RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Synthesis of 4-substitutedimino-4*H*-benzo[*d*][1,3]thiazin-2-amines via palladium-catalysed isocyanide insertion in 2-bromophenylthioureas

Garima Pandey,[a] Subhendu Bhowmik[a] and Sanjay Batra*[a,b]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

The palladium-catalysed isocyanide insertion in 2-bromophenylthioureas results into the formation of 4-substitutedimino-4*H*-benzo[*d*][1,3]thiazin-2-amines via C-S cross coupling reaction of the intermediate imidoylpalladium species. The investigations into the substrate scope revealed that whereas reactions of cyclohexyl isocyanide were successful with aromatic as well as aliphatic thioureas, reactions of all other isocyanides (except ethyl 2-isocyanoacetate) were successful with aromatic thioureas only.

Compounds bearing the 4*H*-benzo[*d*][1,3]thiazine core are of significant importance owing to their biological activity[1] and their presence in recording and photographic materials.[2] In particular, 4*H*-benzo[*d*][1,3]thiazin-2-amines are ascribed with cytoprotective properties toward heart and neurons and are useful for treating neurodegenerative pathologies such as cerebral ischemia, neurodegeneration and Alzheimer's disease.[3,4] As a consequence many approaches for the synthesis of 4*H*-benzo[*d*][1,3]thiazin-2-amines are reported. The classical methods involve the condensation of aromatic amine or thioureas bearing an *ortho* halomethyl, hydroxymethyl or cycloalkyl or oxirane with thioamides or thioureas in the presence of base or bronsted acid.[5-7] But recently the approach involving a 6-exo-dig type addition/ cyclization of 2-ethynylaniline with isothiocyanate or related compounds or 2-ethynylphenylisothiocyanates with amines often promoted by silver catalyst, DMAP, silica gel or iodine has attracted considerable attention.[8] Simultaneously, another protocol involving tandem addition/ cyclization of 2-aminocinnamate with isothiocyanates promoted by Lanthanide salts or reaction of 3-(2-isothiocyanatophenyl)propenoic acid derivatives with secondary amines under heating for preparing 4*H*-benzo[*d*][1,3]thiazin-2-amines has also been expounded recently.[9] Nevertheless newer routes to the synthesis of this scaffold with varying substituents are desirable.

The palladium-catalysed isocyanide insertion into the carbon-halogen bond[10-11] for the synthesis of heterocycles is an emerging area in synthetic chemistry.[12] Encouraged by the advancement of this reaction, we envisioned that palladium-catalysed isocyanide insertion into 2-bromobenzothioureas followed by cross coupling reaction by the thiol group would offer an unprecedented approach to 4-substitutedimino-4*H*-benzo[*d*][1,3]thiazin-2-amines (Fig. 1). The proposed route (Route A) to the synthesis of

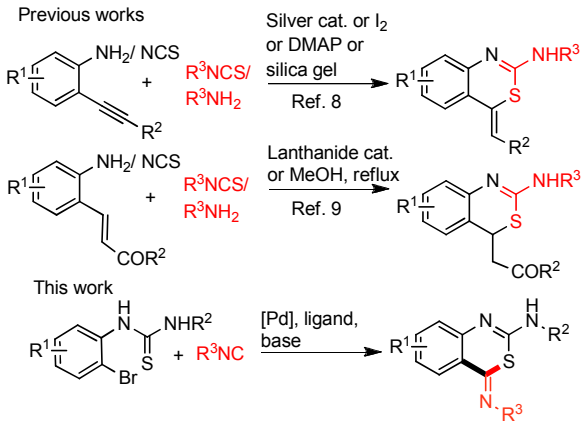
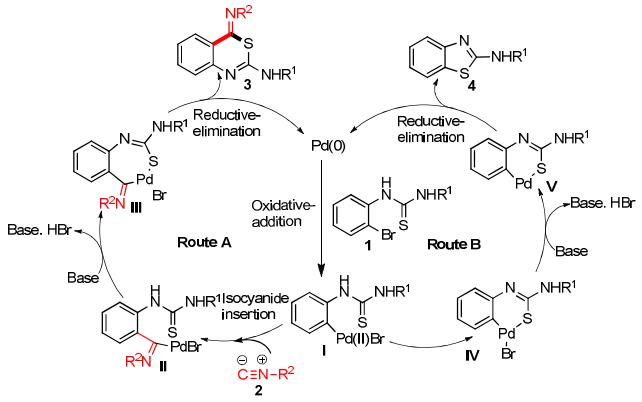


Fig. 1 Comparison of previous synthesis of 4*H*-benzo[*d*][1,3]thiazin-2-amines with our design (for classical methods see SI)

the title compound is presented in Scheme 1. An oxidative addition of Pd(0) to the 2-bromobenzothiourea **1** would afford the Pd(II) species **I** which would then undergo an insertion with the isocyanide **2** leading to imidoyl palladium intermediate **II**. Subsequent deprotonation of the thioamidine would result in a seven-member transition state **III**. The 4-imino-4*H*-benzo[*d*][1,3]thiazin-2-amine **3** would be formed by reductive elimination with regeneration of Pd(0) catalyst concurrently. However, 2-halobenzothioureas under the influence of transition-metal catalysts or simply a base are widely reported to furnish 2-aminobenzothiazoles.[13-14] Therefore a competing direct

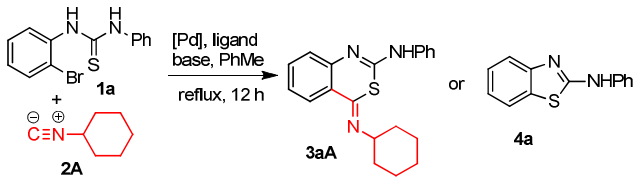


Scheme 1 Proposed mechanistic pathway for the isocyanide insertion in 2-bromophenylthiourea

intramolecular thionation in the intermediate **I** leading to 2-aminobenzothiazole **4** via thioamidine intermediate **IV** which undergoes deprotonation followed by reductive elimination (Route B) cannot be ruled out. It is intriguing to note that though Whitby et al. achieved the synthesis of thioimidates via isocyanide insertion followed by coupling with sodium salt of isopropane thiol,[10b] there is lack of report concerning C-S cross-coupling reaction between imidoyl palladium species and the sulphur group for the synthesis of heterocycles. Hence we decided probing the envisaged reaction and herein we disclose our successful results related to this study.

We initiated our investigations using 1-(2-bromophenyl)-3-phenylthiourea **(1a)** (1.0 equiv) and cyclohexyl isocyanide **2A** (1.5 equiv) as the model substrates in a reaction employing $PdCl_2$ (10 mol%) and PCy_3 (20 mol%) as the catalytic system in toluene with K_3PO_4 (2.0 equiv) as the base under heating at reflux. The reaction was worked up after 12 h to afford the major product in 27% yield (Table 1, entry 1). To our delight the mass and NMR spectral data of the product delineated its structure as **3aA**. The signal for the NH proton at 6.9 ppm in $CDCl_3$, which shifts to 7.9 ppm in DMSOd_6 confirmed the exocyclic N-H group.[9b,9d] But low yield of **3aA** impelled us to optimize the reaction in terms of palladium-source, ligand and base. Altering the base from K_3PO_4 to Cs_2CO_3 or KOAc increased the yield of **3aA** to 33% and 35%, respectively (Table 1, entries 2 and 3), but highly hygroscopic nature of KOAc led us to discard its use for further optimization. Screening of different Pd (II) sources using Cs_2CO_3 as the base revealed that $PdCl_2(PPh_3)_2$ (10 mol%) furnished **3aA** in 43% while $Pd(OAc)_2$ (10 mol%) afforded **3aA** in 57% yield (Table 1, entry 4). With K_3PO_4 as base, the reaction using $Pd(OAc)_2$ (10 mol%) gave **3aA** in 53% yield only (Table 1, entry 6).

Table 1. Optimization of the palladium-catalysed isocyanide insertion in 2-bromophenylthioureas



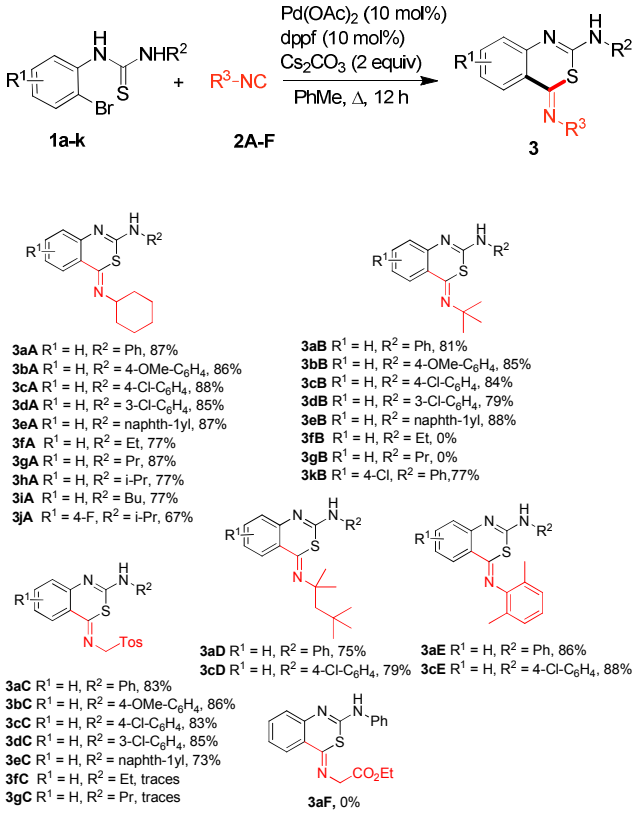
Entry[a]	[Pd] source (mol%)	Ligand (mol%)	Base (equiv)	Yield (%)[b] 3aA	4a
1	$PdCl_2$ (10)	PCy_3 (20)	K_3PO_4 (2)	27	-
2	$PdCl_2$ (10)	PCy_3 (20)	Cs_2CO_3 (2)	33	-
3	$PdCl_2$ (10)	PCy_3 (20)	KOAc (2)	35	-
4	$PdCl_2(PPh_3)_2$ (10)	PCy_3 (20)	Cs_2CO_3 (2)	43	-
5	$Pd(OAc)_2$ (10)	PCy_3 (20)	Cs_2CO_3 (2)	57	-
6	$Pd(OAc)_2$ (10)	PCy_3 (20)	K_3PO_4 (2)	53	-
7	$Pd(OAc)_2$ (10)	dppf (20)	Cs_2CO_3 (2)	83	-
8	$Pd(OAc)_2$ (10)	dppf (10)	Cs_2CO_3 (2)	87	-
9	$Pd(OAc)_2$ (5)	dppf (5)	Cs_2CO_3 (2)	85	-
10	$Pd(OAc)_2$ (10)	dppf (10)	K_3PO_4 (2)	67	-
11	$PdCl_2$ (10)	dppf (10)	Cs_2CO_3 (2)	61	-
12	$PdCl_2(PPh_3)_2$ (10)	dppf (10)	Cs_2CO_3 (2)	49	-
13	-	-	Cs_2CO_3 (2)	-	68
14[c]	$Pd(OAc)_2$(10)	dppf (10)	-	nd	-

[a] All reactions were performed using 100 mg (0.33 mmol) of **1a** and 61µl (0.49 mmol) of cyclohexyl isocyanide **(2A)**, PhMe (2.0 mL); [b]Isolated yields of chromatographically pure product. [c]nd = Not detected.

Gratifyingly, changing the ligand from PCy_3 to bidentate dppf (20 mol%) in the reaction catalysed by $Pd(OAc)_2$ and Cs_2CO_3,improved the yield of **3aA** to 83% (Table 1, entry 7). Titrating the amount of the catalyst and ligand indicated that 10 mol% of each produced the best result (Table 1, compare entries 7-9). Use of $Pd(OAc)_2$ and dppf with K_3PO_4 however made the reaction less efficient (Table 1, entry 10). Similarly replacing the palladium source with $PdCl_2$ or $PdCl_2(PPh_3)_2$ in the presence of dppf and Cs_2CO_3 furnished the product in inferior yield (Table 1, entries 11-12). The negative control experiment in the absence of palladium catalyst and ligand afforded the 2-aminobenzothiazole **(4a)** whereas no product was detected in the absence of base**.** Thus the best condition identified for the isocyanide insertion into 2-bromophenylthiourea was $Pd(OAc)_2$ (10 mol%), dppf (10 mol%), Cs_2CO_3 (2.0 equiv) in toluene as medium at reflux temperature under inert atmosphere. It may be noted that during the optimization we also evaluated the reaction of cyclohexyl isocyanide with 1-(2-iodophenyl)-3-phenylthiourea instead of **1a** and found that though it afforded **3aA** (69%), benzothiazole **4a** was also formed in 21% yield.

Having defined the optimized conditions for the reaction, we then investigated the generality of this palladium-catalysed isocyanide insertion followed by cross coupling with respect to the 2-bromophenylthioureas **1** and isocyanides **2**. The results of the study are summarized in Table 2. Several 2-benzophenylthioureas were efficiently prepared by reacting 2-bromoaniline with aryl or alkylisothiocyanates in methanol. Under the standard conditions, aromatic as well as aliphatic 2-bromophenylthioureas **(1a-j)** underwent smooth isonitrile insertion of the cyclohexyl isocyanide **(2A)** to furnish the respective products **(3aA-3jA)** in 67-88% yields. Presence of substituent on the phenyl ring **(2b-e)** or the 2-bromophenyl ring **(1j)** did not have any influence on the outcome of the reaction. But we noticed that the aliphatic thioureas **(1f-1j)** furnished relatively lower yields of the products **(3fA, 3h-j)** with **3gA** an exception. Subsequently the protocol was tested with different commercially available isocyanides **(2B-F)**. But, we discovered that the extension of the protocol to other isocyanides other than cyclohexyl isocyanide was limited to the aromatic 2-bromophenylthioureas. When tert-butylisocyanide **(2B)** was used as the reactant, all aromatic 2-bromophenylthioureas **(1a-e, 1k)** furnished the corresponding products **(3aB-3eB, 3kB)** in 77-88% yields. Unlike, the two aliphatic 2-bromophenylisothioureas **(1f, 1g)** instead of affording 4-substitutedimino-4*H*-benzo[*d*][1,3]thiazin-2-amines **(3fB, 3gB)** gave the respective 2-substituted aminobenzothiazoles **4f** and **4g** (see SI). Likewise the TosMIC **(2C)** underwent the insertion reaction with aromatic 2-bromophenylthioureas **(1a-e)** affording the expected products **3aC-3eC** in good yields. However here too with aliphatic 2-bromophenylthioureas **1f** and **1g** we could isolate benzothiazoles **4f** and **4g** though the mass spectra of the crude product display the corresponding molecular ion peak for **3fC** and **3gC**. The formation of benzothiazoles for these isocyanides suggests that for aliphatic thioureas the route **B** overrides the route **A**. Next the reactions of tetramethylbutyl isocyanide **(2D)** and 2,6-dimethylphenylisocyanide **(2E)** with aromatic 2-bromophenylthioureas **1a** and **1c** were conducted and in all reactions, the expected products **3aD**, **3cD**, **3aE** and **3cE** were isolated in good yields. To further extend the scope of the

Table 2 Substrate scope for the synthesis of 4-substitutedimino-4*H*-benzo[*d*][1,3]thiazin-2-amines via isocyanide insertion into 2-bromophenylthioureas[a,b]



[a] Reactions were performed with substituted 2-bromophenylthioureas **1** (1 equiv), isocyanides **2** (1.5 equiv), $Pd(OAc)_2$ (0.1 equiv), dppf (0.1 equiv), and Cs_2CO_3 (2.0 equiv) in PhMe (4.0 ml) for 12 h at 110 °C. [b]Yields after column chromatography.

methodology, 1-(2-bromophenyl)-3-phenylthiourea **(1a)** was treated with ethyl 2-isocyanoacetate **(2F)** but the reaction afforded 2-aminobenzothiazole **4a** exclusively. Several variations in reaction conditions with this isocyanide failed to furnish the desired product **3aF**. Perhaps the unsuccessful reaction with ethyl 2-isocyanoacetate may be attributed to high acidity of the α-CH proton resulting in reduced nucleophilicity of the isocyanide carbon.[15]

Conclusions

In conclusion, we have demonstrated the palladium-catalysed isonitrile insertion into 2-bromophenylthioureas for the synthesis of 4-substitutedimino-4*H*-benzo[*d*][1,3]thiazin-2-amines. This strategy is considered attractive as it requires starting materials which are readily available. The study for scope of the protocol revealed that though the reaction of cyclohexyl isocyanide was successful with both aromatic as well as aliphatic 2-bromophenylthioureas, all other isocyanides except for 2-isocyanoacetate afforded the title compounds with aromatic 2-bromophenylthioureas only.

Two authors (GP and SB) acknowledge the financial assistance in the form of fellowship from Council of Scientific and Industrial Research, New Delhi. The authors acknowledge the SAIF division of CSIR-CDRI for providing the spectroscopic data. The financial assistance from the network project BSP0014 (HOPE) is acknowledged.

Notes and references

[a] *Medicinal & Process Chemistry Division, CSIR-Central Drug Research Institute, BS-10/1, Sector 10, Jankipuram Extension, PO Box 173, Lucknow-226031, UP, India. Fax: +91-522-2771941; Tel: +91-522-2772450/2772550 Extn. 4705, 4727; E-mail: batra_san@yahoo.co.uk*
[b] *Academy of Scientific and Innovative Research, New Delhi, India.*

† Electronic Supplementary Information (ESI) available: [Experimental protocols, spectroscopic details and copies of ^{1}H and ^{13}C-NMR spectra of all the compounds are included]. See DOI: 10.1039/b000000x/

‡ CDRI Communication no MS No 220/2014/SB.

1 (a) J. Matysiak, *Bioorg. Med. Chem,* 2006, **14**, 2613; (b) Y. Su, Q Guo, G. Wang, S. Guo, Faming Zhuanli Shenqing Gongkai Shuomingshu Patent 1683349, 2005, *Chem. Abstr.,* 2006, **145**, 124577 (c) J. A. Gauthier, A. A. Asselin, Can. Patent, 1212396, 1986 *Chem. Abstr.,* 1987, **106**, 176409; (d) S. Kluge, S. Leistner, G Wagner, G. Schuster, D. Lohmann, G. Laban,. Ger. Patent 293713, 1991, *Chem. Abstr.,* 1992, **116**, 53664; (e) B. A. Dreikorn, U.S. Patent 4001227, 1977, *Chem. Abstr.,* 1977, **86**, 155674; (f) Fr. Patent 7359, 1969 *Chem. Abstr*., 1971, **75**, 151817; (g) S.Umio, K. Kariyone, T. Kishimoto, Jpn Patent 45037020, 1970, *Chem. Abstr.,* 1971, **74**, 76433; (h) S. Umio, K. Kariyone, T. Kishimoto, Jpn. Patent 45015030, 1970, *Chem. Abstr.,* 1970, **73**, 45525.

2 (a) T. Obayashi, A. Okawa, Jpn. Patent 2001253172, 2001, *Chem.Abstr.,* 2001, **135**, 233952; (b) Jpn. Patent 59197051, 1984 *Chem. Abstr.,* 1985, **102**, 176471; (c) S. Ishige, H. Usui, K. Saeki, Ger. Patent 2,704,724, 1977, *Chem. Abstr.,* 1977, 87, 144134; (d) H. Usui, S. Ishige, K. Saeki, Ger. Patent 2,658, 246, 1977, *Chem. Abstr.,* 1977, **87**, 137318.

3 J. P Rieu, J. F. Patoiseau, G. W. John, B. Legrand, J. P. Valentin, WO 9705134 A1, *Chem Abstr*., 1997, **126**, 225308.

4 M. Anzini, A. Giordani, F. Makovec, A. Cappelli, S. Vomero, G. Caselli, L. C. Rovati, WO 2009040331A2, *Chem Abstr*., 2009, **150**, 374522.

5 For *ortho* bromomethyl (a) E. Sorkin, W. Hinden, *Helv. Chim. Acta*, 1949, **32**, 63; (b) J.Gonda, P. Kristian, *Coll. Czech. Chem. Commun*., 1986, **51**, 2802.

6 For *ortho* hydroxymethyl (a) J. Prieto, A.Vega, J. Moragues, *J Heterocyclic Chem*., 1976, **13**, 813; (b) J. Gauthier, J. S. Duceppe, *J. Heterocyclic Chem*. 1984, **21**, 1081.

7 For *ortho* cycloalkyl or oxirane (a) A. N. Fedotov, E. V. Trofimova, V. A. Sidorov, K. A Potekhin,. V. A. Romanov, S. S. Mochalov, N. S. Zefirov, *Doklady Chem*. 2005, **405**, 217; (b) A. N. Fedotov, E. V Trofimova, V. A Romanov, S. S Muchalov, Y. S. Shabarov, N. S. Zefirov, *Chem. Heterocycl. Comp*., 2008, **44**, 96; (c) T. Otani, S. Katsurayama, T. Ote, T. Saito, *J Sulfur Chem*., 2009, **30**, 250.

8 For alkynes (a) M. Schmittel, A. Mahajan, J. P. Steffen, *Synthesis,* 2004, 415 (b) Q. Ding, J. Wu, *J. Comb. Chem*., 2008, **10**, 541; (c) R. Y. Tang, P. S. Luo, X. G. Zhang, P. Zhong, J. H. Li, *Synlett*, 2010, 1345; (d) Q. Ding, B. Cao, Z. Zong, Y. Peng, *J. Comb. Chem*., 2010, **12**, 370; (e) M. Kaname, H. Sashida, *Tetrahedron Lett*., 2012, **53**, 748; (f) H. Sashida, M. Kaname, M. Minoura, *Tetrahedron*, 2013, **69**, 6478 and references cited therein.

9 For cinnamates (a) A. Hari, B. L. Miller, *Org. Lett*., 2000, **2**, 3667; (b) S. Fukamachi, H. Konishi, K. Kobayashi, *Synthesis,* 2010, 1593; (c) H. Jie, Y. Yong, H. Lu, Y. Z. Gang, X. Fan, S. Qi, *Chin. Sci. Bull*., 2013, **58**, 717; (d) L. Hua, Z.Yao, F. Xu, Q. Shen, *RSC Adv.,* 2014, **4**, 3113; (e) also see C. Gimbert, A. Vallribera, *Org. Lett*., 2009, **11**, 269.

10 (a) M. Kosugi, T. Ogata, H. Tamura, H. Sano, T. Migita, *Chem. Lett*., 1986, 1197; (b) C. G. Saluste, R. J. Whitby, M. Furber, *Angew. Chem., Int. Ed*. 2000, **39**, 4156.

11 For reviews see (a) S. Lang, *Chem. Soc. Rev.,* 2013, **42**, 4867; (b) G. Qiu, Q. Ding, J. Wu, *Chem. Soc. Rev.* 2013, **42**, 5257; (c) T. Vlaar, E. Ruijter, B. U. W Maes, R. V. A. Orru, *Angew. Chem. Int. Ed*., 2013, **52**, 7084; (d) S. Chakrabarty, S. Choudhary, A. Doshi, F.-Q. Liu, R

Mohan, M. P. Ravindra, D. Shah, X. Yang, F. F. Fleming, *Adv. Synth. Catal*., 2014, **356**,2135–2196.

12 Selected recent references (a) N. Thirupathi, H. B. Madala, V. Dwivedi, R. Kant, M. S. Reddy, *Org. Lett*, 2014, **16**, 2908; (b) T. Fang, Q. Tan, Z. Ding, B. Liu, B. Xu, *Org. Lett*., 2014, 16, 2342; (c) T. -H. Zhu, S. -Y. Wang, Y. -Q. Tao, T. -Q. Wei, S. -J. Ji, *Org. Lett*., 2014, 16, 1260; (d) X. Jiang, T. Tang, J. –M. Wang, Z. Chen, Y.-M Zhu, S. –J. Ji, *J. Org. Chem*., 2014, **79**, 5082 (e) Z. –Y. Gu,. T.–H. Zhu, J. –J Cao, X. –P. Xu, S. -Y Wang, S. –J. Ji, *ACS Catal*., 2014, **4**, 49; (g) V. Estévez, G. V Baelen, B. H. Lentferink, T. Vlaar, E. Janssen, B. U. W. Maes, R. V. A. Orru, E. Ruijter, *ACS Catal*. 2014, 4, 40; (h) T. -H. Zhu, X. -P. Xu, J. -J Cao, T.-Q. Wei, S.-Y. Wang, S.-J. Ji, *Adv. Synth. Catal*., 2014, **356**, 509; (i) T. Tang, X. Jiang, J.-M Wang, Y.-X. Sun, Y.–M. Zhu, *Tetrahedron* 2014, **70**, 2999; (j) T. Nanjo, S.Yamamoto, C. Tsukano, Y. Takemoto, *Org. Lett*., 2013, **15**, 3754; (k) T. –H. Zhu, S. –Yi Wang, G. –N. Wang, S. -J. Ji, *Chem. Eur. J*., 2013, **19**, 5850; (l) F. Ji, M. –F. Lv, W. –B. Yi, C. Cai, *Synthesis,* 2013, 1965.

13 Representative references for metal-catalysed synthesis of 2-aminobenzothiazoles (a) C. Benedí, F. Bravo, P. Uriz, E. Fernandez, C. Claver, S. Castillon, *Tetrahedron Lett*., 2003, **44**, 6073; (b) L. L Joyce, G. Evindar, R. A. Batey,. *Chem. Commun*., 2004, 446; (c) G. Evindar, R. A Batey, *J. Org. Chem*., 2006, **71**, 1802; (d) J. Wang, F Peng, J. Jiang, Z. Lu, L. Wang, J. Bai,. Y. Pan, *Tetrahedron Lett*., 2008, **49**, 467; (e) H. C Ma,. X. Z. Jiang,. *Synlett* 2008, 1335; (f) G. Shen, X. Lv, W. Bao, *Eur. J. Org. Chem.,* 2009, 5897; (g) S. Murru, P. Mondal, R. Yella, B. K. Patel, *Eur. J. Org. Chem.,* 2009, 5406; (h) D. Ma, S. Xie, P. Xue, X. Zhang, J. Dong, Y. Jiang, *Angew. Chem. Int. Ed.,* 2009, **48**, 4222; (i) E. A. Jaseer, D. J. C Prasad, A. Dandapat, G. Sekar, *Tetrahedron Lett.,* 2010, **51**, 5009; (j) J.Liu, Y. Deng, C.T. Lin, A. W. Lei , *Chem. Sci.,* 2012, **3**, 1211.

14 Base-mediated synthesis of 2-aminobenzothiazole (a) R. Wang, Z Chen,. L.Yue, W. Pan, J. –J. Zhao,. *Tetrahedron Lett*., 2012, **53**, 4529; (b) E. G. Feng, H. Huang, Y. Zhou, D. J. Ye, H. L. Jiang, H. J Liu, *Comb. Chem*., 2010, **12**, 4229.

15 (a) A. V. Gulevich, A. G. Zhdanko, R. V. A. Orru, V. G. Nenajdenko, *Chem. Rev*. 2010, **110***,* 5235; (b) C.Lalli, M. J. Bouma, D. Bonne, G. Masson, J. Zhu, *Chem. Eur. J.,* 2011, **17**, 880 and references cited therein.