Metal-free new synthesis of 1,3-naphthoxazines *via* intramolecular cross dehydrogenative-coupling reaction of 1-(α-aminoalkyl)-2-naphthols using hypervalent iodine(III) reagent

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PII: S0040-4039(15)30531-1
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.12.117
Reference: TETL 47164

To appear in: *Tetrahedron Letters*

Received Date: 31 October 2015
Revised Date: 28 December 2015
Accepted Date: 30 December 2015

Please cite this article as: Waghmode, N.A., Kalbandhe, A.H., Thorat, P.B., Karade, N.N., Metal-free new synthesis of 1,3-naphthoxazines *via* intramolecular cross dehydrogenative-coupling reaction of 1-(α-aminoalkyl)-2-naphthols using hypervalent iodine(III) reagent, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.12.117

Graphical Abstract

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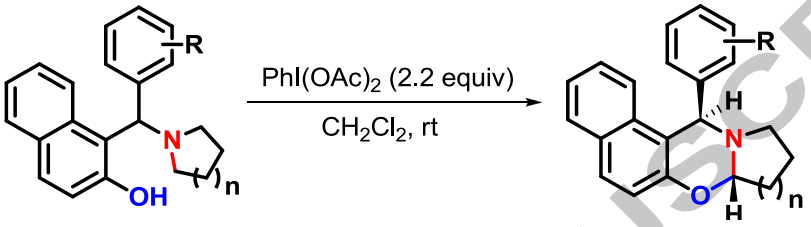

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Metal-free new synthesis of 1,3-naphthoxazines *via* intramolecular cross dehydrogenative-coupling reaction of 1-(α-aminoalkyl)-2-naphthols using hypervalent iodine(III) reagent

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:

Betti reaction,
hypervalent iodine reagents,
cross dehydrogenative-coupling (CDC),
1,3-naphthoxazines,
imminium ion

ABSTRACT

A series of 1-(α–aminoalkyl)-2-naphthols were synthesized *via* three-component Betti reaction of β-naphthol, aldehyde and cyclic secondary amine under reflux conditions. The subsequent reactions of 1-(α-aminoalkyl)-2-naphthols with (diacetoxyiodo)benzene resulted in the formation of 1,3-napthoxazines. This reaction demonstrates the formation of C-O bond formation via cross dehydrogenative-coupling (CDC) under transition metal-free conditions.

Cross-dehydrogenative coupling (CDC) involves the elimination of a hydrogen atom from each molecule leading to the formation of C-C and C-heteroatom bond. This synthetic strategy is emerging as a popular tool in modern organic chemistry due to the accomplishment of certain principles of Green Chemistry.[1] Some of the features associated with CDC are (a) high atom economical efficiency, (b) the reduction of number of steps of the organic synthesis, (c) avoids the preactivation of substrates in the form of functional groups such as such as -Hal, -OTf, -BR_2, -SnR_3, -SiR_3, -ZnHal, -MgHal, and (d) minimization of byproduct. CDC can be induced using Ru,[2] Fe,[3] Rh,[4] V,[5] and Cu[6] based transition metal oxidants. The toxicity of certain transition metals along with the cost, high loading of the catalyst and harsh reaction conditions demands the search for new oxidizing agents for executing CDC reactions. Among them, hypervalent iodine reagents are promising as an alternative to the transition metal oxidants.[7] The environmentally benign nature, mild reaction conditions and commercial availability makes them preferred oxidizing agents over transition metal oxidants in modern organic synthesis.[8]

Dihydro-1,3-oxazine heterocycles act as a privileged structural motif of various pharmacological active molecules displaying antibacterial,[9] fungicidal,[10] antitumor,[11] and antituberculosis,[12] (Figure 1). Some 1,3-naphthoxazine have found applications in synthesis of chiral 1-(α-aminoalkyl) naphthols.[13] Owing to the biological and synthetic importance of benzofused 1,3-oxazines, various methods have been developed for its synthesis involving: (i) Mannich three-component condensation of 2-naphthol, formaldehyde and secondary amine,[14] (ii) aza-acetalizations of aromatic aldehydes with 2-(*N*-substituted aminomethyl)phenols in presence of an acid as catalyst,[15] (iii) electrooxidative cyclization of hydroxyamino compounds,[16] (iv) visible light photooxidative cyclization of amino alcohols,[17] and (v) cross-dehydrogenative coupling (CDC) using transition metal oxidant.[18-20]

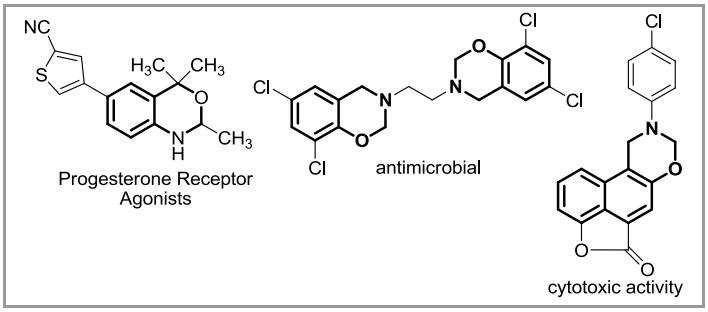
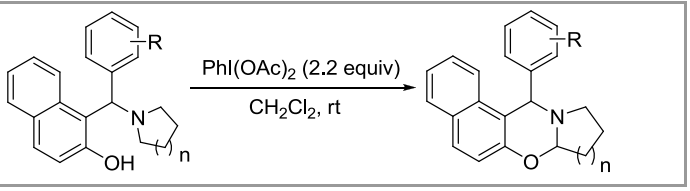


Figure 1 Biologically active molecules with 1,3-oxazines as sub-structural heterocyclic unit

Three component condensation of 2-naphthol, aldehydes, and cyclic amines under refluxing conditions form 1-(α-aminoalkyl)-2-naphthols via a century old Betti reaction.[21] Owing to the simplicity in the synthesis of 1-(α-aminoalkyl)-2-naphthols by Betti reaction, its applications in the synthesis of 1,3-naphthoxazines via oxidative cross-dehydrogenative coupling has received considerable attention. A copper-mediated

intramolecular α-functionalization of tertiary amines through C–H bond oxidative activation (benzylic and non-benzylic) is employed to synthesize diverse dihydro-1,3-oxazines through C–O bond formation. The method is very simple and uses inexpensive $Cu(OAc)_2 \cdot H_2O$ as the catalyst.[18a] The similar kind of transformation for the synthesis of 1,3-naphthoxazine has been recently reported using stoichiometric Ag_2O[19] as well as CuI[20] as the catalysts and *L*-proline as the ligand. In spite of these advances, there is a need to develop *transition metal-free oxidative* conditions for the synthesis of 1,3-naphthoxazines from the 1-(α-aminoalkyl)-2-naphthols. 1-(α-Aminoalkyl)-2-naphthols, a Betti base is a typical phenolic substrate with the speculation of oxidation with hypervalent iodine reagents. Therefore, its reaction study with hypervalent iodine reagents is worth to investigate. Herein, we report a facile synthesis of 1,3-naththoxazines from 1-(α-aminoalkyl)-2-naphthols using (diacetoxyiodo)benzene as the oxidant under exceptionally mild conditions.



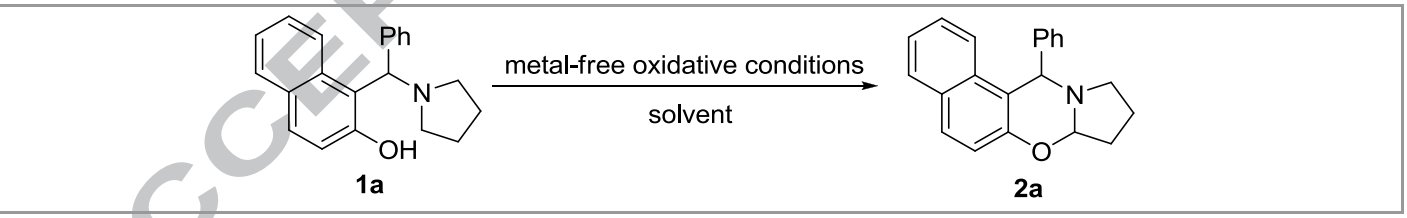
Scheme 1 (Diacetoxyiodo)benzene mediated 1,3-naphthoxazines synthesis

We examined the conversion of **1a** into **2a** as a model for optimization of the reaction conditions. Different solvents and hypervalent iodine reagents as oxidizing agents were screened (Table 1). The trivalent iodine reagent, (diacetoxyiodo)benzene (DIB) was found to induce the CDC for the formation of **2a** (entry 1). Increasing the quantity of DIB up to 2.2 equivalents (entries 2-3) improved yield of the product **2a**.[22] The other solvents such as CH_3CN and THF (entries 4-5) failed to produce any isolable yield of **2a**. The other trivalent iodine reagents such as $PhICl_2$ and $PhI(OCOCF_3)_2$ were unsuccessful for the formation of **2a** (entries 6-8). Encouraged by the result of DIB reaction with **1a**, we attempted the CDC coupling for C-O bond formation using the *in situ* generated hypervalent iodine(III) reagents from the reactions of catalytic iodoarene with terminal oxidants such as MCPBA or oxone (entries 9-10). However in both the cases, we couldn't get corresponding **2a**.

With the optimized conditions, we continued to study the substrate scope by using a variety of substituted 1-(α-aminoalkyl)-2-naphthols **1**, as summarized in Table 2.[23] The resultant 1,3-naphthoxazines **2** which contain a broad range of substituents could be obtained in moderate to excellent yields. The pyrolidine derivatives of Betti bases provided better yield of 1,3-naphthoxazines compared to those of piperidine and morphiline. The effect of substituents on the phenyl ring (Ar) was also examined and found that there was no such large reactivity difference between substrates bearing electron-donating and electron-withdrawing groups. The reaction was found to be completely diastereoselective as only one diastereomer was formed according to the ^{1}H NMR spectra of all the products **2** (Supplementary material).

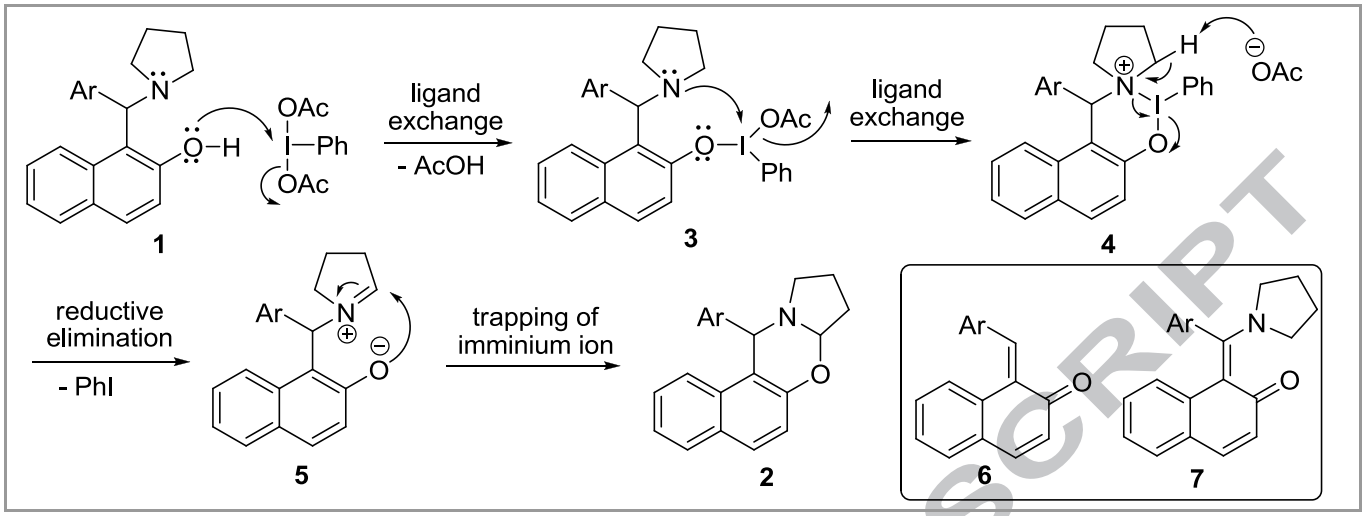
The tentative mechanism for CDC induced by DIB is shown in Scheme 2. The trivalent iodine reagents are well documented for the oxidative aromatization of phenol to form quinone-type product.[23] The *o*-quinone methide **6** or **7** as intermediate has been previously proposed in the reaction of 1-(α-aminoalkyl)-2-naphthols with $Cu(OAc)_2$,[18a] Ag_2O[19] and CuI[20] to form 1,3-naphthoxazines. However, the reaction of DIB with phenolic substrate **1** can inhibit the oxidative dearomatization due to the formation of putative six membered iodine(III) heterocycle **4**.[24] The propensity of **4** for reductive elimination of iodobenzene will generate the requisite imminium ion **5** which will be intramolecularly trapped by phenoxide anion to form *trans*-1,3-naphthoxazine **2**.

Table 1 Optimization of reaction conditions



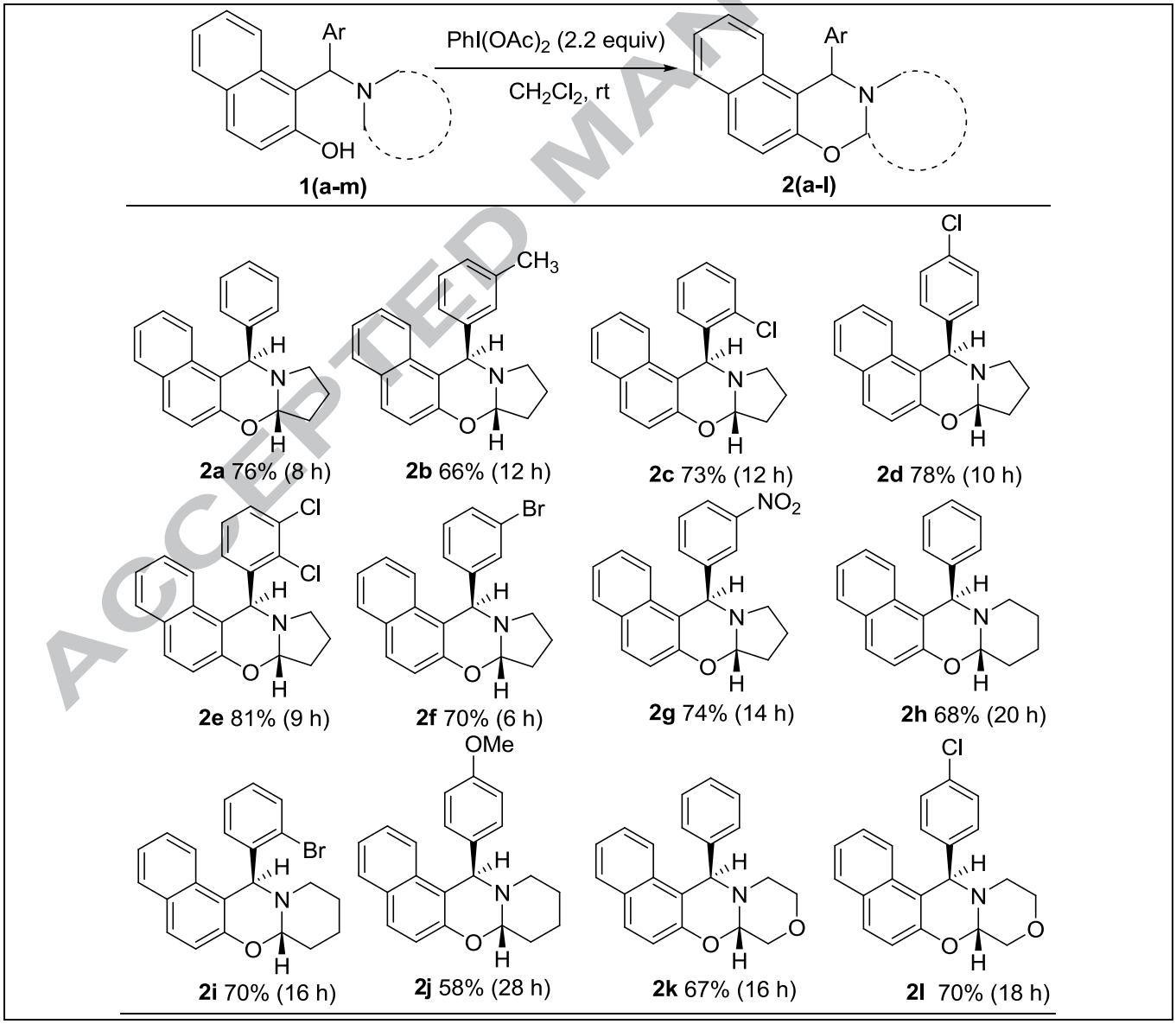
Entry	Oxidizing agent (equiv)	Solvent	Reaction time (h)	Yield of **2a** (%)[a]
1	$PhI(OAc)_2$ (1.1 equiv)	CH_2Cl_2	24	39
2	$PhI(OAc)_2$ (1.5 equiv)	CH_2Cl_2	24	62
3	$PhI(OAc)_2$ (2.2 equiv)	CH_2Cl_2	8	77
4	$PhI(OAc)_2$ (2.0 equiv)	CH_3CN	24	00
5	$PhI(OAc)_2$ (2.0 equiv)	THF	24	00
6	$PhICl_2$ (1.5 equiv)	CH_2Cl_2	24	00
7	$PhICl_2$ (2.0 equiv), pyridine (1.5 equiv)	CH_2Cl_2	24	00
8	$PhI(OCOCF_3)_2$ (2.0 equiv)	CH_2Cl_2	24	00
9	PhI (0.5 equiv), MCPBA (3 equiv), reflux	AcOH, CH_2Cl_2	24	00
10	PhI (0.5 equiv), oxone (1.5 equiv), reflux	AcOH, CH_2Cl_2	24	00

[a]Isolated yields



Scheme 2 Mechanism for dehydrogenative C-O bond formation using (diacetoxyiodo)benzene

Table 2 Synthesis of 1,3-naphthoxazines from 1-(α-aminoalkyl)-2-naphthols using (diacetoxyiodo)benzene[a]



Reaction conditions: 1-(α-aminoalkyl)-2-naphthols (1 equiv), DIB (2.2 equiv), and CH_2Cl_2 (5 mL) at room temperature stirring

In conclusion, we have developed an efficient intramolecular CDC reaction of 1-(α-aminoalkyl)-2-naphthols using (diacetoxyiodo)benzene as the oxidant to form 1,3-naphthoxazine in moderate to good yield. This synthesis of 1,3-naphthoxazine involves transition metal-free cross-dehydrogenative C-O bond formation at sp^3 C-H bond adjacent to tertiary nitrogen. The product formation took place under exceptionally mild reaction conditions compared to literature methods employing transition metal oxidants.

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000084.

Acknowledgment

The authors are thankful to the Department of Science and Technology, New Delhi, India (No. SR/S1/OC-72/2009) for the financial support. The authors are also grateful to SAIF, Punjab University, Chandigarh, India, for recording the NMR spectra.

References

(1) Reviews on CDC: (a) Mehta, V. P.; Punji, B. *RSC Adv.* **2013**, *3*, 11957; (b) Samanta, R.; Matcha, K.; Antonchick, A. P. *Eur. J. Org. Chem.* **2013**, 5769; (c) Krylov, I. B.; Vil, V. A.; Terent'ev *Beilstein J. Org. Chem.* **2015**, *11*, 92.

(2) (a) Murahashi, S. I.; Zhang, D. *Chem. Soc. Rev.* **2008**, *37*, 1490; (b) Condie, A. G.; Gonz_alez-Go_mez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464; (c) Rueping, M.; Vila, C.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C. *Chem. Commun.* **2011**, *47*, 2360; (d) Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. *Org. Lett.* **2012**, *14*, 94.

(3) (a) Han, W.; Ofial, A. R. *Chem. Commun.* **2009**, 5024; (b) Han, W.; Mayer, P.; Ofial, A. R. *Adv. Synth. Catal.* **2010**, *352*, 1667; (c) Ghobrial, M.; Harhammer, K.; Mihovilovic, M. D.; Schnurch, M. *Chem. Commun.* **2010**, *46*, 8836; (d) Richter, H.; Mancheno, O. G. *Eur. J. Org. Chem.* **2010**, 4460; (e) Liu, P.; Zhou, C.-Y.; Xiang, S.; Che, C. M. *Chem. Commun.* **2010**, *46*, 2739; (f) Volla, C. M. R.; Vogel, P. *Org. Lett.* **2009**, *11*, 1701.

(4) Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648.

(5) (a) Singhal, S.; Jain, S. L.; Sain, B. *Chem. Commun.* **2009**, 2371; (b) Sud, A.; Sureshkumar, D.; Klussmann, M. *Chem. Commun.* **2009**, 3169.

(6) Modak, A.; Dutta, U.; Kancherla, R.; Maity, S.; Bhadra, M.; Mobin, S. M.; Maiti, D. *Org. Lett.* **2014** *16*, 2602.

(7) Reviews on CDC using hypervalent iodine reagents: (a) Samanta, R.; Matcha, K.; Antonchick, A. P. *Eur. J. Org. Chem.* **2013**, 5769; (b) Narayan R.; Manna S.; Antonchick A. P. ***Synlett*** 2015, *26*, 1785; (c) Narayan R.; Matcha, K.; Antonchick A. P. *Chem. Eur. J.* **2015**, *21*, 14678.

(8) For selected reviews, see: (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123; (b) Grushin, V. V. *Chem. Soc. Rev.* **2000**, *29*, 315. (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523; (d) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299.

(9) (a) Gomez, P. G.; Pabon, H. P.; Carvajal, M. A.; Rincon, J. M. *Rev. Colomb. Cienc. Quim.-Farm.* **1985**, *8*, 15; (b) Waisser, K.; Gregor, K.; Kubicova, L.; Klimesova, V.; Kunes, J.; Machacek, M.; Kaustova, J. *Eur. J. Med. Chem.* **2000**, *35*, 733.

(10) (a) Bouaziz, Z.; Riondel, J.; Mey, A.; Berlion, M.; Villard, J.; Filliond, H. *Eur. J. Med. Chem.* **1991**, *26*, 469; (b) Arthington-Skaggs, B. A.; Motley, M.; Warnock, D. W.; Morrison, C. J. *J. Clin. Microbiol.* **2000**, *38*, 2254.

(11) (a) Chylinska, J. B.; Urbanski, T.; Mordarski, M. *J. Med. Chem.* **1963**, *6*, 484; (b) Benameur, L.; Bouaziz, Z.; Nebois, P.; Bartoli, M. H.; Boitard, M.; Fillion, H. *Chem. Pharm. Bull.* **1996**, *44*, 605.

(12) (a) Mathew, B. P.; Kumar, A.; Sharma, S.; Shula, P. K ; Nath, M. *Eur. J. Med. Chem*. **2010**, *45*, 1502; (b) Petrl_kov, E.; Waisser, K.; DiviSova, H.; Husakov, P.; Vrabcova, P.; Kunes, J. ; Kolr, K.; Stolarikov, J. *Bioorg. Med. Chem.* **2010**, *18*, 8178.

(13) (a) Cimarelli, C.; Palmieri, G.; Volpini, E. *Tetrahedron* **2001**, *57*, 6089; (c) Wang, X.; Dong, Y.; Sun, J.; Xu, X.; Li, R.; Hu, Y. *J. Org. Chem.* **2005**, *70*, 1897; (d) Yamazaki, N.; Ito T.;, Kibayashi, C. *Org. Lett.* **2000**, *2*, 465; (e) Cheng, G.; Wang, X. ; Su, D.; Liu, H.; Liu, F.; Hu, *J. Org. Chem.* **2010**, *75*, 1911; (g) Jurberg, I. D.; Peng, B.; Wçstefeld, E.; Wasserloos, M.; Maulide, N. *Angew. Chem.* **2012**, *124*, 1986 *Angew. Chem. Int. Ed*. **2012**, *51*, 1950.

(14) (a) Burke, W. J. *J. Am. Chem. Soc*. **1949**, *71*, 609; (b) Burke, W. J.; Kolbezen, M. J.; Stephens, C. W.; *J. Am. Chem. Soc*. **1952**, *74*,3601; (c) Burke, W. J.; Murdock, K. C.; Ec, G. *J. Am. Chem. Soc* .**1954**, *76*, 1677; (d) Burke, W. J.; Reynolds, R. J. *J. Am. Chem. Soc.* **1954**, *76*, 1291; (e) Burke, W. J.; Hammer, C. R.; Weatherbee, C. *J. Org. Chem.* **1961**, *26*, 4403; (f) Fields, D. L.; Miller, J. B.; Reynolds, D. D. *J. Org. Chem.* **1962**, *27*, 2749; (g) Katritzky, A. R.; Xu, Y.-J.; Jain, R. *J. Org. Chem.* **2002**, *67*, 8234; (h) Burke, W. J.; Stephens, C. W.; J. *Am. Chem. Soc.* **1952**, *74*, 1518.

(15) (a) Tang, Z. ; Zhu, Z.; Xia, Z. ; Liu, H. Chen, J. ; Xia, W.; Ou, X. *Molecules* **2012**, *17*, 8174; (b) Lu, J.; Xu, X.; Wang, S.; Wang, C.; Hu, Y.; Hu, H. *J. Chem.Soc. Perkin Trans. 1* **2002**, 2900; (c) Dong, Y.; Sun, J.; Wang, X.; Xu, X.; Cao, L.; Hu, Y. *Tetrahedron: Asymmetry* **2004**, *15*, 1667; (d) Zhang, P. ; Terefenko, E. A.; Fensome, A.; Zhang, Z.; Zhu, Y.; Cohen, J.; Winneker, R.; Wrobel, J.; Yardley, J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 787.

(16) Okimoto, M.; Ohashi, K.; Yamamori, H.; Nishikawa, S.; Hoshi, M. ; Yoshida, T. *Synthesis* **2012**, *44*, 1315.

(17) Mathis, C. L.; Gist, B. M. ; Frederickson, C. K. ; Midkiff, K. M. ; Marvin, C. C. *Tetrahedron Lett.* **2013**, *54*, 2101.

(18) (a) Deb, M. L.; Dey, S. S.; Bento, I.; Barros, M. T.; Maycock, C. D. *Angew. Chem. Int. Ed*. **2013**, *52*, 9791; (b) Chen, C.-K. ; Hortmann, A. G.; Marzabadi, M. R. *J. Am. Chem. Soc.* **1988**, *110*, 4829; (c) Kienzle, F. *Tetrahedron Lett*. **1983**, *24*, 2213

(19) Mahato, S.; Haldar, S.; Jana, C. K. *Chem. Commun.* **2014**, *50*, 332.

(20) Shahrisa, A.; Mofrad, R. T.; Nazari, M. G. *Synlett* **2015**, *8*, 1031.

(21) (a) Betti, M. *Org. Synth. Collect*. **1941**, *1*, 381; (b) Betti, M. *Gazz. Chim. Ital*. **1900**, *30*, 301; (c) Lu, J.; Xu, X.; Wang, C.; He, J.; Hu, Y.; Hu, H. *Tetrahedron Lett.* **2002**, *43*, 8367; (d) Wang, X.; Dong, Y.; Sun, J.; Xu, X.; Li, R.; Hu, Y. *J. Org. Chem.* **2005**, 70, 1897.

(22) *General procedure for the synthesis of 1, 3- naphthoxazines (2a-2l):* To the solution of substrate 1-(α-aminoalkyl)-2-naphthols **1** (1 mmol) in dichloromethane (5 mL), diacetoxyiodobenzene (DIB) (2.2 mmol) was added. Reaction mixture was stirred for 6–24 h. The progress of reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, solvent mixture was evaporated. The crude product was further purified by column chromatography by using ethyl acetate and petroleum ether as eluent.

(23) (a) Traore, M.; Ahmed-Ali, S.; Peuchmaur, M.; Wong, Y. S. *Tetrahedron* **2010**, *66*, 5863; (b) Dohi, T.; Uchiyama, T.; Yamashita, D.; Washimi, N.; Kita, Y. *Tetrahedron Lett.* **2011**, *52*, 2212.

(24) (a) Shelke, A. V.; Bhong, B. Y.; Karade, N. N. *Synthesis* **2014**, *46*, 752; (b) Prakash, O.; Saini, R. K.; Singh, S. P.; Varma, R. S. *Tetrahedron Lett.* **1997**, *38*, 3147.