Heterocycle Synthesis

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Domino Condensation/S-Arylation/Heterocyclization Reactions: Copper-Catalyzed Three-Component Synthesis of 2-N-Substituted Benzothiazoles**

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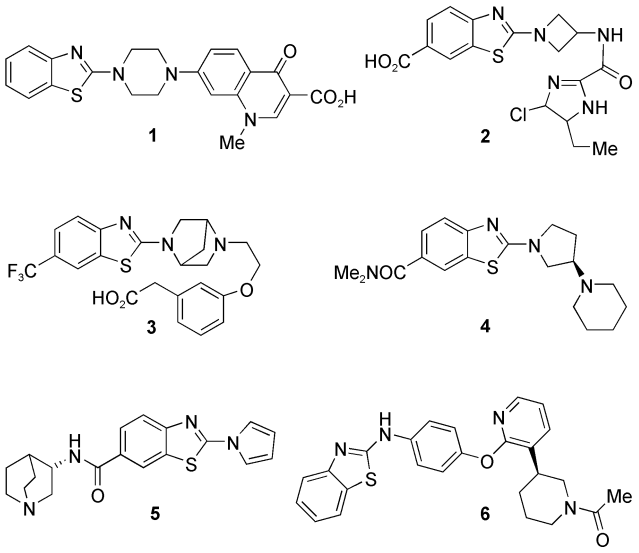
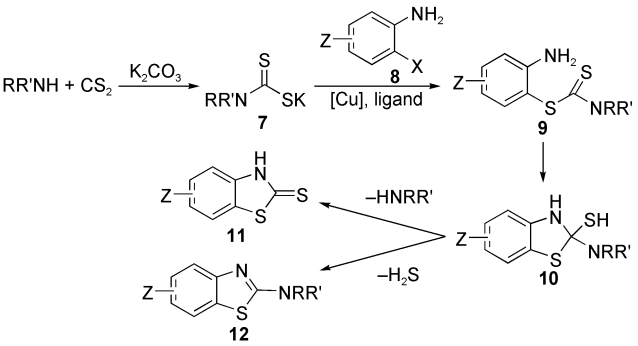
Benzothiazoles with a nitrogen substituent in the 2-position have frequently been used as core structures for the development of pharmaceutically important agents. Recent successful examples include the anti-HIV agent **1**,[1] the antibacterial compound **2**,[2] the PPAR agonist **3**,[3] the H_3-receptor ligand **4**,[4] the nicotinic-acetylcholine-receptor ligand **5**,[5] and the phosphodiesterase 10 inhibitor **6** (Scheme 1).[6] Normally, 2-N-substituted benzothiazoles are synthesized by substitution reactions of 2-halobenzothiazoles (or 2-thiobenzothiazoles) with N nucleophiles.[7] This method usually requires several steps and harsh reaction conditions for the synthesis of the desired products from commercially available aniline derivatives. Recently, four approaches based on metal catalysis have been developed for the assembly of these heterocycles: 1) metal-catalyzed intramolecular C–S bond formation[8] with 2-halobenzothioureas that were generated in situ or presynthesized from suitable isothiocyanates and amines; 2) copper- or silver-catalyzed direct oxidative coupling of simple benzothiazoles with amines;[9,10] 3) palladium-catalyzed direct oxidative cyclization of N-aryl thioureas;[11] and 4) palladium-catalyzed amination of 2-halobenzothioureas.[12] The requisite substrates for these reactions are generally not conveniently available, which limits their application in synthesis.



Scheme 1. Structures of bioactive 2-N-substituted benzothiazoles.

During the past few years we have witnessed great progress in ligand-promoted Ullmann-type coupling reactions.[13] With the newly developed catalytic systems in hand, we started a program aimed at extending the reaction scope through the use of unusual nucleophiles.[14] It is well-known that amines can react with carbon disulfide in the presence of bases to give dithiocarbamate salts **7** (Scheme 2).[15] We speculated that these salts might serve as novel coupling partners to provide dithiocarbamates **9** by reaction with 2-haloanilines **8**. The amine group in **9** could in turn attack the C–S double bond to give cyclization products **10**, which would deliver cyclic dithiocarbamates **11** or 2-N-substituted benzothiazoles **12** upon elimination of an amine HNRR′ or hydrogen sulfide, respectively.



Scheme 2. Possible reaction course for the formation of 2-N-substituted benzothiazoles from N nucleophiles, CS_2, and 2-haloanilines.

To test our hypothesis, we investigated the reaction of 2-iodobenzamine with carbon disulfide and piperidine. Under the catalysis of CuI (10 mol%) and L-proline (20 mol%), the reaction took place in *N*,*N*-dimethylformamide (DMF) at

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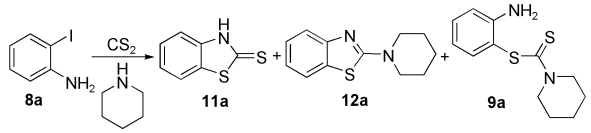
Table 1: Screening of reaction conditions for the reaction of 2-iodoaniline, carbon disulfide, and piperidine.[a]



Entry	Catalyst, ligand, additive	*T* [°C]	Yield of **12a** [%][b]
1	CuI, L-proline	80	22[c]
2	CuI, L-proline	110	36[d]
3	CuI, L-proline, $AgNO_3$ (1.5 equiv)	110	74
4	CuI, L-proline, $CuBr_2$ (1.5 equiv)	110	80
5	$CuBr_2$ (1.5 equiv)	110	78
6	$CuBr_2$ (1.0 equiv)	110	88
7	$CuCl_2{\cdot}2H_2O$ (1.0 equiv)	110	92
8[e]	$CuCl_2{\cdot}2H_2O$ (1.0 equiv)	110	92
9	$CuCl_2{\cdot}2H_2O$ (1.0 equiv)	90	84
10[f]	$CuCl_2{\cdot}2H_2O$ (1.0 equiv)	110	85
11[g]	$CuCl_2{\cdot}2H_2O$ (1.0 equiv)	110	80
12	$Cu(OAc)_2{\cdot}H_2O$ (1.0 equiv)	110	88
13	$CuSO_4{\cdot}5H_2O$ (1.0 equiv)	110	82
14[h]	$CuCl_2{\cdot}2H_2O$ (1.0 equiv)	110	70
15[i]	$CuCl_2{\cdot}2H_2O$ (1.0 equiv)	110	70

[a] Reaction conditions: **8a** (0.5 mmol), CS_2 (0.6 mmol), piperidine (1 mmol), CuI (0.05 mmol, for entries 1–4), L-proline (0.1 mmol, for entries 1–4), additive (0.5–0.75 mmol, for entries 3–15), K_2CO_3 (1.5 mmol), DMF (1 mL), 6 h. [b] Yield of the isolated product. [c] Compound **9a** was isolated in 77% yield. [d] Compounds **9a** and **11a** were isolated in 8 and 30% yield, respectively. [e] The reaction was carried out with 0.75 mmol of piperidine. [f] K_3PO_4 was used as the base. [g] Cs_2CO_3 was used as the base. [h] DMSO was used as the solvent. [i] Dioxane was used as the solvent.

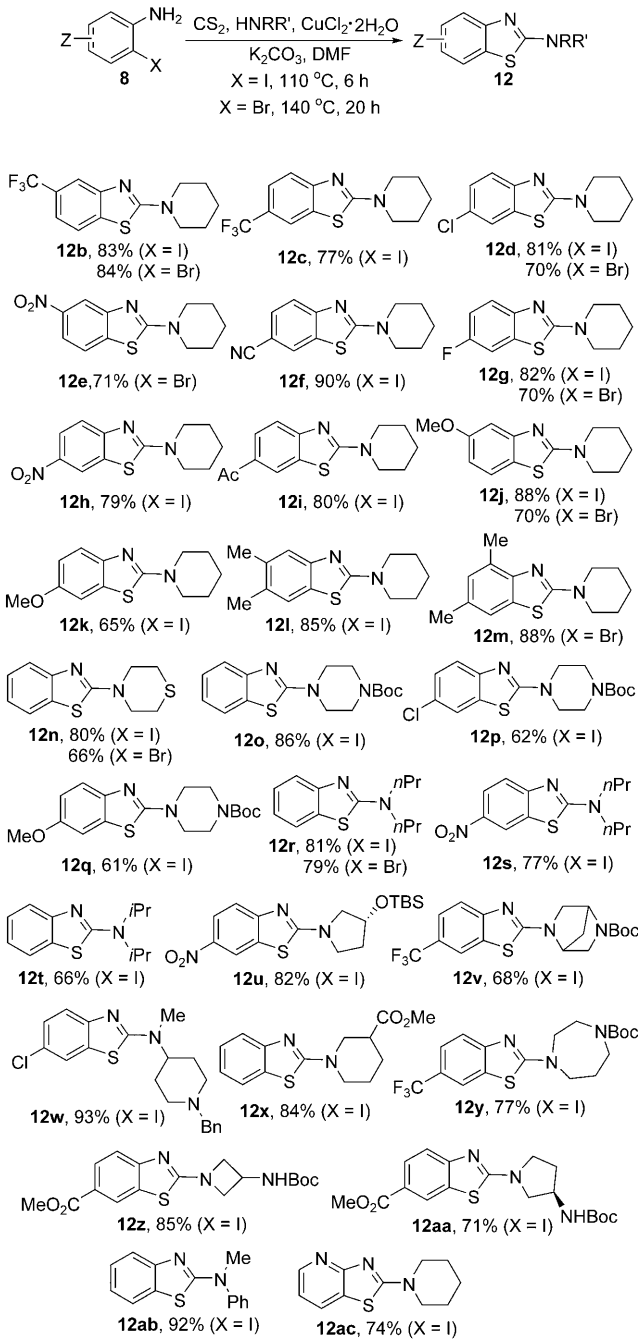
80 °C to give the desired product **12a** in 22% yield together with the simple coupling product **9a** in 77% yield (Table 1, entry 1). The isolation and characterization of **9a** provided direct evidence for the mechanism proposed in Scheme 2. To facilitate the further conversion of **9a**, we increased the reaction temperature to 110 °C. In this case, the yield of **12a** was still low, mainly because of the formation of **11a** (Table 1, entry 2). To solve this problem, we examined the use of desulfurizing agents to promote the formation of **12a**. Indeed, the yield of **12a** was increased to 74% by the addition of silver nitrate (1.5 equiv; Table 1, entry 3). When $CuBr_2$ was used as the additive, the yield was further improved to 80% (Table 1, entry 4). Further exploration indicated that in the presence of $CuBr_2$, neither CuI nor L-proline was necessary for this transformation (Table 1, entry 5). A decrease in the amount of $CuBr_2$ used to 1 equivalent led to further improvement of the yield (Table 1, entry 6). Exchange of the copper salt for cheaper $CuCl_2{\cdot}2H_2O$ delivered the best result (Table 1, entry 7). In this case, the amount of piperidine could be decreased to 1.5 equivalents without alteration of the yield (Table 1, entry 8). This amount was used in subsequent studies (but not in the other reactions shown in Table 1). Under the action of $CuCl_2{\cdot}2H_2O$, the reaction proceeded to completion even at 90 °C to produce **12a** in 84% yield (Table 1, entry 9). When the base was changed to K_3PO_4 or Cs_2CO_3, the reaction yield decreased only slightly (Table 1, entries 7, 10, and 11). A similar slight decrease in the yield was observed when other copper salts, such as $Cu(OAc)_2{\cdot}H_2O$ and $CuSO_4{\cdot}5H_2O$ (Table 1, entries 12 and 13), or the solvents dioxane and dimethyl sulfoxide (DMSO; entries 14 and 15) were used.

Having optimized the reaction conditions through the use of $CuCl_2{\cdot}2H_2O$ as both the catalyst and the desulfurizing agent, we explored the scope and limitations of this three-component reaction. We first examined the reaction of a number of monosubstituted 2-haloanilines with piperidine as a coupling partner (Scheme 3). Generally, the reaction proceeded well with these substrates to deliver the 2,5- and 2,6-disubstituted benzothiazoles **12b**–**12k** in good to excellent yields. The results demonstrated that both the electronic features and the orientation of the additional substituent on the 2-haloaniline have limited influence on this cascade reaction. 2-Bromoanilines also underwent this transformation, although they required higher reaction temperatures than the corresponding iodides, and the products were formed in slightly lower yields. The synthesis of trisubstituted benzothiazoles **12l** and **12m** from two disubstituted 2-haloanilines indicates that this method enables the introduction of functional groups at 4-, 5-, and/or 6-positions of benzothiazoles.

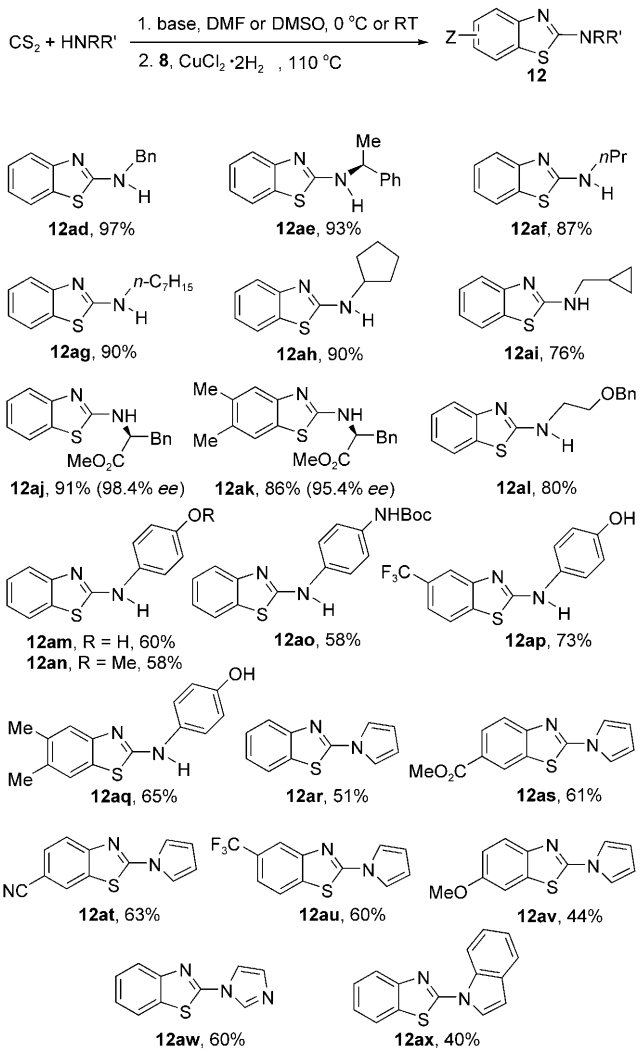
We further explored the generality of the present method by varying the secondary amine and found that thiomorpholine, Boc-protected piperazine, simple and sterically hindered acyclic amines, functionalized cyclic amines, as well as *N*-methylaniline, were compatible with this process. Thus, benzothiazoles **12n**–**12ab** were formed in 61–93% yield. Additionally, the substituted thiazolo[4,5-*b*]pyridine **12ac** was obtained from 3-iodopyridin-2-amine and piperidine in 74% yield.

Another notable characteristic of this reaction is that a wide range of functional groups, including nitro, keto, ester, nitrile, methoxy, chloro, and trifluoromethyl substituents, remain intact under the reaction conditions. This advantage makes our method a very powerful tool for the assembly of bioactive benzothiazoles. Indeed, products **12o**–**12q** could be used for the synthesis of serotonin-receptor modulators,[15] PDE4 inhibitors,[16] modulators of metabotropic glutamate receptor 5 (mGluR5),[17] and the anti-HIV agent **1**;[1] compound **12w** is a precursor for the synthesis of analogues of sabeluzole with an inhibitory effect on gastric-acid secretion;[18] benzothiazole **12y** could be applied to the preparation of CB2-receptor modulators;[19] whereas benzothiazoles **12z**, **12v**, and **12aa** could be employed for the assembly of the antibacterial agent **2**,[2] PPAR agonist **3**,[3] and H_3-receptor ligand **4**,[4] respectively.

We next turned our attention to the use of other N nucleophiles (Scheme 4). When benzylamine was treated with 2-iodoaniline under the described reaction conditions, the desired product **12ad** was obtained in only 15% yield. We found that the yield could be improved to 97% if benzylamine was first treated with carbon disulfide at 0 °C, and the reaction mixture was heated after the addition of 2-iodoaniline and $CuCl_2{\cdot}2H_2O$ (3.5 equiv). These modified conditions were found to be suitable for a number of primary amines, including aliphatic amines with a range of functionality and electron-rich anilines; the corresponding 2-aminobenzothia-



Scheme 3. Scope of the formation of 2-N-substituted benzothiazoles from secondary amines and 2-haloanilines. Reaction conditions: **8** (0.5 mmol), CS_2 (0.6 mmol), amine (0.75 mmol), $CuCl_2 \cdot 2H_2O$ (0.5 mmol), K_2CO_3 (1.5 mmol), DMF (1 mL), 110 °C, 6 h (for iodides) or 140 °C, 20 h (for bromides). Bn = benzyl, Boc = *tert*-butoxycarbonyl, TBS = *tert*-butyldimethylsilyl.



Scheme 4. Scope of the formation of 2-N-substituted benzothiazoles by the coupling of 2-iodoanilines with primary amines and N heterocycles. Reaction conditions: CS_2 (0.6–1.0 mmol), amine (0.75–1.0 mmol) or N heterocycle (0.75 mmol), K_2CO_3 (1.5 mmol, with an amine) or KOH (1.5 mmol, with an N heterocycle), DMF (1 mL, with an amine) or DMSO (1 mL, with an N heterocycle), 0 °C or room temperature, 1–3 h, then **8** (0.5 mmol), $CuCl_2 \cdot 2H_2O$ (0.5–1.75 mmol), 110 °C, 6 h.

zoles **12ae**–**12aq** were obtained in good to excellent yield. However, the desired products were not indentified when electron-deficient anilines were used (data not shown), presumably because of their poor nucleophilicity. The formation of products **12aj** and **12ak** with 98.4 and 95.4% *ee*, respectively, indicates that only slight racemization occurred during the reaction course. Thus, this cascade reaction provides facile access to benzothiazoles that bear a chiral amino ester moiety. Further investigations revealed that benzothiazoles **12ar**–**12ax** could be constructed from the corresponding 2-iodoaniline and pyrrole, imidazole, or indole if the base was changed to KOH, although the yield was only moderate in some cases. Compounds **12as** and **12am** are suitable for the elaboration of the nicotinic-acetylcholine-receptor ligand **5**[5] and phosphodiesterase 10 inhibitor **6**,[6] respectively.

In conclusion, we have identified that dithiocarbamate salts are excellent coupling partners for copper-catalyzed arylation. The products of their reaction with 2-haloanilines can undergo intramolecular condensation to afford 2-N-substituted benzothiazoles. Since these salts could be prepared in situ from amines and nitrogen-containing heterocycles, we were able to develop a cascade three-component

reaction for the synthesis of 2-N-substituted benzothiazoles from conveniently available starting materials.[20] This method enables the assembly of 2-N-substituted benzothiazoles with great diversity and should therefore find broad application in organic synthesis.

Experimental Section

Typical procedure: A mixture of 2-iodoaniline (**8a**; 0.5 mmol), CS_2 (0.6 mmol), an amine (0.75 mmol), $CuCl_2 \cdot 2H_2O$ (0.5 mmol), and K_2CO_3 (1.5 mmol) in DMF (1 mL) was stirred at 110 °C for 6 h. The cooled solution was partitioned between ethyl acetate and water, and the organic layer was washed with water and brine, and then dried over Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by silica-gel chromatography to give the desired benzothiazole.

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[1] HIV = human immunodeficiency virus; S. Massari, D. Daelemans, M. L. Barreca, A. Knezevich, S. Sabatini, V. Cecchetti, A. Marcello, C. Pannecouque, O. Tabarrini, *J. Med. Chem.* **2010**, *53*, 641.

[2] T. Soneda, H. Takeshita, Y. Kagoshima, Y. Yamamoto, T. Hosokawa, T. Konosu, N. Masuda, T. Uchida, I. Achiwa, J. Kuroyanagi, T. Fujisawa, A. Yokomizo, T. Noguchi, WO 2009084614, **2009**.

[3] PPAR = peroxisome proliferator-activated receptor; A. Itai, S. Muto, R. Tokuyama, H. Fukazawa, T. Ohara, T. Kato, WO 2007023882, **2007**.

[4] L. A. Black, M. D. Cowart, G. A. Gfesser, B. D. Wakefield, R. J. Altenbach, H. Liu, C. Zhao, G. C. Hsieh, WO 2009085945, **2009**.

[5] A. Tehim, B. Herbert, T. M. Nguyen, W. Xie, C. M. Gauss, WO 2004029050, **2004**.

[6] J. R. Allen, K. Biswas, F. Chavez, N. Chen, F. F. Demorin, J. R. Falsey, M. Frohn, P. Harrington, D. Horne, E. Hu, M. R. Kaller, R. Kunz, H. Monenschein, T. Nguyen, A. Pickrell, A. Reichelt, S. Rumfelt, R. Rzasa, K. Sham, G. Yao, WO 2010057126, **2010**.

[7] a) G. W. Stewart, C. A. Baxter, E. Cleator, F. J. Sheen, *J. Org. Chem.* **2009**, *74*, 3229; b) I. Ćaleta, M. Kralj, M. Marjanović, B. Bertoša, S. Tomić, G. Pavlović, K. Pavlović, G. Karminski-Zamola, *J. Med. Chem.* **2009**, *52*, 1744, and references therein.

[8] a) C. Benedí, F. Bravo, P. Uriz, E. Fernández, C. Claver, S. Castillón, *Tetrahedron Lett.* **2003**, *44*, 6073; b) L. L. Joyce, G. Evindar, R. A. Batey, *Chem. Commun.* **2004**, 446; c) J.-W. Qiu, X.-G. Zhang, R.-Y. Tang, P. Zhong, J.-H. Li, *Adv. Synth. Catal.* **2009**, *351*, 2319; d) G. Shen, X. Lv, W. Bao, *Eur. J. Org. Chem.* **2009**, 5897; e) P. Saha, T. Ramana, N. Purkait, M. A. Ali, R. Paul, T. Punniyamurthy, *J. Org. Chem.* **2009**, *74*, 8719.

[9] a) S. H. Cho, J. Y. Kim, S. Y. Lee, S. Chang, *Angew. Chem.* **2009**, *121*, 9291; *Angew. Chem. Int. Ed.* **2009**, *48*, 9127; b) D. Monguchi, T. Fujiwara, A. Mori, *Org. Lett.* **2009**, *11*, 1607.

[10] For a brief review, see: A. Armstrong, J. C. Collins, *Angew. Chem.* **2010**, *122*, 2332; *Angew. Chem. Int. Ed.* **2010**, *49*, 2282.

[11] a) L. L. Joyce, R. A. Batey, *Org. Lett.* **2009**, *11*, 2792; b) K. Inamoto, C. Hasegawa, K. Hiroya, T. Doi, *Org. Lett.* **2008**, *10*, 5147.

[12] a) Q. L. Shen, T. Ogata, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 6586; b) J. J. Yin, M. M. Zhao, M. A. Huffman, J. M. McNamara, *Org. Lett.* **2002**, *4*, 3481.

[13] For recent reviews, see: a) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054; b) D. Ma, Q. Cai, *Acc. Chem. Res.* **2008**, *41*, 1450; c) F. Monnier, M. Taillefer, *Angew. Chem.* **2009**, *121*, 7088; *Angew. Chem. Int. Ed.* **2009**, *48*, 6954; d) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2010**, *1*, 13.

[14] a) D. Ma, S. Xie, P. Xue, X. Zhang, J. Dong, Y. Jiang, *Angew. Chem.* **2009**, *121*, 4286; *Angew. Chem. Int. Ed.* **2009**, *48*, 4222; b) Y. Jiang, S. Xie, Y. Qin, X. Zhang, D. Ma, *Org. Lett.* **2009**, *11*, 5250.

[15] A. Monge, M. d. C. Pena, J. A. Palop, J. M. Caldero, J. Roca, E. Garcia, G. Romero, J. del Rio, B. Lasheras, *J. Med. Chem.* **1994**, *37*, 1320.

[16] P. Pouzet, R. Anderskewitz, H. Dollinger, D. Fiegen, T. Fox, R. Goeggel, C. Hoenke, D. Martyres, P. Nickolaus, K. Klinder, WO 2009050242, **2009**.

[17] M. G. Bursavich, A. M. Gilbert, J. R. Stock, WO 2009143404, **2009**.

[18] G. Domany, G. Barta-Szalai, J. Matuz, E. Ezer, I. Schoen, *Pharmazie* **1996**, *51*, 427.

[19] P. F. Cirillo, E. R. Hickey, D. Riether, L. Wu, R. Zindell, P. Amouzegh, M. Ermann, E. Walker, WO 2009055357, **2009**.

[20] For selected recent examples of heterocycle synthesis on the basis of copper-catalyzed cross-coupling reactions, see: a) D. Ma, Q. Geng, H. Zhang, Y. Jiang, *Angew. Chem.* **2010**, *122*, 1313; *Angew. Chem. Int. Ed.* **2010**, *49*, 1291; b) X. Liu, H. Fu, Y. Jiang, Y. Zhao, *Angew. Chem.* **2009**, *121*, 354; *Angew. Chem. Int. Ed.* **2009**, *48*, 348; c) W. Bao, Y. Liu, X. Lv, W. Qian, *Org. Lett.* **2008**, *10*, 3899; d) A. Coste, M. Toumi, K. Wright, V. Razafimahaleo, F. Couty, J. Marrot, G. Evano, *Org. Lett.* **2008**, *10*, 3841; e) B. Wang, B. Lu, Y. Jiang, Y. Zhang. D. Ma, *Org. Lett.* **2008**, *10*, 2761; f) B. Zou, Q. Yuan, D. Ma, *Org. Lett.* **2007**, *9*, 4291; g) B. Zou, Q. Yuan, D. Ma, *Angew. Chem.* **2007**, *119*, 2652; *Angew. Chem. Int. Ed.* **2007**, *46*, 2598; h) R. Martín, R. Rodríguez, S. L. Buchwald, *Angew. Chem.* **2006**, *118*, 7237; *Angew. Chem. Int. Ed.* **2006**, *45*, 7079.

