ORGANIC LETTERS

2012
Vol. 14, No. 23
6004–6007

Efficient 2-Aryl Benzothiazole Formation from Aryl Ketones and 2-Aminobenzenethiols under Metal-Free Conditions

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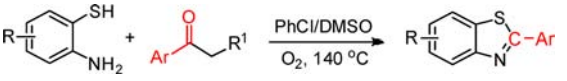
Received October 21, 2012

ABSTRACT



2-Aryl benzothiazole formation from aryl ketones and 2-aminobenzenethiols under metal- and I_2-free conditions was described. Various 2-aryl benzothiazoles were selectively obtained in good yields using molecular oxygen as oxidant. DMSO played an important role in this transformation. Functional groups such as methyl, methoxy, fluoro, chloro, bromo and nitro groups were tolerated under the optimized reaction conditions.

Aryl-substituted benzothiazoles are one of the most important classes of heterocycles and have shown a wide range of biological activities, such as antitumor, antiviral, and antimicrobial activities.[1] In addition, benzothiazole moieties have been found frequently in other molecules such as industrial dyes, natural products, functional materials, and agrochemical compounds.[2] Consequently, development of efficient methods for rapid construction of aryl-substituted benzothiazoles has stimulated considerable interest. The conventional methods for the synthesis of these important compounds typically involve two approaches. One is the metal-catalyzed intramolecular cyclization of *o*-haloanilides or their analogues (Scheme 1, a).[3] The second approach mainly involes the condensation of 2-aminobenzenethiol with either a carboxylic acid derivative under strong acid/high temperature conditions or an aromatic aldehyde under strong oxidative conditions (Scheme 1, b).[4] Recently, Ma and Jiang developed a novel and practical synthesis of substituted benzothiazoles from 2- haloanilides and metal sulfides using CuI as catalyst under mild reaction conditions.[5] Meanwhile, aryl-substituted benzothiazoles have been successfully synthesized by direct C−H activation and subsequent arylation of benzothiazoles with aryl halides,[6] arylsilanes,[7] aromatic carboxylic acids,[8] aryl boronic acids,[9] sodium sulfinates and aryl triflates,[10] aldehydes,[11] and even with arene C−H bonds via double C−H activations.[12]

The preparation of substituted benzothiazoles under transition-metal free conditions is highly desirable especially for pharmaceutical purposes due to the low threshold

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(1) (a) Zirngibl, L. *Antifungal Azoles: A Comprehensive Survey of Their Structures and Properties*; Wiley-VCH: Weinheim, 1998. (b) Katritzky, A. R.; Rees, C. W.; Scriven, E. F. *Comprehensive Heterocyclic Chemistry III*; Pergamon: Oxford, 1999; Vol. 1. (c) Katritzky, A.; Pozharskii, A. *Handbook of Heterocyclic Chemistry*, 1st ed.; Pergamon: Oxford, 2003.

(2) Hartley, D.; Kidd, H. *The Agrochemical Handbook*; Royal Society of Chemistry: Nottingham, 1983. (b) Baker, D. R.; Basarab, G. S.; Fenyes, J. G. *Synthesis and Chemistry of Agrochemicals IV*; American Chemical Society: Washington D. C., 1995.

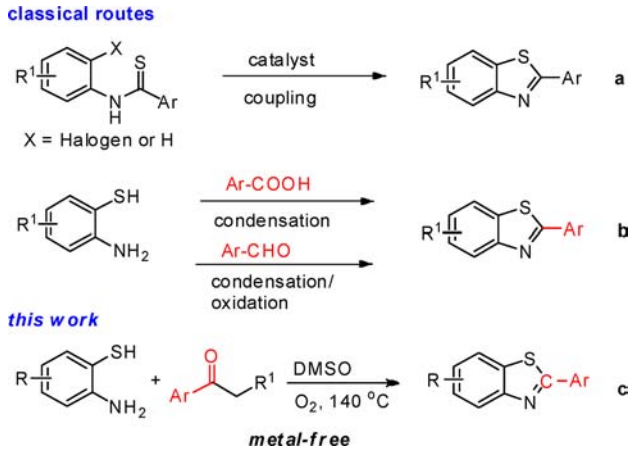
(3) For selected examples, see: (a) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802. (b) Bose, D. S.; Idrees, M. *J. Org. Chem.* **2006**, *71*, 8261. (c) Itoh., T.; Mase, T. *Org. Lett.* **2007**, *9*, 3687. (d) Saha, P.; Ramana, T.; Purkait, N.; Ali, M.; Paul, R.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 8719. (e) Wang, H.; Wang, L.; Shang, J.; Li, X.; Wang, H.; Gui, J.; Lei, A. W. *Chem. Commun.* **2012**, *48*, 76. (f) Bernardi, D.; Ba, L. A.; Kirsch, G. *Synlett* **2007**, 2121. (g) Benedi, C.; Bravo, F.; Uriz, P.; Fernandez, E.; Claver, C.; Castillon, S. *Tetrahedron Lett.* **2003**, *44*, 6073.

(4) (a) Riadi, Y.; Azzalou, R.; Lazar, S.; Mamouni, R.; Haddad, M.; Routier, S.; Guillaumet, G. *Tetrahedron Lett.* **2011**, *52*, 3492. (b) Bose, D. S.; Idrees, M. *Synthesis* **2010**, 398. (c) Chen, F.; Shen, C.; Yang, D. *Tetrahedron Lett.* **2011**, *52*, 2128. (d) Kangani, C.; Kelley, D.; Day, B. *Tetrahedron Lett.* **2006**, *47*, 6497. (e) Wang, Y.; Sarris, K.; Sauer, D.; Djuric, S. *Tetrahedron Lett.* **2006**, *47*, 4823. (f) Seijas, J.; Vazquez-Tato, M.; Carballido-Reboredo, M.; Crecente-Campo, J.; Romar-Lopez, L. *Synlett* **2007**, 313.

(5) Ma, D.; Xie, S.; Xue, P.; Zhang, X.; Dong, J.; Jiang, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 4222.

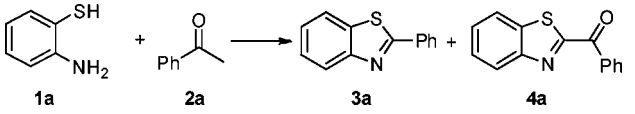
10.1021/ol302902e
Published on Web 11/14/2012

Scheme 1. Pathways for 2-Arylbenzothiazole Formation



residual tolerance of metals. Aromatic ketones are cheap, commercially available and relatively stable. The sp^3 C−H bond of aromatic ketones can be activated by transition metals under oxidative reaction conditions.[13] Very recently, the research groups of Wu and Prabhu developed various efficient approaches for aryl ketone sp^3 C−H bond functionalization under transition-metal-free conditions. However, in most cases, I_2 or *N*-iodosuccinamide (NIS) is used to activate the less reactive sp^3 C−H bond adjacent to the carbonyl group in aromatic ketones.[14] The preparation of 2-aryl benzothiazoles from aryl ketones under metal and I_2 free conditions is a challenge. Herein, we report an efficient approach for 2-aryl substituted benzothiazoles from 2-aminobenzenethiols and aryl ketones under metal- and I_2-free conditions using molecular oxygen as oxidant (Scheme 1, c).

Table 1. Optimization of the Reaction Conditions[a]



			yield (%)[b]	
entry	solvent	additive	**3a**	**4a**
1	toluene		0	0
2	DMF		0	0
3	PhCl		0	0
4	DMSO		54	30
5	PhCl	DMSO (1 mL)	53	13
6	PhCl	DMSO (1.5 mmol)	60	trace
7	**PhCl**	**DMSO (1.0 mmol)**	**82**	**trace**
8	PhCl	DMSO (0.5 mmol)	50	0
9	toluene	DMSO (1.0 mmol)	50	0
10	NMP	DMSO (1.0 mmol)	20	1
11	H_2O	DMSO (1.0 mmol)	28	2
12[c]	PhCl	DMSO (1.0 mmol)	59	0
13[d]	PhCl	DMSO (1.0 mmol)	65	0
14[e]	PhCl	DMSO (1.0 mmol)	trace	0

[a] Conditions: **1a** (0.9 mmol), **2a** (0.5 mmol), solvent (2.0 mL), 16 h, 140 °C under oxygen unless otherwise noted. [b] GC yield based on **2a** using dodecane as internal standard. [c] Under air. [d] At 120 °C. [e] Under argon.

We began our study by examining the reaction of 2-aminobenzenethiol (**1a**) with acetophenone (**2a**) in organic solvents by using molecular oxygen (1 atm) as oxidant at 140 °C. When acetophenone reacted with 1.8 equiv of 2-aminobenzenethiol in the absence of any catalyst, no desired product **3a** was obtained in common organic solvents such as toluene, DMF and chlorobenzene as determined by GC and ^{1}H NMR methods (Table 1, entries 1−3). DMSO was proved to be an efficient reaction media for this kind of transformation, and the use of DMSO resulted the desired product **3a** in 54% yield together with 30% yield of acylated adduct **4a** (entry 4). A mixture of DMSO with chlorobenzene was also proved to be good solvent for the condensation reaction. Good yield was obtained when the amount of DMSO decreased to 2 equiv, and the desired product was obtained in 82% yield, and only trace amount of byproduct **4a** was observed (entry 7). DMSO played an important role for this kind of transformation. Decreasing the amount of DMSO decreased the reaction yield significantly (entry 8). The replacement of chlorobenzene with other solvents decreased the reaction yield (entries 9−11).

(6) For selected reviews on C−H functionalization, see: (a) Dyker, G. *Handbook of C-H Transformations: Applications in Organic Synthesis*; Wiley-VCH: Weinheim, 2005. (b) Yu, J.; Shi, Z. *C−H Activation*; Springer: Berlin, 2010. (c) Goldberg, K. I.; Goldman, A. S. *Activation and Functionalization of C−H Bond, ACS Symposium Series 885*; American Chemical Society: Washington D. C., 2004. For recent selected examples, see: (d) Turner, G.; Morris, J.; Greaney, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 7996. (e) Do, H.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (f) Canivet, J.; Yamaguchi, J.; Ban, I.; Itami, K. *Org. Lett.* **2009**, *11*, 1733. (g) Zhao, D.; Wang, W.; Yang, F.; Lan, J.; Yang, L.; Gao, G.; You, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3296. (h) Huang, J.; Chan, J.; Chen, Y.; Borths, C.; Kyle, K.; Larsen, R.; Margaret, M. *J. Am. Chem. Soc.* **2010**, *132*, 3674. (i) Shibahara, F.; Yamaguchi, E.; Murai, T. *Chem. Commun.* **2010**, *46*, 2471. (j) Shibahara, F.; Yamaguchi, E.; Murai, T. *J. Org. Chem.* **2011**, *76*, 2680. (k) Yamamoto, T.; Muto, K.; Komiyama, M.; Canivet, J.; Yamaguchi, J.; Itami, K. *Chem.—Eur. J.* **2011**, *17*, 10113.

(7) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2202.

(8) Zhang, F.; Greaney, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2768.

(9) (a) Liu, B.; Qin, X.; Li, K.; Li, X.; Guo, Q.; Lan, J.; You, J. *Chem.—Eur. J.* **2010**, *16*, 11836. (b) Ranjit, S.; Liu, X. *Chem.—Eur. J.* **2011**, *17*, 1105. (c) Kirchberg, S.; Tani, S.; Ueda, K.; Yamaguchi, J.; Studer, A.; Itami, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2387.

(10) (a) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem, Int. Ed.* **2008**, *48*, 201. (b) Roger, J.; Doucet, H. *Org. Biomol. Chem.* **2008**, *6*, 169. (c) Ackermann, L.; Barfusser, S.; Pospech, J. *Org. Lett.* **2010**, *12*, 724. (d) Chen, R.; Liu, S.; Liu, X.; Yang, L.; Deng, G. J. *Org. Biomol. Chem.* **2011**, *9*, 7675. (e) Liu, B.; Guo, Q.; Cheng, Y.; Lan, J.; You, J. S. *Chem.—Eur. J.* **2011**, *17*, 13415. (f) So, C.; Lau, C.; Kwong, F. *Chem.—Eur. J.* **2011**, *17*, 761.

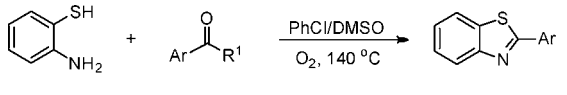
(11) Liu, S.; Chen, R.; Guo, X.; Yang, H.; Deng, G. J.; Li, C.-J. *Green Chem.* **2012**, *14*, 1577.

(12) (a) Han, W.; Mayer, P.; Ofial, A. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 2178. (b) Malakar, C.; Schmidt, D.; Conrad, J.; Beifuss, U. *Org. Lett.* **2011**, *13*, 1378. (c) Wang, Z.; Li, K.; Zhao, D.; Lan, J.; You, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5365. (d) Zhu, M.; Fujita, K.; Yamaguchi, R. *Chem. Commun.* **2011**, *47*, 12876. (e) Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 6993.

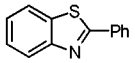
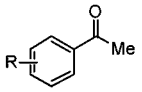
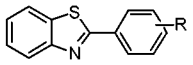
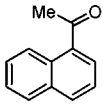
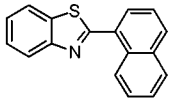
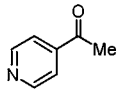
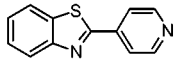
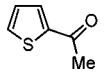
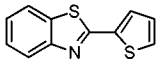
(13) Du, F.; Ji, J. X. *Chem. Sci.* **2012**, *3*, 460.

(14) (a) Zhu, Y.; Jia, F.; Liu, M.; Wu, A. X. *Org. Lett.* **2012**, *14*, 4414. (b) Zhu, Y.; Jia, F.; Liu, M.; Wu, L.; Cai, Q.; Gao, Y.; Wu, A. X. *Org. Lett.* **2012**, *14*, 5378. (c) Zhu, Y.; Lian, M.; Jia, F.; Liu, M.; Yuan, J.; Gao, Q.; Wu, A. X. *Chem. Commun.* **2012**, *48*, 9086. (d) Lamani, M.; Prabhu, K. R. *Chem.—Eur. J.* **2012**, *18*, 14638. (e) Zhu, Y.; Jia, F.; Yuan, J.; Gao, Q.; Lian, M.; Wu, A. X. *Org. Lett.* **2012**, *14*, 3392. (f) Zhu, Y.; Gao, Q.; Lian, M.; Yuan, J.; Liu, M.; Zhao, Q.; Yang, Y.; Wu, A. X. *Chem. Commun.* **2011**, *47*, 12700.

Table 2. Reaction of 2-Aminobenzenethiol (**1a**) with Various Ketones[a]



1a **2** **3**

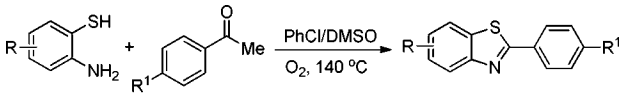
entry	ketone		product		yield (%)[b]
					
1	R^1 = Me	**2a**		**3a**	72
2	R^1 = Et	**2b**		**3a**	66
3	R^1 = CH_2CO_2Et	**2c**		**3a**	68
4	R^1 = H	**2d**		**3a**	80
					
5	R = 4-Me	**2e**		**3b**	76
6	R = 4-OMe	**2f**		**3c**	62
7	R = 4-F	**2g**		**3d**	74
8	R = 4-Cl	**2h**		**3e**	70
9	R = 2-Cl	**2i**		**3f**	65
10	R = 3-CF_3	**2j**		**3g**	60
11	R = 3-NO_2	**2k**		**3h**	66
12		**2l**		**3i**	68
13		**2m**		**3j**	55
14		**2n**		**3k**	60

[a] Conditions: **1a** (0.9 mmol), **2** (0.5 mmol), DMSO (1.0 mmol), PhCl (2.0 mL), 140 °C, 16 h, under oxygen. [b] Isolated yield based on **2**.

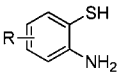
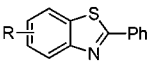
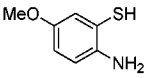
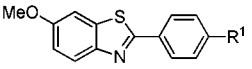
Moderate yield was obtained when the reaction was carried out under an atmosphere of air (entry 12). The reaction temperature was another important factor for the yield of the product. The reaction yield decreased to 65% when the reaction temperature was decreased to 120 °C (entry 13).

Under the optimized reaction conditions, the scope and generality of the oxidative condensation was explored (Table 2). Besides acetophenone, other aromatic carbonyl compounds such as propiophenone (**2b**), ethyl benzoylacetate (**2c**) and benzaldehyde (**2d**) were also successfully reacted with **1a** and gave the desired products in good yields (entries 2−4). The reactions with aromatic ketones bearing electron-donating groups at the aromatic ring proceeded smoothly to give the desired products in good yields (entries 5 and 6). The position of substituents on phenyl ring of aryl ketones affected the reaction yield slightly (entries 8 and 9). Functional groups such as fluoro, chloro, trifluoromethyl and nitro were well tolerated under the optimized conditions (entries 7−11). Notably, the

Table 3. Reaction of Various 2-Aminobenzenethiols with Aryl Ketones[a]



1 **2** **3**

entry	substrate 1		substrate 2		product		yield (%)[b]
							
1	R = 5-CH_3	**1b**	**2a**			**3l**	74
2	R = 5-OCH_3	**1c**	**2a**			**3m**	80
3[c]	R = 5-Cl	**1d**	**2a**			**3n**	70
4[c]	R = 5-Br	**1e**	**2a**			**3o**	81
5	R = 3-CH_3	**1f**	**2a**			**3p**	55
6	R = 3-Cl	**1g**	**2a**			**3q**	trace
7	R = 4-Cl	**1h**	**2a**			**3r**	70
							
8	**1c**		R^1 = Me	**2e**		**3s**	76
9	**1c**		R^1 = OMe	**2f**		**3t**	80
10	**1c**		R^1 = F	**2g**		**3u**	70
11	**1c**		R^1 = Cl	**2h**		**3v**	68

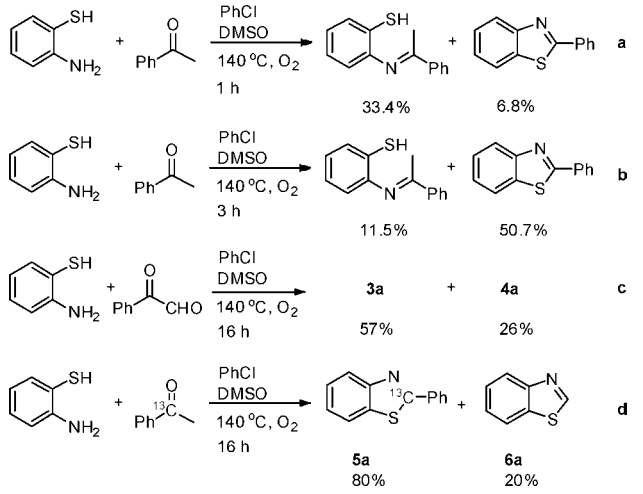
[a] Conditions: **1** (0.9 mmol), **2** (0.5 mmol), DMSO (1.0 mmol), PhCl (2.0 mL), 140 °C, 16 h, under oxygen. [b] Isolated yield based on **2**. [c] 1 equiv of DMSO was used.

coupling of heteroaromatic ketones such as 4-acetylpyridine (**2m**) and 2-acetylthiophene (**2n**) with **1a** afforded **3j** and **3k** in 55 and 60% yields, respectively (entries 13 and 14). Unfortunately, aliphatic ketones are not suitable substrates for this kind of transformation under the optimal conditions.

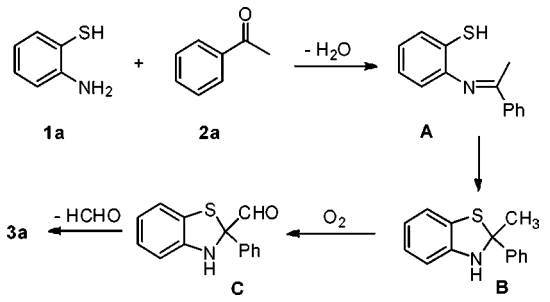
To further explore the scope of the reaction, various 2-aminobenzenethiols were employed to react with **2a** under the optimized conditions (Table 3). A series of functional groups including methyl, methoxy, chloro and bromo were well tolerated under the optimal conditions, and the desired products were obtained in moderate to good yields (Table 3, entries 1−4). The position of the substituents on the phenyl ring of 2-aminobenzenethiols affected the reaction yield significantly, and the use of 2-amino-3-chlorothiophenol (**1g**) only gave a trace amount of product (entry 6). An electron-donating group in the phenyl ring of 2-aminobenzenethiol could improve the reaction yield slightly, and the reaction of 2-amino-5-methoxythiophenol (**1c**) with various aromatic ketones all resulted the desired products in good yields (entries 8−11).

To get more information about the reaction mechanism, several control experiments were set up under the standard conditions. The reaction of 2-aminobenzenethiol with acetophenone in 1 h mainly gave an imine intermediate

Scheme 2. Control Experiments



Scheme 3. Proposed Mechanism



and the desired product **3a** was formed in only 6.8% yield as determined by GC (Scheme 2, a). However, the desired product could be improved to 50.7% when the reaction time was prolonged to 3 h (Scheme 2, b). The reaction of 2-aminobenzenethiol with phenylglyoxal, which is a key intermediate in the ketone functionalization under I_2 promoted oxidative conditions,[14] gave a mixture of **3a** and **4a** (Scheme 2, c). Further treatment of **4a** under the standard reaction conditions did not yield **3a**. This means the reaction did not take a decarbonylative pathway. In addition, we performed a ^{13}C labeling experiment under the optimized conditions with acetophenone-α-^{13}C, and the desired product **5a** was obtained in 80% yield together with 20% of **6a** (Scheme 2, d). On the basis of these observations, a plausible mechanism to rationalize this transformation is illustrated in Scheme 3, although the role of DMSO is not clear at this stage. Condensation of **1a** with **2a** generates the corresponding imine intermediate **A**, which can be cyclized to form an intermediate **B**. Oxidation of the methyl group generates an aldehyde compound **C**. The elimination of a proton and CHO group generates the final product **3a**.

In summary, we have developed an efficient 2-aryl benzothiazole formation from 2-aminobenzenethiols and aryl ketones using molecular oxygen as oxidant under metal- and I_2-free conditions. Solvent played an important role in this transformation, and the best yield was obtained in a mixture of DMSO/chlorobenzene. Functional groups such as methyl, methoxy, fluoro, chloro, bromo and nitro groups were all well tolerated under the optimized reaction conditions. This method affords a cheap and efficient alternative route for the rapid synthesis of heteroaromatic biaryls. The scope, mechanism, and synthetic applications of this reaction are under investigation.

Acknowledgment. This work was supported by the National Natural Science Foundation of China (20902076, 21172185), the Hunan Provincial Natural Science Foundation of China (11JJ1003), the New Century Excellent Talents in University from Ministry of Education of China (NCET-11-0974) and the Scientific Research Foundation for Returned Scholars, Ministry of Education of China (2011-1568).

Supporting Information Available. General experimental procedure and characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.