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One Pot Synthesis of Substituted Imidazopyridines and Thiazoles from Styrenes in Water Assisted by NBS

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Abstract: Just heating of commercially available styrenes with NBS in water followed by reaction with 2-aminopyridines and thioamides, important heterocyclic scaffold were prepared in one pot manner. Reaction proceed via co-oxidant free, *in-situ* formation of α-bromoketone using NBS as bromine source as well as oxidant followed by trapping with suitable nuclephiles to provide imidazopyridines and thiazoles.

Nitrogen and sulphur containing privileged heterocyclic scaffolds such as Imidazo[1,2-*a*]pyridines and thiazoles plays an important role in the modern synthetic and medicinal chemistry due to their promising biological and pharmaceutical activities.[1] Of particular, imidazo[1,2-*a*]pyridine is important motif due to presence in various top commercial drugs such as zolpidem, zolimidine, olprinone, GSK812397, anxiolytic agents alpidem, necopidem, saripidem (Figure 1).[2] Imidazo[1,2-*a*]pyridines also have applications in *N*-heterocyclic carbene chemistry[3] and material chemistry.[4] The thiazole nucleus is present in several biologically active natural products such as epothilone, leinamycin, barakacin.[5] Numerous thiazole based drug are also known such as ritonavir, abafungin, sulfathiazole.[6] Various synthetic methods have been reported for the construction of these motifs such as C-H amination, oxidative cyclization, multicomponent reaction, hydroamination and tandem processes from various starting materials.[7] Most of these reaction are metal catalysed and/or use of oxidants. Traditional method for the construction of these scaffolds includes condensation of α-haloketones with suitable nucleophiles in the various organic solvents and bases which involves the heating for longer time (Scheme 1).[8] Most stern issue is the handling of lachrymatic phenacyl bromides or their analogues. *In-situ* preparation of α-haloketones from ketone are also known in literature but

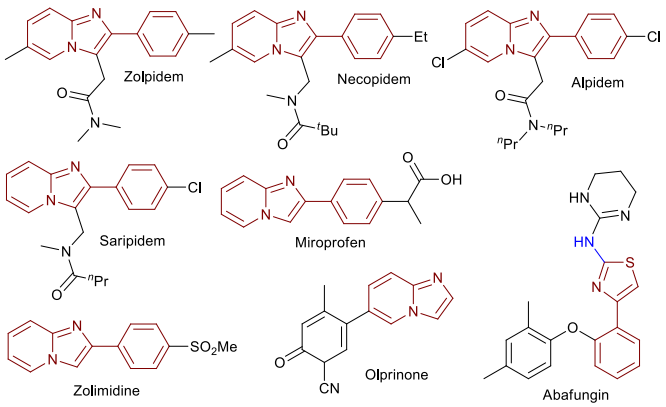
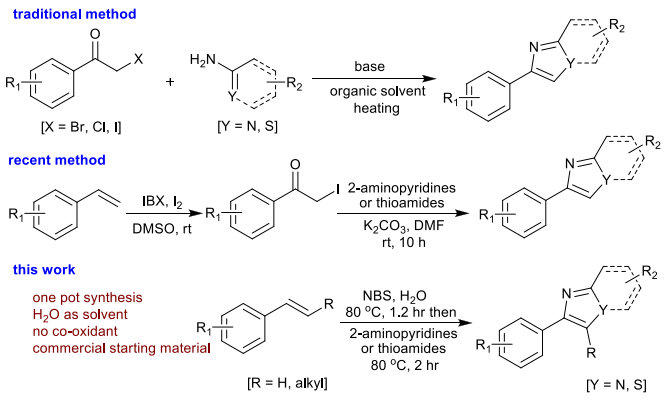


Figure 1. Selected commercial drugs based on imidazo[1,2-*a*]pyridine and thiazole.

involves the use of toxic bromine sources.[9] Donohoe group recently reported two step approach for the synthesis of these heterocycles from alkenes which involves the preparation of α-iodoketone by reaction of olefins with IBX/Iodine in DMSO and these α-iodoketones were treated with suitable nucleophiles in the presence of K_2CO_3/DMF to give the diverse heterocycles.[10]

Use of the water as solvent for organic reactions is the most interesting and attracted step because of its economic and



Scheme 1. Approach for the synthesis imidazo[1,2-*a*]pyridine and thiazole.

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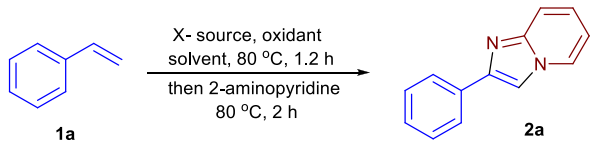
environmentally friendly nature.[11] NBS has numerous applications in the synthetic organic chemistry such as simple and non-toxic cationic and radical bromine source as well as oxidant.[12] In view of this, here we would like to report the NBS promoted, simple, one pot method for the construction of diverse heterocyclic building blocks in water as solvent from commercially available styrenes without using co-oxidant. NBS plays dual role such as safe bromine source and oxidant, whereas reaction was carried out using water which also act as 'O' source for the *in-situ* preparation *α*-bromoketones. These *in-situ* formed *α*-bromoketones upon reacting with appropriate nucleophiles in one pot manner provided the diverse heterocycles.

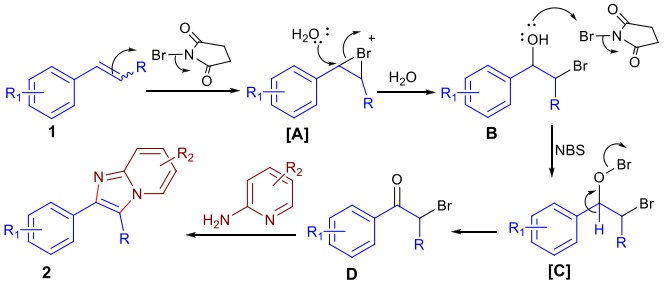
We initiated the optimization of reaction on simple styrene (**1a**) (table 1). Reaction of styrene **1a** with iodine in the presence of *tert*-butyl hydroperoxide (TBHP, entry 1) or 2-iodoxybenzoic acid (IBX, entry 2) as oxidant in DCE and DMSO as solvent at 40 °C or 80 °C followed by addition of 2-aminopyridine gave the desired imidazo[1,2-a]pyridine **2a** product in very trace amount. Treatment of styrene with other iodine source, *N*-iodosuccinimide (NIS) in the presence of IBX as oxidant in DMSO at 40 °C followed by addition of 2-aminopyridine provided desired imidazo[1,2-a]pyridine **2a** in 30% yield (entry 3). When same reaction was carried out at higher temperature, yield was not improved significantly. Use of KI in the presence of oxone was unable to give the desired product (entry 4) but KI in the presence of $K_2S_2O_8$ provided the imidazo[1,2-a]pyridine **2a** in 35% yield (entry 5). Treatment of styrene (**1a**, 1.0 equiv.) with NBS (2.0 equiv.) in H_2O:dioxane at 80 °C for 1.2 hr followed by addition of 2-aminopyridine gave the imidazo[1,2-a]pyridine **2a** in 41% yield after heating at 80 °C for 2 hr (entry 6). Change in the solvent system from H_2O:dioxane to H_2O:acetonitrile or H_2O:acetone, decrease in the yield was observed (entry 7/8). To our delight, when reaction was performed using only water as solvent, it furnished the imidazo[1,2-*a*]pyridine **2a** in 89% yield (entry 9).

Table 1. Optimization of the reaction condition.[a]



entry	Solvent	X-source	oxidant	**2a** (%)[b]
1	DCE	I_2	TBHP	Trace
2	DMSO	I_2	IBX	Trace
3	DMSO	NIS	IBX	30%
4	DMSO:H_2O	KI	oxone	00%
5	CH_3CN:H_2O	KI	$K_2S_2O_8$	35%
6	H_2O:dioxane	NBS	-	41
7	H_2O:CH_3CN	NBS	-	33
8	H_2O: acetone	NBS	-	15
9	**H_2O**	**NBS**	**-**	**89**
10[c]	H_2O	NBS	-	78
11	H_2O	NCS	-	00
12	H_2O	NIS	-	40
13	H_2O	Br_2	air	00
14	H_2O	TBAB	air	00

[a] Condition: Styrene (1 mmol), X-source (2 mmol), oxidant (2 mmol), solvent (2 mL), 80 °C, 1.2 hr, then 2-aminopyridine (2.0 mmol), 80 °C, 2 hr. [b] isolated yields, [c] NBS was added in two portions at 30 min. interval.



Scheme 2. Possible reaction pathway.

Reaction includes the NBS/H_2O promoted formation of bromohydrin (**B**) followed by NBS mediated oxidation of secondary benzylic alcohol for the *in-situ* formation of phenacyl bromide (**D**) (Scheme 2). Condensation of phenacyl bromide with 2-aminopyridine furnished the desired product imidazo[1,2-a]pyridine **2**. No improvement in the yield was observed by portion wise addition of NBS (entry 10). When NBS was replaced with NIS, it gave the compound **2a** in 32% yield (entry 11) whereas with NCS, formation of **2a** was not observed (entry 12). We have also screened other bromine sources such as molecular bromine and tetrabutylammonium bromide (TBAB) using air as oxidant but formation of **2a** was not observed (entry 13/14).

Having optimized condition in hand, we pursued for the exploration of substrate scope. Reacting NBS with aryl olefin with electron withdrawing groups on aromatic ring such as -F and -Br (**1b,c)** provided corresponding imidazo[1,2-a]pyridine (**2b,c**) smoothly in very good yields (82 and 81%). Styrenes

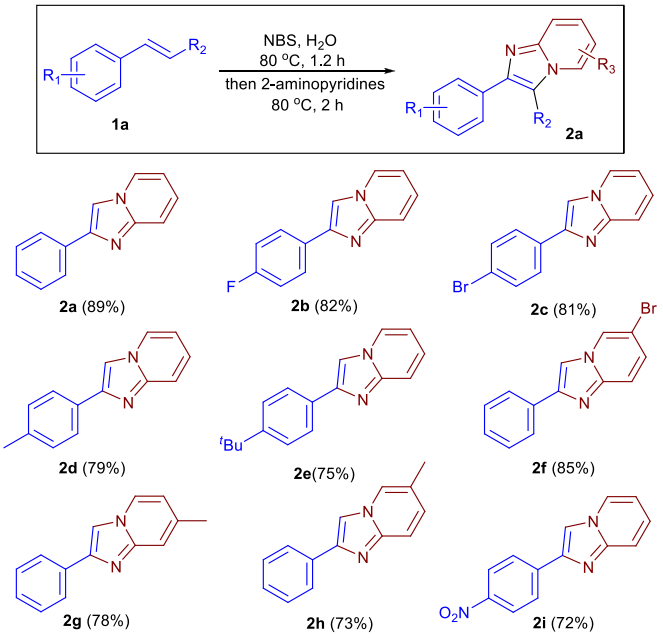


Figure 2. Substrate scope for the imidazo[1,2-a]pyridines.

with electron releasing groups such as 4-methyl and 4-*tert*-butyl also afforded the corresponding imidazo[1,2-a]pyridine (**2d,e**) in very good yield (79 and 75%). Use of 2-amino-5-bromo-pyridine as nucleophilic partner with styrene afforded imidazo[1,2-a]pyridine (**2f**) in 85% yield. Reaction of 4-methoxystyrene with NBS followed by 2-aminopyridine provided complex reaction mixture. Reaction with 4-methyl and 5-methyl-2-aminopyridines afforded corresponding imidazo[1,2-a]pyridine (**2g,h**) in good to moderate yield (78 and 73%). Styrene having strong electron withdrawing group such as NO2 works smoothly to afford the corresponding imidazo[1,2-a]pyridine (**2i**) in 72% yield.

Encouraged by preparing various imidazo[1,2-a]pyridine we shifted to investigate the scope of other nucleophiles. Thioamide was selected as next nucleophilic partner for condensation due to its potential for the formation of thiazoles. Reaction of various styrenes such as styrene (**1a**) and halo substituted styrenes with NBS and subsequent addition of thiobenzamide in water provided 2,4-diarylsubstituted thiazoles (**3a-d**) in good yields (70-77%). Reaction of alkyl substituted styrene such as methyl and *tert*-butyl styrene with thiobenzamide provided corresponding thiazoles (**3e,f**) in 70 and 73% yield. Scope of different thioamides has also been checked. Use of thioacetamide as condensing partner with styrene (**1a**) provided corresponding 2-methyl-4-phenyl thiazoles (**3g**) in good yields (67%). When thionicotinamide was used as nucleophilic partner with styrene (**1a**) and

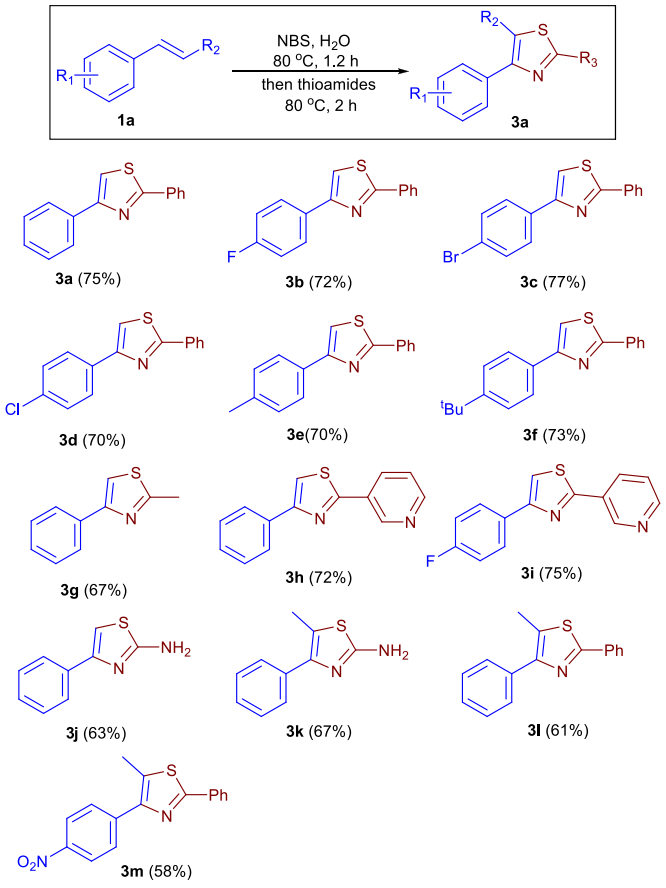


Figure 3. Substrate scope for the substitutes thiazoles.

4-fluoro-styrene, it provided corresponding interesting 2,4-diarylsubstituted thiazoles (**3h,i**) in very good yields (72 and 75%). Thiourea was also explored as nucleophilic partner with styrene (**1a**) to give the 2-amino-4-phenylthiazole (**3j**) in 63% yield. Starting from β-methyl styrenes, highly substituted thiazoles (**3k-m**) were prepared. To afford these 2,4,5-trisubstituted thiazoles (**3k-m**) in moderate yields (67-58%) from β-methyl styrene and β-methyl-4-nitro-styrene required longer time (7 hrs) heating prior the addition of thiourea and thiobenzamide.

Conclusions

In conclusion, we have demonstrated the facile one pot procedure for the synthesis of substituted imidazopyridines and highly substituted thiazoles starting from important feedstock such as styrenes promoted by NBS. Reaction proceeds via formation of α-bromoketone as versatile intermediate followed by condensation with various nucleophiles in one pot manner. Reactions were carried out in water as solvent and are co-oxidant free where the NBS plays dual role.

Acknowledgements

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Notes and references

1 (a) A. R. Katritzky, *Comprehensive heterocyclic chemistry* III, Elsevier, Amsterdam, New York, 2008; (b) A. R. Katritzky, Y.-J. Xu and H. Tu, *J. Org. Chem*., 2003, **68**, 4935; (c) J. Allen, G. Parent and A. Tizot. *Labelled Compd. Radiopharm*., 1986, **23**, 807; (d) M. García-Valverde and T. Torroba, *Molecules*, 2005, **10**, 318.

2 (a) S. Z. Langer, S. Arbilla, J. Benavides and B. Scatton, *Adv. Biochem. Psychopharmacol*., 1990, **46**, 61; (b) K. Mizushige, T. Ueda, K. Yukiiri and H. Suzuki, *Cardiovasc. Drug Rev*., 2002, **20**, 163; (c) L.Almirante, L. Polo, A. Mugnaini, E. Provinciali, P. Rugarli, A. Biancotti, A. Gamba and W. Murmann, *J. Med. Chem*., 1965, **8**, 305; (d) R. J. Boerner and H. J. Moller, *Psychopharmakother*, 1997, **4**, 145; (e) K. Gudmundsson and S. D. Boggs, PCT Int. Appl., WO 2006026703, 2006. (f) H. L. Koo and H. L. Dupont, *Curr. Opin. Gastroenterol*., 2010, **26**, 17.

3 (a) A. John, M. M. Shaikh and P. Ghosh, *Dalton Trans*., 2009, 10581; (b) G. Song, Y. Zhang and X. Li, *Organometallics*, 2008, **27**, 1936.

4 (a) A. Douhal, F. Amat-Guerri and A. U. Acuna, *J. Phys. Chem*., 1995, **99**, 76; (b) A. Douhal, F. Amat-Guerri and A. U. Acuna, *Angew. Chem., Int. Ed*., 1997, **36**, 1514; (c) A. Douhal, *Ber. Bunsen-Ges*., 1998, **102**, 448.

5 Z. Jin, *Nat. Prod. Rep*., 2013, **30**, 869; (b) D. Davyt and G. Serra, *Mar. Drugs*, 2010, **8**, 2755.

6 S. J. Kashyap, V. K. Garg, P. K. Sharma, N. Kumar, R. Dudhe, J. K. Gupta, *Med. Chem. Res*., 2012, **21**, 2123.

7 (a) A. K. Bagdi, S. Santra, K. Monir and A. Hajra, *Chem. Commun*., 2015, **51**, 1555; (b) K. Pericherla, P. Kaswan, K.

Pandey and A. Kumar, *Synthesis*, 2015, **47**, 887; (c) N. Chernyak and V. Gevorgyan, *Angew.Chem., Int. Ed*., 2010, **49**, 2743; (d) P. Liu, L. Fang, X. Lei and G. Lin, *Tetrahedron Lett*., 2010, **51**, 4605; (e) T. Palani, K. Park, M. R. Kumar, H. M. Jung and S. Lee, *Eur. J. Org. Chem*., 2012, 5038; (f) I. Luz, F. X. L. Xamena and A. Corma, *J. Catal*., 2012, 285, 285; (g) P. Liu, C.-L. Deng, X. Lei and G.-Q. Lin, *Eur. J. Org. Chem*., 2011, 7308; (h) M. Chioua, E. Soriano, L. Infantes and M. L. Jimeno, *Eur. J. Org. Chem*., 2013, 35. (i) R.-L. Yan, H. Yan, C. Ma, Z.-Y. Ren, X.-A. Gao, G.-S. Huang and Y.-M. Liang, *J. Org. Chem*., 2012, **77**, 2024; (j) A. K. Bagdi, M. Rahman, S. Santra, A. Majeeand, A. Hajra, *Adv. Synth. Catal*., 2013, **355**, 1741; (k) D. C. Mohan, R. R. Donthiri, S. N. Rao and S. Adimurthy, *Adv. Synth. Catal*., 2013, **355**, 2217.; (l) K. Pericherla, P. Kaswan, P. Khedar, B. I. Khungar, K. Parang and A. Kumar, *RSC Adv*., 2013, **3**, 18923; (m) Z.-J. Cai, S.-Y. Wang and S.-J. Ji, *Adv. Synth. Catal.*, 2013, **355**, 2686; (n) Y. Zhang, Z. Chen, W. Wu, Y. Zhang and W. Su, *J. Org. Chem*., 2013, **78**, 12494. (o) F. Asinger. *Angew. Chem*. 1956, **68**, 413. (p) F. Asinger, M. Thiel, L. Schröder, *Liebigs Ann. Chem*. 1957, **610**, 49. (q) F. Asinger, M. Thiel, W. Dathe, O. Hampel, E. Mittag, E. Plaschil, C. Schröder. *Liebigs Ann. Chem*. 1961, **639**, 146. (r) F. Asinger, M. Thiel, K. Gewald. *Liebigs Ann. Chem*. 1961, **639**, 133.

8 (a) M. Alajarin, J. Cabrera, A. Pastor, P. Sanchez-Anrada and D. Bautista, *J. Org. Chem*., 2006, **71**, 5328; (b) G. Schwarz, *Org. Synth*., 1955, Coll. Vol. **3**, 332; (c) A. Hantzsch, *Ann. Chem*., 1889, **250**, 257; (d) M. H. Fisher and A. Lusi, *J. Med. Chem*., 1972, **15**, 982; (e) B. Li, C. K. F. Chiu, R. F. Hank, J. Murry, J. Roth and H. Tobiassen, *Org. Process Res. Dev*., 2002, **6**, 682; (f) G. Kempter, J. Spindler, H. J. Fiebig and G. Sarodnick, *J. Prakt. Chem*., 1971, **313**, 977.

9 (a) O. A. Attanasi, S. Berretta, G. Favi, G. P. Filippone, G. Mele, G. Moscatelli and R. Saladino, *Org. Lett*., 2006, **8**, 4291; (b) H. Y. Choi and D. Y. Chi, *Org. Lett*., 2003, **5**, 411; (c) S. Paul, V. Gupta and R. Gupta, *Synth. Commun*., 2003, **33**, 1917; (d) J. Goswami and A. Goswami, *J. Indian Chem. Soc*., 2002, **79**, 469; (e) M. Ghiaci and J. Asghari, *Bull. Chem. Soc. Jpn*., 2001, **74**, 1151; (f) Z. Diwu, C. Beachdel and D. H. Klaubert, *Tetrahedron Lett*., 1998, **39**, 4987; (g) B. Sket and M. Zupan, *Synth. Commun*., 1989, **19**, 2481.

10 T. J. Donohoe, M. A. Kabeshov, A. H. Rathi and I. E. D. Smith, *Org. Biomol. Chem*., 2012, **10**, 1093.

11 (a) C. J. Li, *Chem. Rev*. 2005, **105**, 3095; (b) M. O. Simon, C. J. Li, *Chem. Soc. Rev*. 2012, **41**, 1415.

12 (a) W. Z. Yu, F. Chen, Y. A. Cheng and Y.-Y. Yeung, *J. Org. Chem*. 2015, **80**, 2815. (b) J. Zhou and Y.-Y. Yeung, *Org. Biomol. Chem.*, 2014, **12**, 7482. (c) K. K. Rajbongshi, D. Hazarika and P. Phukan, *Tetrahedron Letters*, 2015, **56**, 356. (d) L. Song. S. Luo and J.-P. Cheng, *Org. Lett*., 2013, **15**, 5702. (e) Y. Wei, S. Lin, H. Xue, F. Liang and B. Zhao, *Org. Lett*. 2012, **14**, 712. (f) A. Alix, C. Lalli, P. Retailleau and G. Masson, *J. Am. Chem. Soc*. 2012, **134**, 10389. (g) J. Chen, S. Chng, L. Zhou and Y.-Y. Yeung, *Org. Lett*. 2011, **13**, 6456. (h) L. Zhou, J. Chen, J. Zhou and Y.-Y. Yeung, *Org. Lett*. 2011, **13**, 5804. (i) Y. Cai, X. Liu, Y. Hui, J. Jiang, W. Wang, W. Chen, L. Lin and X. Feng, *Angew. Chem. Int. Ed*., 2010, **49**, 6160. (j) L. Zhou, C. K. Tan, X. Jiang, F. Chen and Y.-Y. Yeung, *J. Am. Chem. Soc*., 2010, **132**, 15474. (k) A. Podgorsek, S. Stavber, M. Zupan and J. Iskra, *Tetrahedron*, 2009, **65**, 4429.