C.; Braunger, J. A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7064. (d) Lee, J.-Y.; Lee, P. H. *J. Org. Chem.* **2008**, *73*, 7413. (e) Fernández-Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180. (f) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587. (g) Alvaro, E.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 7858.

(10) (a) Jammi, S.; Barua, P.; Rout, L.; Saha, P.; Punniyamurthy, T. *Tetrahedron Lett.* **2008**, *49*, 1484. (b) Zhang, Y.; Ngeow, K. C.; Ying, J. Y. *Org. Lett.* **2007**, *9*, 3495. (c) Cristau, H. J.; Chabaud, B.; Chene, A.; Christol, H. *Synthesis* **1981**, 892.

(11) (a) Ma, D.; Xie, S.; Xue, P.; Zhang, X.; Dong, J.; Jiang, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 4222. (b) Carril, M.; SanMartin, R.; Domínguez, E.; Tellitu, I. *Chem.—Eur. J.* **2007**, *13*, 5100. (c) Verma, A. K.; Singh, J.; Chaudhary, R. *Tetrahedron Lett.* **2007**, *48*, 7199. (d) Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863. (e) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803. (f) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517. (g) Kabir, M. S.; Lorenz, M.; Van Linn, M. L.; Namjoshi, O. A.; Ara, S.; Cook, J. M. *J. Org. Chem.* **2010**, *75*, 3626. (h) Firouzabadi, H.; Iranpoor, N.; Gholinejada, M. *Adv. Synth. Catal.* **2010**, *352*, 119. (i) Chen, C.-K.; Chen, Y.-W.; Lin, C.-H.; Lin, H.-P.; Lee, C.-F. *Chem. Commun.* **2010**, 282. (j) Jiang, Y.; Qin, Y.; Xie, S.; Zhang, X.; Dong, J.; Ma, D. *Org. Lett.* **2009**, *11*, 5250. (k) Bhadra, S.; Sreedhar, B.; Ranu, B. C. *Adv. Synth. Catal.* **2009**, *351*, 2369. (l) Zhao, Q.; Li, L.; Fang, Y.; Sun, D.; Li, C. *J. Org. Chem.* **2009**, *74*, 459. (m) Kabir, M. S.; Van Linn, M. L.; Monte, A.; Cook, J. M. *Org. Lett.* **2008**, *10*, 3363. (n) Sperotto, E.; van Klink, G. P. M.; de Vries, J. G.; van Koten, G. *J. Org. Chem.* **2008**, *73*, 5625. (o) Rout, L.; Sen, T. K.; Punniyamurthy, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5583. (p) Gan, J.; Ma, D. *Org. Lett.* **2009**, *11*, 2788.

(12) Wong, Y.-C.; Jayanth, T. T.; Cheng, C.-H. *Org. Lett.* **2006**, *8*, 5613.

(13) (a) Reddy, V. P.; Kumar, A. V.; Swapna, K.; Rao, K. R. *Org. Lett.* **2009**, *11*, 1697. (b) Reddy, V. P.; Swapna, K.; Kumar, A. V.; Rao, K. R. *J. Org. Chem.* **2009**, *74*, 3189.

(14) Weiss, C. J.; Marks, T. J. *J. Am. Chem. Soc.* **2010**, *132*, 10533.

(15) Cao, C.; Fraser, L. R.; Love, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 17614.

(16) (a) Correa, A.; Carril, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 2880. (b) Qiu, J.-W.; Zhang, X.-G.; Tang, R.-Y.; Zhong, P.; Lia, J.-H. *Adv. Synth. Catal.* **2009**, *351*, 2319. (c) Wu, J.-R.; Lin, C.-H.; Lee, C.-F. *Chem. Commun.* **2009**, 4450. (d) Wu, W.-Y.; Wang, J.-C.; Tsai, F.-Y. *Green Chem.* **2009**, *11*, 326.

(17) For selected reviews on domino reactions, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195. (c) Ikeda, S.-I. *Acc. Chem. Res.* **2000**, *33*, 511. (d) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH, Verlag GmbH & Co: Weinheim, Germany, 2006. (e) Hussain, M. M.; Walsh, P. J. *Acc. Chem. Res.* **2008**, *41*, 883. (f) Sun, X. L.; Tang, Y. *Acc. Chem. Res.* **2008**, *41*, 937.

(18) Zeng, F. L.; Alper, H. *Org. Lett.* **2010**, *12*, 3642.

(19) (a) Zeng, F. L.; Alper, H. *Org. Lett.* **2010**, *12*, 1188. (b) Zheng, Z.; Alper, H. *Org. Lett.* **2008**, *10*, 829.

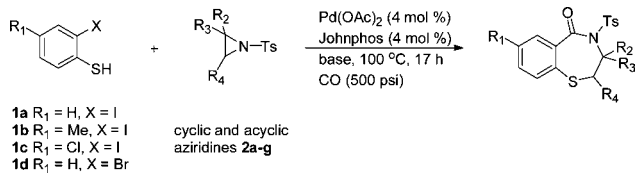
(20) (a) Zheng, Z.; Alper, H. *Org. Lett.* **2008**, *10*, 4903. (b) Chouhan, G.; Alper, H. *Org. Lett.* **2008**, *10*, 4987. (c) Chouhan, G.; Alper, H. *J. Org. Chem.* **2009**, *74*, 6181.

(21) Chouhan, G.; Alper, H. *Org. Lett.* **2010**, *12*, 192.

(22) Zheng, Z.; Alper, H. *Org. Lett.* **2009**, *11*, 3278.

(23) Vieira, T. O.; Meaney, L. A.; Shi, Y.-L.; Alper, H. *Org. Lett.* **2008**, *10*, 4899.

**Table 2.** Domino Ring-Opening/Carboxamidation Reactions of 2-Halothiophenols **1a**−**d** with *N*-Tosyl Aziridines[a]




**1a** $R_1$ = H, X = I
**1b** $R_1$ = Me, X = I
**1c** $R_1$ = Cl, X = I
**1d** $R_1$ = H, X = Br

cyclic and acyclic aziridines **2a-g**

| entry | 1 | 2 | product | yield (%)[b] |
|---|---|---|---|---|
| 1 | **1a** | **2a** | **3a** | 93 |
| 2 | **1b** | **2a** | **3b** | 95 |
| 3 | **1c** | **2a** | **3c** | 94 |
| 4 | **1d** | **2a** | **3d′** | 84 |
| 5 | **1a** | **2b** | **3e** | 79[c] (37[a]) |
| 6 | **1b** | **2b** | **3f** | 74[c] |
| 7 | **1c** | **2b** | **3g** | 75[c] |
| 8 | **1a** | **2c** | **3h** | 64[c] |
| 9 | **1a** | **2d** | **3i′** | 25[c] |
| 10 | **1a** | **2e** | **3j** | 92[c] |
| 11 | **1a** | **2f** | **3k** | 65[c] |
| 12 | **1a** | **2g** | **3l** | 68[c] |

[a] All reactions were carried out with 0.50 mmol of **1,** 0.55 mmol of **2**, $Pd(OAc)_2$/Johnphos/**1** = 4:4:100, 3.0 equiv of $Et_3N$, 6 mL of THF, 500 psi of CO, 100 °C, 17 h. [b] Isolated yield based on 2-halothiophenol. [c] All reactions were carried out with 0.50 mmol of **1,** 0.55 mmol of **2**, $Pd(OAc)_2$/Johnphos/**1** = 4:4:100, 3.0 equiv of $K_2CO_3$, 6 mL of dioxane, 500 psi of CO, 100 °C, 17 h.

The trans stereochemistry of the product **3a** was determined by measuring the coupling constant of the methine proton $H_a$ (ddd, $J$ = 11.6, 11.6, and 3.4 Hz) at 3.80 ppm (−CH−N−) in $^1$H NMR spectrum, and further confirmed by NOESY spectra as no NOE effects were detected between $H_a$ and $H_b$ (see the Supporting Information).

Under the optimized reaction conditions, the scope and generality of the present cascade strategy were explored by reacting *o*-halothiophenols (**1a**−**d**) with various *N*-tosyl aziridines, and the results are summarized in Table 2.

The reaction of the *N*-tosyl aziridine of cyclohexene with 2-iodothiophenol, 4-methyl-2-iodothiophenol, and 4-chloro-2-iodothiophenol furnished the corresponding 1,4-thiazepinone moieties **3a**−**c** in 93%, 95%, and 94% yield, respectively, demonstrating that this transformation tolerates both electron-donating (*p*-Me) and electron-withdrawing (*p*-Cl) groups on the phenyl group of the thiophenol (Table 2, entries 1−3). With the five- and seven-membered ring-fused aziridines instead of **2a**, the yields of the desired products **3e**−**h** decreased slightly (64%−79%, entries 5−8). However, when the eight-membered ring-fused aziridine **2d** was employed, the desired product was not formed, only giving the intermediate **3i′** in 25% yield (Table 2, entry 9). Treatment of 2-bromothiophenol with **2a** afforded the intermediate **3d′** in an 84% yield. The difference in behavior, compared to that of *o*-iodothiophenol (**1a**), may be due to the lower rate of oxidative addition of the Ar−Br moiety to the in situ formed palladium(0) species. The same transformations of 2-iodothiophenol with unsaturated ring-fused aziridines and acyclic aziridine work efficiently, leading to the corresponding 1,4-thiazepinone moieties **3j**−***l*** in good isolated yields (Table 2, entries 10−12). The stereochemistry of the products **3k** and ***3l*** was confirmed by the HSQC and DEPT-135 NMR spectroscopic analysis.

In conclusion, a highly novel and efficient protocol for the synthesis of 1,4-benzothiazepin-5-one moieties has been developed based on the one-pot palladium-catalyzed tandem ring-opening/carboxamidation reactions. A range of 1,4-benzothiazepin-5-one scaffolds were obtained in good to excellent yields. This methodology provides a versatile, practical, and straightforward access to these potentially useful sulfur-containing compounds.

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

**Supporting Information Available:** Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102394H