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ARTICLE TYPE

Iron catalyzed efficient synthesis of 2-arylbenzothiazoles from benzothiazole and olefins using environmentally benign molecular oxygen as oxidant

Ashok B. Khemnar and Bhalchandra M. Bhanage*

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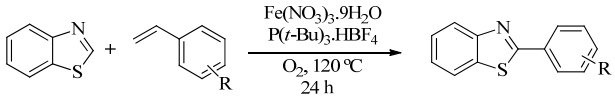
A novel protocol for iron catalyzed arylation of benzothiazole with olefins has been developed using molecular oxygen as greener oxidant. The reaction worked smoothly using inexpensive and easily available iron as a catalyst for the synthesis of 2-arylbenzothiazole derivatives in good to excellent yields.

Introduction

Carbon-carbon bond formation reactions using transition metal catalysts have enormous importance for the synthesis of organic compounds. The benzothiazole derivatives are of much interest as antitumor, antiviral, and antimicrobial agents.[1] In addition, drugs such as zopolrestat[2] and riluzole[3] also contains benzothiazole derivatives which are used for the treatment of diabetes. Furthermore, they are also used as an important building block in pharmaceuticals, agrochemicals and natural products.[4] Hence, the development of simple and efficient methodology for the synthesis of benzothiazole derivatives has attracted much attention in the past decades. The conventional methods for the synthesis of benzothiazole derivatives typically involve the condensation of 2-aminothiophenol or by cross-coupling of benzothiazole with different moieties such as aldehydes,[5] ketones,[6] nitriles,[7] esters,[8] halides,[9] amines,[10] and sodium arylsulfinates.[11] Subsequently, intramolecular cyclization of various moieties for arylation of benzothiazole were also developed.[12] Whereas metal free protocol for arylation of benzothiazole with aldehyde or acid using potassium persulfate oxidant under the nitrogen atmosphere was also reported.[13]

Recently, the synthesis of heteroaryl compounds using an iron catalyst has attracted much interest in the transition metal-catalyzed cross-coupling reactions. Liu et al. have reported the arylation[14] and acylation[15] of benzothiazole with aldehydes and ketones respectively using iron catalyst under oxygen atmosphere. Most recently, Deb et al. have synthesized 2-arylbenzothiazoles by cross coupling of benzothiazole with boronic acids using iron catalyst and potassium persulfate as an oxidant.[16] Similarly, Song and co-workers reported the copper catalyzed synthesis of 2-arylbenzothiazoles.[17] However, most of these protocols have limitations such as multistep synthesis, stoichiometric amount of inorganic oxidants, readily oxidizable 2-aminothiophenols, and need of inert atmosphere.

Hence, to develop economical and sustainable protocol for the arylation of heteroaryl compounds that operates under environmentally friendly condition is of great interest. In continuation of our research in the development of efficient catalytic system for arylation of heterocyclic moieties.[9a] Herein, we report an efficient and homogeneous methodology for the synthesis of 2-arylbenzothiazole using inexpensive and easily available iron catalyst under environmentally benign oxygen as oxidant.



Scheme 1: Arylation of benzothiazole with olefins.

Results and discussion

Initially, to optimise the reaction conditions benzothiazole (**1a**) and styrene (**2a**) were chosen as a model substrate for the iron catalyzed arylation reaction. A series of experiments were carried out to study the effect of various reaction parameters such as catalysts, solvents, oxidants, temperature and time (Table 1). Firstly, we screened various iron catalysts under oxygen atmosphere as an oxidant for the model reaction (Table 1, entries 1–6). It was observed that among the various iron catalysts, ferric nitrate gave the good yield of the arylation product along with minor acylation product and hence was used for further studies (Table 1, entry 6). Encouraged by this result, we studied the effect of other oxidants such as TBHP (5–6 in decane), $K_2S_2O_8$ and air (Table 1, entries 7–9), among the screened oxidants molecular oxygen furnished good yield of the desired product (Table 1, entry 6). As the correct combination of catalyst with ligands was crucial for such reactions, we performed reaction by using ferric nitrate with ligands like DPPM and P(*t*-Bu)$_3$.HBF$_4$ (Table 1, entries 10–11). It was found that P(*t*-Bu)$_3$.HBF$_4$ provided the excellent result (Table 1, entry 11). Furthermore,

*Department of Chemistry, Institute of Chemical Technology, Matunga, Mumbai-400019. India.
Tel.: +91-22-33612601; fax: +91-22-33611020;
E-mail: bm.bhanage@gmail.com, bm.bhanage@ictmumbai.edu.in

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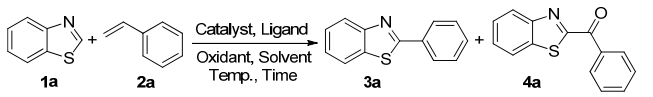
we studied the effect of catalyst as well as ligand concentration

Table 1: Optimization of the reaction conditions[a]



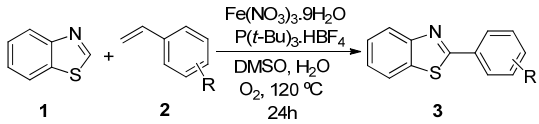
Entry	Catalyst (mol%)	Ligand (mol%)	Solvent (ml)	Temp. (°C)	Yield (%)[b] 3a	4a
1	$FeSO_4.7H_2O$ (20)	—	DMSO:H_2O	120	37	20
2	$Fe_2(SO_4)_3.H_2O$ (20)	—	DMSO:H_2O	120	17	05
3	$FeCl_3$ (20)	—	DMSO:H_2O	120	25	07
4	Fe_2O_3 (20)	—	DMSO:H_2O	120	05	02
5	$Fe(OAc)_2$ (20)	—	DMSO:H_2O	120	07	02
6	$Fe(NO_3)_3.9H_2O$ (20)	—	DMSO:H_2O	120	54	12
7[c]	$Fe(NO_3)_3.9H_2O$ (20)	—	DMSO:H_2O	120	22	09
8[d]	$Fe(NO_3)_3.9H_2O$ (20)	—	DMSO:H_2O	120	13	06
9[e]	$Fe(NO_3)_3.9H_2O$ (20)	—	DMSO:H_2O	120	03	00
10	$Fe(NO_3)_3.9H_2O$ (20)	DPPM	DMSO:H_2O	120	43	07
11	$Fe(NO_3)_3.9H_2O$ (20)	P(*t*-Bu)$_3$.HBF_4	DMSO:H_2O	120	74	04
12	$Fe(NO_3)_3.9H_2O$ (5)	P(*t*-Bu)$_3$.HBF_4	DMSO:H_2O	120	88	05
13	$Fe(NO_3)_3.9H_2O$ (5)	P(*t*-Bu)$_3$.HBF_4	Diglyme:H_2O	120	10	03
14	$Fe(NO_3)_3.9H_2O$ (5)	P(*t*-Bu)$_3$.HBF_4	DMF:H_2O	120	02	00
15	$Fe(NO_3)_3.9H_2O$ (5)	P(*t*-Bu)3.HBF_4	DMSO	120	04	00
16	$Fe(NO_3)_3.9H_2O$ (5)	P(*t*-Bu)$_3$.HBF_4	H_2O	120	15	06
17	$Fe(NO_3)_3.9H_2O$ (5)	P(*t*-Bu)$_3$.HBF_4	DMSO:H_2O	130	89	08
18	$Fe(NO_3)_3.9H_2O$ (5)	P(*t*-Bu)$_3$.HBF_4	DMSO:H_2O	110	74	05

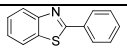
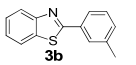
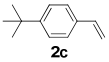
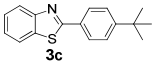
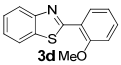
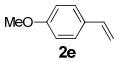
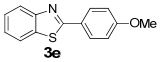
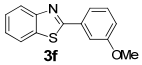
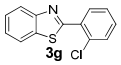
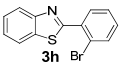
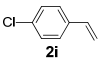
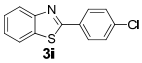
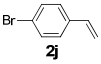
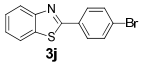
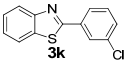
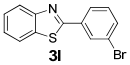
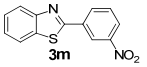
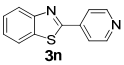
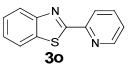
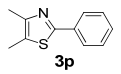
[a] Reaction conditions: **1a** (1 mmol), **2a** (2.5 mmol), catalyst (5–20 mol %), ligand (25 mol %), solvent (1.6 ml, 3:1), 120 °C, 24 h, under oxygen. [b] GC yield. [c] TBHP (5-6 M in decane). [d] $K_2S_2O_8$. [e] air atmosphere.

and it was found that 5 mol% catalyst and 25 mol% ligand furnished the excellent yield (Table 1, entry 12). Subsequently, we studied the effect of various solvents for this transformation (Table 1, entries 13–16). It was observed that the combination of DMSO and water was essential for present reaction (Table 1, entry 12). In addition, the effect of temperature and time were also investigated (Table 1, entries 17–18). It was found that 120 °C was the optimum temperature required for the arylation of benzothiazole (Table 1, entry 12). Whereas, yield of the product decreases with decrease in reaction time. Therefore, 24 h was the optimum time required for the completion of the reaction. Furthermore, we also examined the mole ratio of **1a**:**2a** and it was observed that 1 mmol of benzothiazole with 2.5 mmol of styrene i.e. 1:2.5 mole ratio furnished the highest yield of the desired arylation product (Table 1, entry 12).

Hence, the optimized reaction parameters for the arylation of benzothiazole are: benzothiazole (**1a**, 1 mmol), styrene (**2a**, 2.5 mmol), 5 mol% catalyst, P(*t*-Bu)$_3$.HBF_4 ligand (25 mol%), DMSO:H_2O (3:1, 1.6 ml) solvent under the oxygen atmosphere at 120 °C for 24 h. With these optimized reaction parameters, the scope of developed protocol was further extended for the wide range of substrates. Various aromatic olefins bearing electron donating and withdrawing substituents on the phenyl ring were well tolerated under the present reaction condition and afforded the corresponding arylated products **3a**-**3n** in good yield (Table 2). 3-methyl styrene and 4-*tert*. butyl styrene were also provided the excellent yield of **3b** and **3c** products respectively (Table 2,

Table 2: Arylation of benzothiazole with various olefins[a]



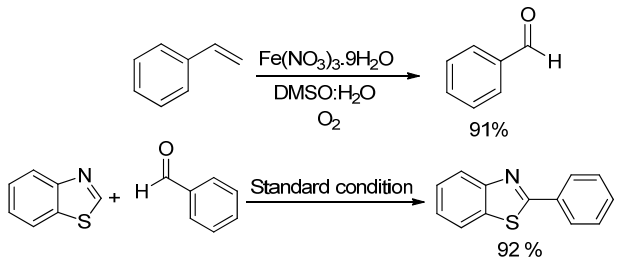
Entry	Thiazole	Olefin	Product	Yield (%)[b]
1				81
2	**1a**			80
3	**1a**			84
4	**1a**			72
5	**1a**			60
6	**1a**			75
7	**1a**			73
8	**1a**			66
9	**1a**			69
10	**1a**			60
11	**1a**			77
12	**1a**			68
13	**1a**			57
14	**1a**			42
15	**1a**			44
16				00

[a] Reaction conditions: **1** (1mmol), **2** (2.5 mmol), $Fe(NO_3)_3.9H_2O$ (5 mol %), P(*t*-Bu)$_3$.HBF_4 (25 mol%), DMSO:H_2O (1.6 ml, 3:1), 120 °C, 24 h, under oxygen. [b] isolated yield.

entries 2–3). The reaction of benzothiazole with olefins having electron donating group provided the arylated products in good yields (Table 2, entries 4–6). Subsequently, we studied the impact of electronic and structural variations of substituents on the phenyl ring of olefins. The *ortho*-substituted olefins were well tolerated as compared to *para*-substituted olefins which indicate that there is no effect of steric hindrance (Table 2, entries 4–10). The *meta*-substituted olefin also furnished good yield (Table 2, entries 2, 6 and 11–12). The phenyl ring of olefin with halogen substituents like bromo, chloro were compatible under this procedure, and the desired arylated products were isolated in good yields (Table 2, entries 7–12). In addition, electron

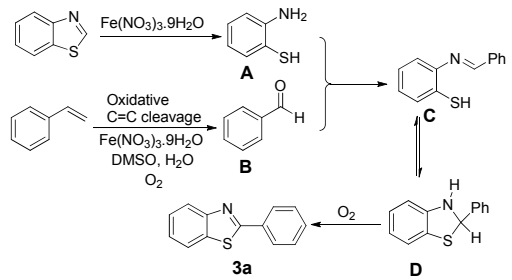
withdrawing group on the phenyl ring of olefin afforded the moderate yield (Table 2, entry 13). Furthermore, heteroaromatic olefin also provided the arylation product in moderate yield (Table 2, entries 14–15). However, aliphatic olefins were unreactive under the optimized reaction conditions. When optimized reaction condition applied for the reaction of 4,5-dimethylthiazole with styrene, arylated product was not observed (Table 2, entry 16). The reactions of benzoxazole and *N*-methyl benzimidazole were failed to provide the desired arylated product under present catalytic conditions.

To explore the reaction mechanism some control experiments have been carried out. Recently, Friedrich and Hong reported the conversion of styrene into benzaldehyde[18] or benzoic acid[19] respectively. Based on the above reports, we have carried out the reaction of benzaldehyde and benzoic acid with the benzothiazole under the optimized reaction condition. Only benzaldehyde provided the 92% **3a** arylation product (Scheme 2); whereas the benzoic acid does not work (SI, Scheme S1). It was found that styrene was converted into the benzaldehyde using ferric nitrate catalyst in the oxygen atmosphere (scheme 2). Additionally, benzothiazole converted into the 3% of 2-aminothiophenol and 10% dimer of 2-aminothiophenol (SI, Scheme S1). The reaction of 2-aminothiophenol and styrene were carried out to get an idea whether the reaction was going through the ring opening pathway or not and it was observed that 2-arylbenzothiazole with 2-benzoylbenzothiazole was obtained in 35% and 08% yield respectively (SI, Scheme S1). These results indicate that the reaction may be proceeding through ring opening pathway. When the reaction of benzothiazole and styrene were carried out in the presence of radical scavenger TEMPO the formation of arylation (**3a**) product was not observed (SI, Scheme S1).



Scheme 2: Control experiments.

Based on our experimental observation, a plausible reaction mechanism for the arylation of benzothiazole was shown in scheme 3. Firstly the benzothiazole was transformed into the 2-aminothiophenol (**A**) through ring opening reaction in the presence of iron catalyst. In the meanwhile, styrene is oxidized to



Scheme 3: Plausible reaction mechanism of arylation.

aldehyde (**B**). In the subsequent step, 2-aminothiophenol condensed with benzaldehyde giving the imine (**C**) which undergoes intramolecular cyclization provided the intermediate (**D**). Finally, oxidative dehydrogenation of (**D**) afforded the arylation product **3a**.

Conclusion

In conclusion, we have developed a novel, simple, efficient and useful protocol for the arylation of benzothiazole with various olefins using iron as a catalyst and oxygen as oxidant. In addition the developed methodology has significant advantages as compared to the earlier methods such as (i) first time arylation of benzothiazole by using olefin was successfully achieved, (ii) use of less toxic and inexpensive iron catalyst compared with other transition metals, (iii) use of oxygen as an oxidant, (iv) wider substrate applicability. Thus, the developed catalytic system constitutes a highly efficient, economically attractive and environmentally favourable process for the synthesis of 2-arylbenzothiazoles. Further application of this catalytic system and the detailed mechanistic study is under progress.

Experimental

General procedure for the synthesis of 2-aryl benzothiazole: To an oven dried 15 ml glass vial with a magnetic bar was charged with benzothiazole (**1a**, 1 mmol), styrene (**2a**, 2.5 mmol), ferric nitrate (5 mol %), P(*t*-Bu)$_3$.HBF$_4$ (25 mol%), and solvent (DMSO:H$_2$O, 3:1). The vial was then flush with oxygen and sealed with a cap. The reaction mixture was stirred at 120 ^{o}C for 24 h monitored by TLC and GC. After completion, cool the reaction mixture to room temperature. Extract the product with ethyl acetate (3×15 ml), dried the organic layer over Na_2SO_4 and evaporated to afford the crude product. The product was purified by column chromatography (silica gel, 100-200 mesh; petroleum ether/ethyl acetate) to afford the pure product. The product was confirmed by GC-MS, ^{1}H and ^{13}C NMR spectroscopic analysis.

Acknowledgements

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Notes and references

1. a) L. W. Wattenberg, M. A. Page and J. L. Leong, *Cancer Res.*, 1968, **28**, 2539; b) R. B. Trigg, J. V. Warrington and P. J. Palmer, *J. Med. Chem.*, 1971, **14**, 248; c) S. E. O'Brien, H. L. Browne, T. D. Bradshaw, A. D. Westwell, M. F. G. Stevens and C. A. Laughton, *Org. Biomol. Chem.*, 2003, **1**, 493; d) T. D. Bradshaw and A. D. Westwell, *Curr. Med. Chem.*, 2004, **11**, 1009; e) M. Chakraborty, K. J. Jin, S. C. Brewer III, H.-L. Peng, M. S. Platz and M. Novak, *Org Lett.*, 2009, **11**, 4862; f) P. P. Nandekar, K. M. Tumbi, N. Bansal, V. P. Rathod, L. B. Labhsetwar, N. Soumya, S. Singh and A. T. Sangamwar, *Med Chem Res.*, 2013, **22**, 3728.
2. T. A. Beyer, P. J. Scott, C. E. Aldinger, M. F. Dee, T. W. Siegel, W. J. Zembrowski and B. L. Mylari, *J. Med. Chem.*, 1992, **35**, 457.
3. J.-H. Song, C.-S. Huang, K. Nagata, J. Z. Yeh and T. Narahashi, *J. Pharmacol. Exp. Ther.*, 1997, **282**, 707.
4. a) C. J. Paget, K. Kisner, R. L. Stone and D. C. DeLong, *J. Med. Chem.*, 1969, **12**, 1016; b) V. G. Shirke, A. S. Bobad, R. P. Bhamaria, B. G. Khadse and S. R. Sengupta, *Indian Drugs*, 1990, **27**,

350; c) T. Kondo and T.-A. Mitsudo, *Chem. Rev.*, 2000, **100**, 3205; d) R. H. Tale, *Org. Lett.*, 2002, **4**, 10; e) I. P. Beletskaya and V. P. Ananikov, *Chem. Rev.*, 2011, **111**, 1596; f) Y. Liu and J.-P. Wan, *Org. Biomol. Chem.*, 2011, **9**, 6873.
5. K. Bahrami, M. M. Khodaei and F. Naali, *J. Org. Chem.*, 2008, **73**, 6835.
6. Y. Liao, H. Qi, S. Chen, P. Jiang, W. Zhou and G.-J. Deng, *Org. Lett.*, 2012, **14**, 6004.
7. Y. Sun, H. Jiang, W. Wu, W. Zeng and X. Wu, *Org. Lett.*, 2013, **15**, 1598.
8. S. Rostamizadeh, M. Nojavan and F. Heshmatpoor, *Heterocycl. Commun.*, 2007, **13**, 305.
9. a) N. S. Nandurkar, M. J. Bhanushali, M. D. Bhor and B. M. Bhanage, *Tetrahydron Lett.*, 2008, **49**, 1045; b) J. Canivet, J. Yamaguchi, I. Ban and K. Itami, *Org. Lett.*, 2009, **11**, 1733; c) J. Huang, J. Chan, Y. Chen, C. J. Borths, K. D. Baucom, R. D. Larsen and M. M. Faul, *J. Am. Chem. Soc.*, 2010, **132**, 3674; d) T. Yamamoto, K. Muto, M. Komiyama, J. Canivet, J. Yamaguchi, K. Itami, *Chem. Eur. J.*, 2011, **17**, 10113; e) W. Zhang, Q. Zeng, X. Zhang, Y. Tian, Y. Yue, Y. Guo and Z. Wang, *J. Org. Chem.*, 2011, **76**, 4741; f) J. Yamaguchi, K. Muto and K. Itami, *Eur. J. Org. Chem.*, 2013, 19.
10. a) F. Su, S. C. Mathew, L. Mohlmann, M. Antonietti, X. Wang and S. Blechert, *Angew. Chem. Int. Ed.*, 2011, **50**, 657; b) T. B. Nguyen, L. Ermolenko, W. A. Dean and A. Al-Mourabit, *Org. Lett.*, 2012, **14**, 5948; c) Z. Yang, A. Wang, X. Chen, Q. Gui, J. Liu, Z. Tan, H. Wang and J.-C. Shi, *Synlett.*, 2013, **24**, 1549; d) T. Xiao, S. Xiong, Y. Xie and X. D. L. Zhou, *RSC Adv.*, 2013, **3**, 15592.
11. M. Wang, D. Li, W. Zhou and L. Wang, *Tetrahedron*, 2012, **68**, 1926.
12. a) L. L. Joyce, G. Evindar and R. A. Batey, *Chem. Commun.*, 2004, 446; b) D. Ma, S. Xie, P. Xue, X. Zhang, J. Dong and Y. Jiang, *Angew. Chem. Int. Ed.*, 2009, **48**, 4222; c) H. Wang, L. Wang, J. Shang, X. Li, H. Wang, J. Gui and A. Lei, *Chem. Commun.*, 2012, **48**, 76; d) Y. Cheng, J. Yang, Y. Qu and P. Li, *Org. Lett.*, 2012, **14**, 98.
13. Z. Yang, X. Chen, S. Wang, J. Liu, K. Xie, A. Wang and Z. Tan, *J. Org. Chem.*, 2012, **77**, 7086.
14. S. Liu, R. Chen, X. Guo, H. Yang, G. Deng and C.-J. Li, *Green Chem.*, 2012, **14**, 1577.
15. S. Liu, R. Chen, H. Chen and G.-J. Deng, *Tetrahedron Lett.*, 2013, **54**, 3838.
16. A. Deb, S. Manna, A. Maji, U. Dutta and D. Maiti, *Eur. J. Org. Chem.,* 2013, 5251.
17. Q. Song, Q. Feng, and M. Zhou, *Org. Lett.*, 2013, **15**, 5990–5993.
18. J. Valand, H. Parekh, H. B. Friedrich, *Catal. Commun*., 2013, **40**, 149–153.
19. T. M. Shaikha and F.-E Hong, *Adv. Synth. Catal*., 2011, **353**, 1491–1496.