Copper(II) Acetate Promoted Intramolecular Carboamination of Alkenes: An Efficient Synthesis of Pentacyclic Sultams

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Abstract: Copper(II) acetate promoted intramolecular carboamination reactions of 5-allyl-*N*-sulfonylated coumarins and quinolones have been described. The hitherto unreported pentacyclic sultams, obtained by the oxidative cyclization in high yields, are potential intermediates in the synthesis of nitrogen-containing heterocyclic compounds.

Key words: aza-Claisen rearrangement, sultams, copper(II) acetate, oxidative cyclization, intramolecular carboamination

The importance of sulfonamide moiety and its derivatives is well recognized due to their extensive chemical and biological profiles in drug discovery.[1] Recently, most famous example of sulfonamide functionality is Sildenafil (Viagra). Besides, sulfonamides being used for the development of novel peptidomimetics,[2] glycoprotein IIB/IIA inhibitors,[3] nonpeptidal HIV protease inhibitors,[4] and endothelin-A receptor antagonists.[5] High interest has also been directed to their cyclic counterparts, the sultams. Though sultams are not found in nature[6] but show wide applications in biological chemistry;[7] being used as NF-κB inhibitors,[8] anti-inflammatory agent,[9] glucokinase activator,[10] antiviral and anticancer activator.[11] Some other bioactive sultams are brinzolamide[12] for the treatment of glaucoma, antiepileptic agent sulthiame,[13] COX-2 inhibitors S-2474,[14] selective inhibitors of calpain I,[15] benzodithiazine dioxides[11] displaying anti-HIV-1 activity, and most recently pyrrolo[1,2-*b*][1,2,5]benzothiadiazepines,[7a] a new class of potential agent for the treatment against chronic myelogenous leukemia. Besides, from chemical point of view sultams have been used as efficient chiral auxiliaries[16] or reagents.[17]

On the other hand, coumarin and quinolones are subunits in numerous natural products that exhibit a wide range of biological activities such as antibacterial, antifungal, antiallergic, and DNA-gyrase inhibition.[18] In continuation of our interest in the synthesis of bioactive heterocycles using Pd-[19] and Ru-[20]catalyzed intramolecular cyclization, we became interested to synthesize polycyclic sultams containing a bioactive coumarin or quinolone subunit. These particular analogues may be interesting to medicinal chemists and pharmacologists.

From the last decades several methodologies have been developed for the synthesis of various sultams – such as Pictet–Spengler cyclization,[21] Friedel–Crafts reaction,[22] sulfonamide dianion alkylation,[23] cyclization of aminosulfonyl chlorides,[24] [3+2] cycloadditions,[25] and Diels–Alder reactions.[26] Recently, a number of transition-metal-catalyzed approaches for the synthesis of sultams have come to light, including the use of Pd-[27], Au-[28], Rh-,[29] and Ru-[30]catalyzed cyclization. But in all the cases the catalysts used are costly. Chemler et al. have reported the synthesis of sultams using less expensive Cu catalyst.[31] Besides, there are little report on the ability of Cu(II) salts to promote the addition of unfunctionalized nitrogen to olefins to form sp^3-carbon centers.[31,32] Therefore, in order to explore the importance of Chemler's methodology, we have used this less expensive copper(II)-promoted intramolecular oxidative cyclization methodology for the synthesis of coumarin- and quinolone-containing sultams which may possess potential bioactivity. Herein, we report our results.

The required carboamination precursors **5a**–**h** were prepared by the arylsulfonylation of compounds **4a**–**c** in pyridine at 80 °C for 2 hours. Substrate **4c** failed to give the corresponding 4-methoxybenzene sulfonyl derivative, instead the 2,3-dihydropyrrolocoumarin derivative **6** was obtained. The compounds **4a**–**c** in turn can be prepared by aza-Claisen rearrangement of compounds **2a**–**c**. The aza-Claisen precursors **2a**–**c** can in turn be prepared by the reaction of 6-amino coumarin **1c** or 6-amino quinolones **1a**,**b** and allyl bromide in refluxing acetone in the presence of anhydrous K_2CO_3 (Scheme 1). We also tried to synthesize compound **5b** by first tosylation of **2a** and then by aza-Claisen rearrangement of the compound **3b**. But the desired product was not obtained. Presence of an additional alkyl group in the *N*-allyl aniline greatly increases the rate of the aromatic aza-Claisen rearrangement.[33] That is the reason why **3b** – with strong electron-withdrawing substituent (tosyl) – failed to undergo aza-Claisen rearrangement to give the product **5b**. The aza-Claisen rearrangements of the substrates **2a**–**c** are better carried out in a sealed tube with $BF_3{\cdot}OEt_2$ as catalyst in chlorobenzene for 6 hours.

We next turned our attention to the synthesis of tetracyclic sultams by carboamination reaction of compounds **5a**–**h**. Substrate **5a**, when treated with $Cu(OAc)_2$ (3 equiv) and Cs_2CO_3 (1 equiv) in MeCN in a sealed tube for 7 hours, gave the carboamination product **7a** in 82% yield.[34] The

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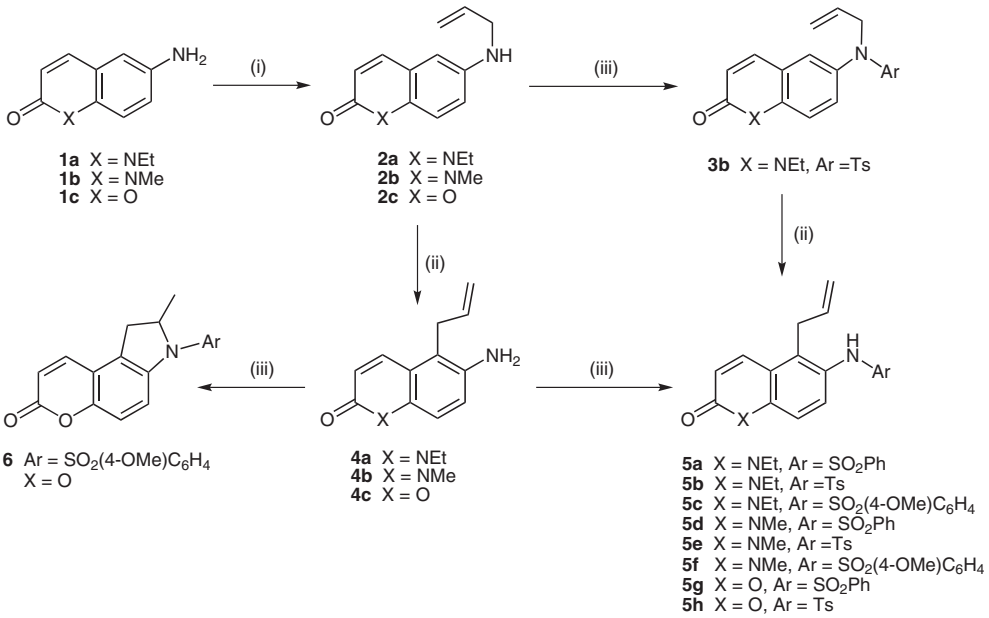
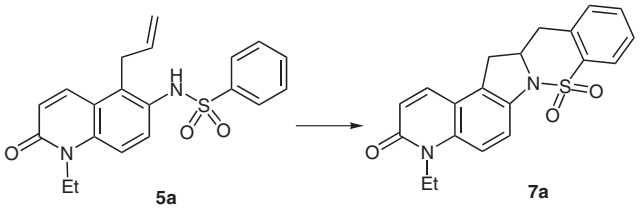


Scheme 1 *Reagents and conditions*: (i) allyl bromide, acetone, K_2CO_3, reflux, 3 h (ii) $BF_3{\cdot}OEt_2$, chlorobenzene, sealed tube, 140 °C, 6 h; (iii) pyridine, $ArSO_2Cl$, 80 °C, 2 h.

optimized conditions for the carboamination reaction has been achieved through a series of experiments by changing solvent, base, and temperature (Table 1).

Treatment of **5a** with $Cu(OAc)_2$ (3 equiv) and Cs_2CO_3 (1 equiv) in MeCN at 90 °C in a sealed tube provided 25% yield of the desired product **7a** after 7 hours (entry 1). When the same reaction was carried out at 120 °C for 7 hours the product was obtained in 82% yield (entry 2). A 32% yield of the product was obtained when K_2CO_3 (2 equiv) was used as a base in place of Cs_2CO_3 (entry 3). In the absence of any base the reaction became very sluggish, and only 9% yield of the product **7a** was obtained after 7 hours (entry 4). Addition of DMSO (4 equiv) in the reaction mixture did not improve the yield of the product (entry 5). Similarly, change of the solvent did not influence the yield of the product (entry 6). Only 22% yield was obtained when DMF was used as a solvent and K_2CO_3 (2 equiv) as a base (entry 7). The requirement of overstoichiometric amounts of Cu(II) salt is perhaps due to the disproportionation reaction of Cu(II) to Cu(I) and Cu(III) intermediates. Among the various conditions employed it had been observed that the reaction in MeCN as solvent and Cs_2CO_3 (1 equiv) as base gave the best result (Table 1).

Table 1 Effect of Reaction Conditions on Oxidative Cyclization of **5a**



Entry	Solvent	Base (equiv)	Temp (°C)	Time (h)	Yield (%)
1	MeCN	Cs_2CO_3 (1)	90	7	25
2	MeCN	Cs_2CO_3 (1)	120	7	82
3	MeCN	K_2CO_3 (2)	120	7	32
4	MeCN	–	120	7	9
5[a]	MeCN	Cs_2CO_3 (1)	120	7	80
6	DMF	Cs_2CO_3 (1)	120	7	79
7	DMF	K_2CO_3 (2)	120	7	22

[a] DMSO (4 equiv) was added.

Using the optimized conditions, we have examined the oxidative cyclization (or carboamination) reaction of various starting materials **7b–h**. The results are listed in Table 2.

Treatment of **5b** with $Cu(OAc)_2$ and Cs_2CO_3 (1 equiv) in MeCN at 120 °C for 7 hours in a sealed tube gave product **7b** in 85% yield. Similarly, compound **5c** furnished product **7c** in 74% yield. When the same reactions were carried out with **5d** and **5e** products **7d** and **7e** were obtained in 79% and 80% yields, respectively. The product **7f** was obtained in 68% yield when the reaction was carried out with **5f**. Under the similar reaction conditions **5g** and **5h** afforded products **7g** and **7h** in 75% and 78% yields, respectively, after 12 hours. The products were characterized from their elemental analyses and spectroscopic data.

Table 2 Oxidative Cyclization Reaction of **5a–h**

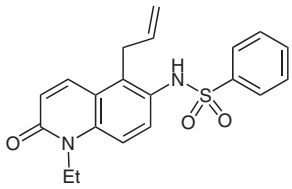
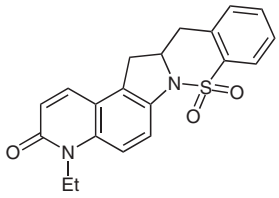
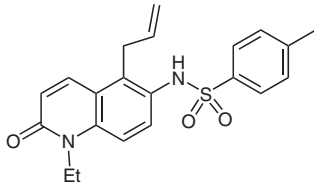
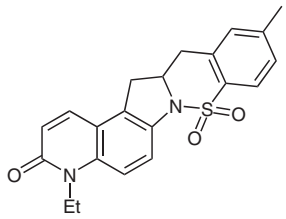
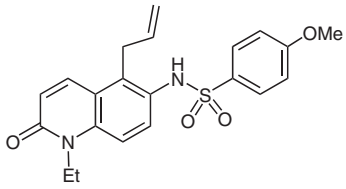
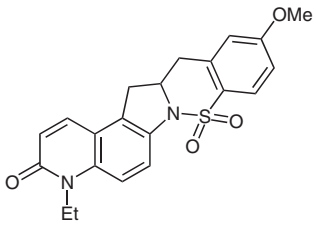
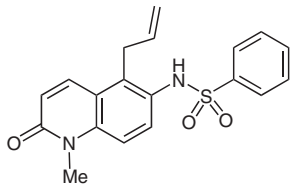
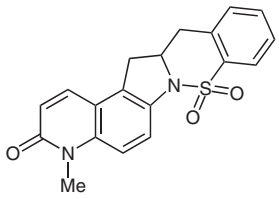
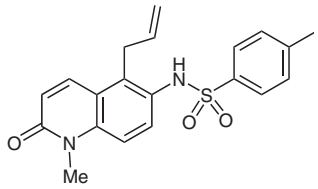
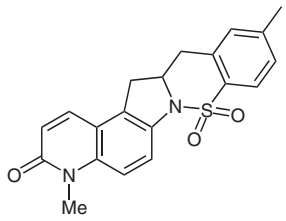
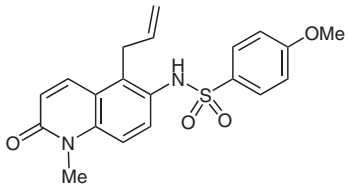
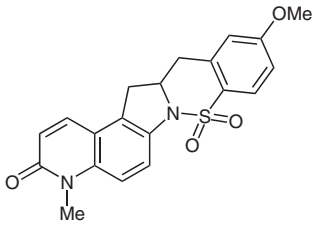
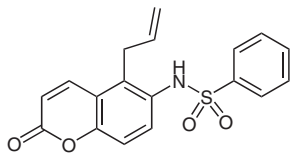
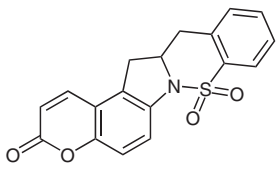
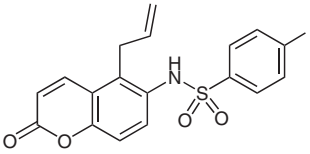
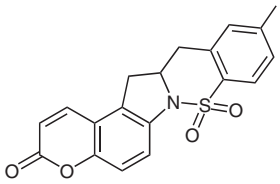
Entry	Substrate **5**	Product **7**	Yield (%)[a]
1[b]	 **5a**	 **7a**	82
2[b]	 **5b**	 **7b**	85
3[b]	 **5c**	 **7c**	74
4[b]	 **5d**	 **7d**	79
5[b]	 **5e**	 **7e**	80
6[b]	 **5f**	 **7f**	68
7[c]	 **5g**	 **7g**	75

Table 2 Oxidative Cyclization Reaction of **5a–h** (continued)

Entry	Substrate **5**	Product **7**	Yield (%)[a]
8[c]	 **5h**	 **7h**	78

[a] Isolated yields.
[b] All the reactions were carried out for 7 h.
[c] The reactions were carried out for 12 h.

Based on analogy to Chemler's mechanistic proposal, it is likely that these transformations proceed by the way depicted in Scheme 2. We failed to isolate the intermediates but it is reasonable to assume that the first step is the formation of N–Cu bond to give the intermediates **8** which on migratory insertion give the intermediates **9**. The intermediates **9** subsequently add to the aromatic ring to give the radical intermediates **10** which on aromatization give the final products **7**.

In conclusion, we have achieved the synthesis of pentacyclic sultams containing bioactive coumarin or quinolone moieties by intramolecular copper(II) acetate promoted carboamination (oxidative cyclization) reaction. The extended methodology is simple, mild, and provides high yield of the products.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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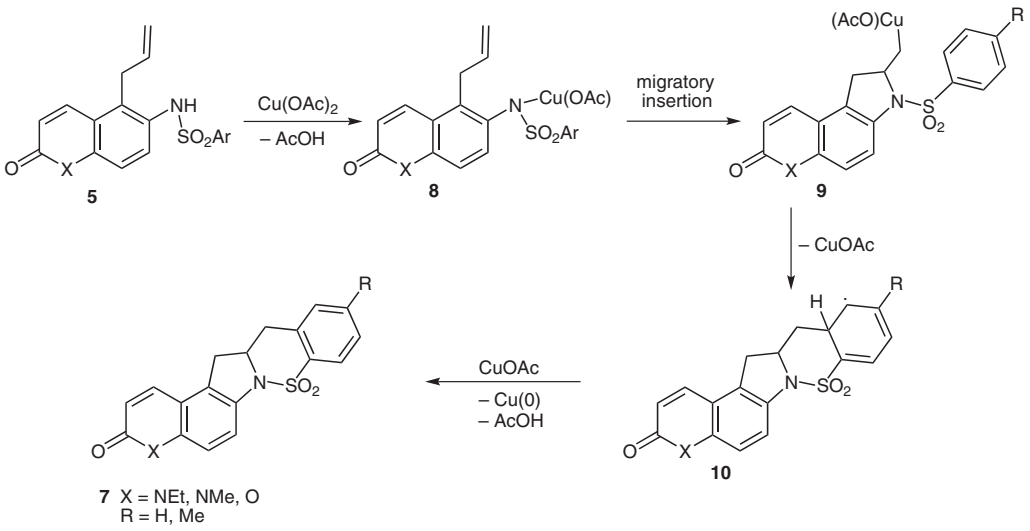
References and Notes

(1) (a) Drews, J. *Science* **2000**, *287*, 1960. (b) Scozzafava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C. T. *Curr. Med. Chem.* **2003**, *10*, 925.
(2) (a) de Bont, D. B. A.; Sliedregt-Bol, K. M.; Hofmeyer, L. J. F.; Liskamp, R. M. J. *Bioorg. Med. Chem.* **1999**, *7*, 1043. (b) Roush, W. R.; Gwaltney, S. L. II; Cheng, J.; Scheidt, K. A.; McKerrow, J. H.; Hansell, E. *J. Am. Chem. Soc.* **1998**, *120*, 10994.
(3) Brashear, K. M.; Cook, J. J.; Bednar, B.; Bednar, R. A.; Gould, R. J.; Halczenko, W.; Holahan, M. A.; Lynch, R. J.; Hartman, G. D.; Hutchinson, J. H. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2793.



Scheme 2 Probable mechanism for carboamination reaction

(4) Radkiewicz, J. L.; McAllister, M. A.; Goldstein, E.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 1419.
(5) Bradbury, R. H.; Bath, C.; Butlin, R. J.; Dennis, M.; Heys, C.; Hunt, S. J.; James, R.; Mortlock, A. A.; Summer, N. F.; Tang, E. K.; Telford, B.; Whiting, E.; Wilson, C. *J. Med. Chem.* **1997**, *40*, 996.
(6) Hanessian, S.; Sailes, H.; Therrien, E. *Tetrahedron* **2003**, *59*, 7047.
(7) (a) Silvestri, R.; Marfè, G.; Artico, M.; La Regina, G.; Lavecchia, A.; Novellino, E.; Morgante, M.; Di Stefano, C.; Catalano, G.; Filomeni, G.; Abruzzese, E.; Ciriolo, M. R.; Russo, M. A.; Amadori, S.; Cirilli, R.; La Torre, F.; Salimei, P. S. *J. Med. Chem.* **2006**, *49*, 5840. (b) Lebegue, N.; Gallet, S.; Flouquet, N.; Carato, P.; Pfeiffer, B.; Renard, P.; Léonce, S.; Pierré, A.; Chavatte, P.; Berthelot, P. *J. Med. Chem.* **2005**, *48*, 7363.
(8) Xie, Y.; Gong, G.; Liu, Y.; Deng, S.; Rinderspacher, A.; Branden, L.; Landry, D. W. *Tetdrahedron Lett.* **2008**, *49*, 2320.
(9) Levy, L. *Drugs Future* **1992**, *17*, 451.
(10) McKerrecher, D.; Pike, K. G.; Waring, M. J. WO 2006125972, **2006**.
(11) Brzozowski, Z.; Saczewski, F.; Neamati, N. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5298.
(12) Wroblewski, T.; Graul, A.; Castaner, J. *Drugs Future* **1998**, *23*, 365.
(13) Tanimukai, H.; Inui, M.; Harigushi, S.; Kaneko, J. *Biochem. Pharmacol.* **1965**, *14*, 961.
(14) Inagaki, M.; Tsuri, T.; Jyoyama, H.; Ono, T.; Yamada, K.; Kobayashi, M.; Hori, Y.; Arimura, A.; Yasui, K.; Ohno, K.; Kakudo, S.; Koizumi, K.; Suzuki, R.; Kawai, S.; Kato, M.; Matsumoto, S. *J. Med. Chem.* **2000**, *43*, 2040.
(15) Wells, G. J.; Tao, M.; Josef, K. A.; Bihovsky, R. *J. Med. Chem.* **2001**, *44*, 3488.
(16) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241.
(17) (a) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919. (b) Differding, E.; Lang, R. *Helv. Chim. Acta* **1989**, *72*, 1248.
(18) (a) Raski, S. R.; Williams, R. M. *Chem. Rev.* **1998**, *98*, 2723. (b) Murakami, A.; Gao, G.; Omura, M.; Yano, M.; Ito, C.; Furukawa, H.; Takahasi, D.; Koshimizu, K.; Ohigash, H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 59. (c) Hagen, S. E.; Domagala, J. M.; Heifetz, C. L.; Sanchez, J. P.; Solomon, M. *J. Med. Chem.* **1990**, *33*, 849. (d) Laborde, E.; Kiely, J. S.; Culbertson, T. P.; Lesheski, L. E. *J. Med. Chem.* **1993**, *36*, 1964. (e) Gozalbes, R.; Brun-Pascaud, M.; García-Domenech, R.; Galvez, J.; Girard, P.; Doucet, J.; Derouin, F. *Antimicrob. Agents Chemother.* **2000**, *44*, 2764.
(19) (a) Majumdar, K. C.; Chattopadhyay, B.; Taher, A. *Synthesis* **2007**, 3647. (b) Majumdar, K. C.; Pal, A. K.; Taher, A.; Debnath, P. *Synthesis* **2007**, 1707. (c) Majumdar, K. C.; Chakravorty, S.; Shyam, P. K.; Taher, A. *Synthesis* **2009**, 403. (d) Majumdar, K. C.; Debnath, P.; Taher, A.; Pal, A. K. *Can J. Chem.* **2008**, *86*, 325. (e) Majumdar, K. C.; Taher, A.; Debnath, P. *Synthesis* **2009**, 793.
(20) (a) Majumdar, K. C.; Debnath, P.; Taher, A. *Lett. Org. Chem.* **2008**, *5*, 169. (b) Majumdar, K. C.; Chakravorty, S.; Taher, A. *Synth. Commun.* **2008**, *38*, 3159.
(21) Silvestri, R.; Marfè, G.; Artico, M.; La Regina, G.; Lavecchia, A.; Novellino, E.; Morgante, M.; Di Stefano, C.; Catalano, G.; Filomeni, G.; Abruzzese, E.; Ciriolo, M. R.; Russo, M. A.; Amadori, S.; Cirilli, R.; La Torre, F.; Salimei, P. S. *J. Med. Chem.* **2006**, *49*, 5840.
(22) (a) Bravo, R. D.; Cánepa, A. S. *Synth. Commun.* **2002**, *32*, 3675. (b) Katritzky, A. R.; Wu, J.; Rachwal, S.; Rachwal, B.; Macomber, D. W.; Smith, T. P. *Org. Prep. Proced. Int.* **1992**, *24*, 463. (c) Orazi, O. O.; Corral, R. A.; Bravo, R. *J. Heterocycl. Chem.* **1986**, *23*, 1701.
(23) Lee, J.; Zhong, Y.-L.; Reamer, R. A.; Askin, D. *Org. Lett.* **2003**, *5*, 4175.
(24) Enders, D.; Moll, A.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, 1271.
(25) Chiacchio, U.; Corsaro, A.; Rescifina, A.; Bkaithan, M.; Grassi, G.; Piperno, A. *Tetrahedron* **2001**, *57*, 3425.
(26) (a) Greig, I. R.; Trozer, M. J.; Wright, P. T. *Org. Lett.* **2001**, *3*, 369. (b) Plietker, B.; Seng, D.; Fröhlich, R.; Metz, P. *Tetrahedron* **2000**, *56*, 873. (c) Rogatchov, V. O.; Bernsmann, H.; Schwab, P.; Fröhlich, R.; Wibbeling, B.; Metz, P. *Tetrahedron Lett.* **2002**, *43*, 4753. (d) Wanner, J.; Harned, A. M.; Probst, D. A.; Poon, K. W. C.; Klein, T. A.; Snelgrove, K. A.; Hanson, P. R. *Tetrahedron Lett.* **2002**, *43*, 917.
(27) (a) Majumdar, K. C.; Mondal, S.; De, N. *Synlett* **2008**, 2851. (b) Majumdar, K. C.; Mondal, S.; De, N. *Synthesis* **2008**, 3127. (c) Merten, S.; Fröhlich, R.; Kataeva, O. *Adv. Synth. Catal.* **2005**, *347*, 754. (d) Vasudevan, A.; Tseng, P.-S.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 8591.
(28) Liu, X.-Y.; Li, C.-H.; Che, C.-M. *Org. Lett.* **2006**, *8*, 2707.
(29) (a) Padwa, A.; Flick, A. C.; Leverett, C. A.; Stengel, T. *J. Org. Chem.* **2004**, *69*, 6377. (b) Liang, J.-L.; Yuan, S.-X.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* **2002**, *4*, 4507.
(30) (a) Jimenez-Hopkins, M.; Hanson, P. R. *Org. Lett.* **2008**, *10*, 2223. (b) Hanson, P. R.; Probst, D. A.; Robinson, R. E.; Yau, M. *Tetrahedron Lett.* **1999**, *40*, 4761.
(31) (a) Sherman, E. S.; Fuller, P. H.; Kasi, D.; Chemler, S. R. *J. Org. Chem.* **2007**, *72*, 3896. (b) Sherman, E. S.; Chemler, S. R.; Tan, T. B.; Gerlits, O. *Org. Lett.* **2004**, *6*, 1573. (c) Zeng, W.; Chemler, S. R. *J. Am. Chem. Soc.* **2007**, *129*, 12948. (d) Zeng, W.; Chemler, S. R. *J. Org. Chem.* **2008**, *73*, 6045.
(32) (a) Fuller, P. H.; Chemler, S. R. *Org. Lett.* **2007**, *9*, 5477. (b) Zabawa, T. P.; Chemler, S. R. *Org. Lett.* **2007**, *9*, 2035. (c) Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 11250.
(33) Krowichi, K.; Paillous, N.; Riviere, M.; Lattes, A. *J. Heterocycl. Chem.* **1976**, *13*, 555.
(34) **Procedure for the Preparation of Compound 7a**
A mixture of compound **5a** (100 mg, 0.272 mmol), $Cu(OAc)_2$ (148 mg, 0.815 mmol), and Cs_2CO_3 (89 mg, 0.272 mmol) in MeCN (7 mL) was heated in a sealed tube for 7 h. After completion of the reaction, the reaction mixture was cooled and filtered through Celite. The solvent was distilled off. The resulting crude product was purified by column chromatography over silica gel (60–120 mesh) using PE–EtOAc (50:50) mixture as eluent to give compound **7a**. Yield 82%, colorless solid; mp 276 °C. IR (KBr): ν_{max} = 1592, 1663, 2923 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.1 Hz, 3 H), 3.08–3.16 (m, 2 H), 3.49 (dd, *J* = 9.2, 15.9 Hz, 1 H), 3.75 (dd, *J* = 5.9, 15.7 Hz, 1 H), 4.28 (q, *J* = 7.1 Hz, 2 H), 5.07–5.13 (m, 1 H), 6.68 (d, *J* = 9.5 Hz, 1 H), 7.20 (d, *J* = 9.0 Hz, 1 H), 7.32 (d, *J* = 7.5 Hz, 1 H), 7.36 (t, *J* = 7.5 Hz, 1 H), 7.46 (d, *J* = 9.5 Hz, 1 H), 7.48 (t, *J* = 7.5 Hz, 1 H), 7.76 (d, *J* = 9.1 Hz, 1 H), 7.83 (d, *J* = 7.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7, 33.1, 34.5, 37.6, 61.7, 114.1, 117.3, 119.6, 122.8, 124.3, 127.6, 127.9, 129.7, 132.8, 134.2, 134.4, 136.3, 137.0, 138.5, 161.2 ppm. HRMS: *m/z* calcd for $C_{20}H_{18}N_2O_3S$ $[M + Na]^+$: 389.0936; found: 389.0936.