Tetrahedron Letters 55 (2014) 5462–5464

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Acid ionic liquid promoted addition of C(sp^3)–H bond to aldehyde

Xue-Yan Zhang [a], Dao-Qing Dong [a], Tao Yue [b], Shuang-Hong Hao [a], Zu-Li Wang [a,*]

[a] College of Chemistry and Pharmaceutical Sciences, Qingdao Agricultural University, Qingdao 266109, PR China
[b] Chemical Technology Academy of Shandong Province, Jinan, Shandong 250014, PR China

ARTICLE INFO

Article history:
Received 20 May 2014
Revised 27 July 2014
Accepted 9 August 2014
Available online 14 August 2014

Keywords:
2-Methyl pyridine
C–H functionalization
Azaarenes
Acid ionic liquids
Aldehyde

ABSTRACT

A novel protocol for acid ionic liquid promoted C(sp^3)–H bond functionalization of alkyl azaarenes and nucleophilic addition to aldehydes was developed in good to excellent yields, which provides an efficient approach for the synthesis of alkyl-substituted azaarene derivatives. It is worthwhile to note that acid ionic liquid used for this reaction can be recycled and reused six times without a significant decrease in activity.

Introduction

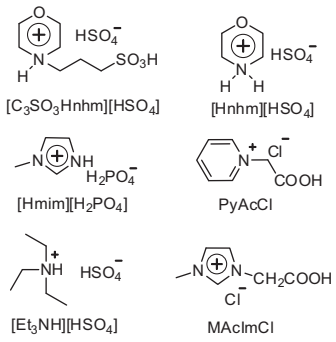
Since alkyl-substituted azaarenes such as pyridine and quinoline derivatives are known to exhibit extremely potent biological, chemical, and pharmaceutical activities,[1] tremendous efforts have been paid to access these compounds.[2] One of the most efficient methods for obtaining pyridine and quinoline derivatives is the direct C(sp^3)–H functionalization of alkyl-substituted azaarene. The direct addition of C(sp^3)–H bond of alkyl-substituted azaarenes to unsaturated chemical bonds was first independently realized in 2010 by Huang and co-workers.[3f] Then lots of efforts were made on this area. At present, examples catalyzed by transition metal,[3] Bronsted acids,[4] and microwave[5] have been reported. Even in some cases, these reactions could also be realized without any catalyst.[5d,3j] Although these methods could meet the demand of C(sp^3)–H bond activation, the discovery of a new, less expensive, less toxic, and more environmental method is urgently needed.

As we all know, ionic liquids have very low vapor pressure and high dissolvabilities toward many organic and inorganic substances. In view of the stable physicochemical properties of ionic liquids, it can be used as a catalyst or solvent in many reactions and recycled many times without loss of activity.[6] In some cases, acid ionic liquids can show similar acidity with Bronsted acids. Acid ionic liquid catalyzed Pechmann reaction,[7] esterification reaction,[8] Mannich reaction,[9] and so on[10] have been disclosed. In this Letter we described that acid ionic liquids were also a good catalyst for C(sp^3)–H bond functionalization of alkyl-substituted azaarenes.

At the outset of our experiment, a series of acid ionic liquids such as $[C_3SO_3Hnhm][HSO_4]$,[11] [Hnhm][HSO_4],[11] [Hmim][H_2PO_4],[12] PyAcCl,[13] $[Et_3NH][HSO_4]$,[14] and MAcImCl[13] were synthesized according to the literature (Scheme 1). Then they were subjected to the model reaction of 2,6-lutidine and *p*-nitrobenzaldehyde in H_2O at 100 °C. As can be seen from Table 1, a moderate yield (61%) of the desired products was isolated when acid ionic liquids [Hmim][H_2PO_4] were used (Table 1, entry 3). Although $[C_3SO_3Hnhm][HSO_4]$, [Hnhm][HSO4], and $[Et_3NH][HSO_4]$ have the strong acidity, the lower yields were obtained when they were used (Table 1, entries 1–2, 5). On the other hand, PyAcCl and MAcImCl which show weak acidity also afforded low yields (Table 1, entries 4, 6). The reason that [Hmim][H_2PO_4] showed the highest efficiency maybe that [Hmim][H_2PO_4] have the most suitable acidity for this reaction. We further investigated other reaction conditions in the presence of acid ionic liquids [Hmim][H_2PO_4]. When the amount of [Hmim][H_2PO_4] was increased to two equivalent, there was still no significant increase in the yield (Table 1, entry 7). We thought that the lower yields of this reaction may somewhat be attributed to the low solubility of 2,6-lutidine and *p*-nitrobenzaldehyde in H_2O. To our delight, when 1,4-dioxane was added as a co-solvent, high yield of 90% was observed (Table 1, entry 8). If we increase the reaction temperature from 100 °C to 110 °C, the yield of the reaction still did not increase (Table 1, entry 9). However, the yield slightly decreased if the reaction temperature was changed to 90 °C (Table 1, entry 10). Finally, we tried to extend the reaction time to 36 h (Table 1, entry 11) and 48 h

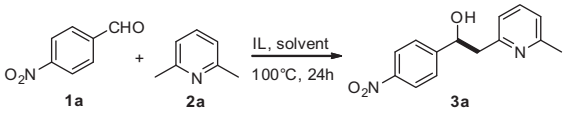
* Corresponding author.
E-mail address: wangzulichem@163.com (Z.-L. Wang).

http://dx.doi.org/10.1016/j.tetlet.2014.08.034
0040-4039/



Scheme 1. Structure of acid ionic liquids.

Table 1
Optimization of the reaction conditions[a]



1a 2a 3a

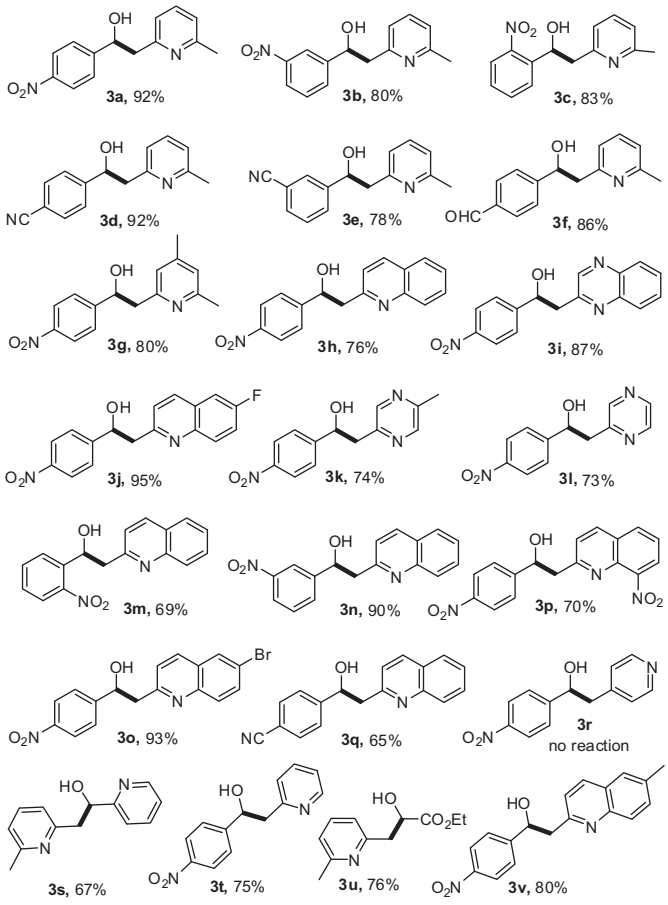
Entry	Acid ionic liquids (IL)	Solvent	T (°C)	Yield **3a** (%)
1	$[C_3SO_3Hnhm][HSO_4]$ (1.0 equiv)	H_2O	100	13
2	$[Hnhm][HSO_4]$ (1.0 equiv)	H_2O	100	25
3	$[Hmim][H_2PO_4]$ (1.0 equiv)	H_2O	100	61
4	PyAcCl (1.0 equiv)	H_2O	100	32
5	$[Et_3NH][HSO_4]$ (1.0 equiv)	H_2O	100	41
6	MAcImCl (1.0 equiv)	H_2O	100	36
7	$[Hmim][H_2PO_4]$ (2.0 equiv)	H_2O	100	62
8	$[Hmim][H_2PO_4]$ (1.0 equiv)	H_2O/dioxane	100	92
9	$[Hmim][H_2PO_4]$ (1.0 equiv)	H_2O/dioxane	110	91
10	$[Hmim][H_2PO_4]$ (1.0 equiv)	H_2O/dioxane	90	85
11	$[Hmim][H_2PO_4]$ (1.0 equiv)	H_2O/dioxane	100	89[b]
12	$[Hmim][H_2PO_4]$ (1.0 equiv)	H_2O/dioxane	100	92[c]
13	$[Hmim][H_2PO_4]$ (0.5 equiv)	H_2O/dioxane	100	82

[a] Unless otherwise stated, all reactions were carried out with **1a** (0.25 mmol), **2a** (0.75 mmol), IL (1 equiv), H_2O/dioxane (0.5 ml/0.5 ml) reacted at 100 °C for 24 h.
[b] Reacted for 36 h.
[c] Reacted for 48 h.

(Table 1, entry 12) to get higher yields, but the yields of the reaction still remained almost unaffected. When the amount of the ionic liquids was reduced to 0.5 equiv, the yields of the product decreased to 82%. Thus the optimized reaction conditions for this reaction were acid ionic liquids $[Hmim][H_2PO_4]$ (1 equiv) in H_2O/dioxane at 100 °C for 24 h.

With the optimized reaction conditions in hand, we set out to explore the substrate scope of the reaction. As shown in Table 2, substituted benzaldehydes with the electron-withdrawing group attached to benzene rings, such as 4-nitrobenzaldehyde, 2-nitrobenzaldehyde, and 3-nitrobenzaldehyde could react with 2,6-lutidine smoothly to generate the corresponding products in good to excellent yields. Because of the smaller hindrance of 4-nitrobenzaldehyde compared with its analogues 3-nitrobenzaldehyde and 2-nitrobenzaldehyde, 4-nitrobenzaldehyde gave a higher yield than that of 2-nitrobenzaldehyde and 3-nitrobenzaldehyde (Table 2, **3a**–**3c**). Additionally, aldehyde with the moderate electron-withdrawing group such as the cyanl group could also react with 2,6-lutidine to produce the products in moderate to good yields (Table 2, **3d**–**3e**). When 1,4-phthalaldehyde was used, only one formyl group took part in this reaction and the other one remained

Table 2
Substrate scope of the 2-alkyl azaarenes and aldehyde[a]



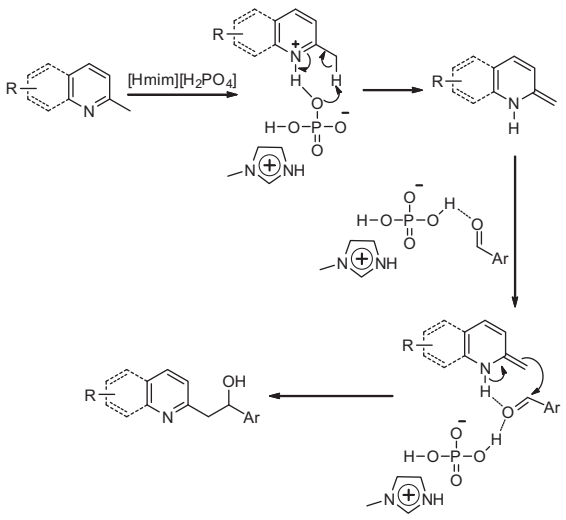
[a] Unless otherwise stated, all reactions were carried out with **1** (0.25 mmol), **2** (0.75 mmol), and [Hmim] H_2PO_4 (1 equiv) in H_2O (0.5 ml) and dioxane (0.5 ml) at 100 °C for 24 h. Isolated yields.

intact, which provides a useful handle for further chemical manipulations (Table 2, **3f**). Furthermore, heteroaromatic aldehyde (Table 2, **3s**) and activated aliphatic aldehyde (Table 2, **3u**) also reacted well with 2,6-lutidine and moderate yields were obtained. To further evaluate the scope of the methodology, the application of other azaarenes to this reaction was investigated. Substituted pyridines such as 2,4,6-trimethylpyridine reacted with *p*-nitrobenzaldehyde smoothly under the optimized reaction conditions (Table 2, **3g**). When 2-methylpyridine was subjected to this reaction, slightly lower yields were realized (Table 2, **3t**) than those of 2,4,6-trimethylpyridine and 2,6-lutidine. The reason may come from the less opportunities to react with 4-nitrobenzaldehyde. However, when 2,5-dimethyl pyrazine and 2-methylpyrazine were used, only moderate yields were obtained (Table 2, **3k**–**3l**). Besides 2-methylpyridine derivatives, 2-methylquinoline, 2,6-dimethylquinoline, and 2-methylquinoxaline derivatives can also react with aldehyde in moderate to high yields (Table 2, **3h**–**3i**, **3m**–**3p**, **3q**, **3v**). Substituents including nitro, halogen groups in phenyl rings of quinoline were well tolerated under reaction conditions (Table 2, **3j**, **3p**–**3o**), which also provide a useful handle for further chemical manipulations. 2-methyl-8-nitroquinoline afforded lower yield than those of 6-fluoroquinaldine and 6-bromoquinaldine and the reason may come from the hindrance of the nitro group. Generally, substituted 2-methylquinoline with the electron-withdrawing group attached to benzene rings afforded higher yields than the

Table 3
Recovery and reuse of recoverable acid ionic liquids[a]

Entry	Yield[b] (%)	Entry	Yield[b] (%)
1	90	4	91
2	92	5	88
3	89	6	88

[a] *p*-Nitrobenzaldehyde (0.25 mmol); 2,6-lutidine (0.75 mmol) and [Hmim][H_2PO_4] (1 equiv) in H_2O (0.5 ml) and dioxane (0.5 ml) at 100 °C for 24 h.
[b] Isolated yields.



Scheme 2. Proposed mechanism of addition of C(sp^3)–H bond to aldehyde.

substituted 2-methylquinoline with the electron-donating group attached to benzene rings (Table 2, **3j**, **3o**, **3v**). However, when 4-methylpyridine was subjected to this system, no desired products were obtained (Table 2, **3r**).

Finally, the recyclability of acid ionic liquids was investigated. After the reaction was over, dioxane was evaporated under vacuum and the residue was extracted with ether three times. After ether was evaporated from the residue under vacuum, the remaining water which contains acid ionic liquids was reused for the next trial. To our delight, the acid ionic liquids can be reused six times without a significant decrease in activity (Table3).

Since 4-methylpyridine was not successful in this reaction (Table 2, **3r**), we presume the mechanism of this reaction maybe as shown in Scheme 2. In the presence of [Hmim][H_2PO_4], 2-methyl azaarene tends to isomerization and the enamine intermediate is formed. Then the nucleophilic addition of the enamine intermediate to aromatic aldehyde which was activated by [Hmim][H_2PO_4] would occur to afford the desired adduct.

In summary, we have developed an efficient acid ionic liquid promoted addition of 2-alkyl azaarenes to aldehydes through C(sp^3)–H bond functionalization in good to excellent yields. The mild reaction conditions make this method attractive for the preparation of biologically active pyridine and quinoline derivatives. Further investigation to apply this method to more useful substrates and mechanistic study are ongoing in our laboratory.

Acknowledgments

Financial support from the research fund of Qingdao Agricultural University's high-level Person [631303], the National Natural Science Foundation of China (21402103), the Scientific Research Foundation of Shandong Province Outstanding Young Scientist Award [BS2013YY024] and the Qingdao Technology R&D Program for Basic Research, China [No. 12-1-4-5-(9)-jch] was gratefully acknowledged.

We thank Qing-Hui Guo for helping us to prepare the supporting information.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.08.034.

References and notes

1. (a) Bagley, M. C.; Glover, C.; Merritt, E. A. *Synlett* **2007**, 2459; (b) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043; (c) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627; (d) Baxter, P. N. W.; Lehn, J. M.; Fischerand, J.; Youinou, M. T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2284; (e) Lehn, J. M. *Science* **2002**, *295*, 2400; (f) Henry, D. *Tetrahedron* **2004**, *60*, 6043; (g) Bagley, M. C.; Gloverand, C.; Merritt, E. A. *Synlett* **2007**, 2459.
2. For reviews, see: (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127; (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644.
3. (a) Jin, J.-J.; Niu, H.-Y.; Qu, G.-R.; Guo, H. M.; Fossey, J. S. *RSC Adv.* **2012**, *2*, 5968; (b) Komai, H.; Yishino, T.; Matsunaga, S.; Kanai, M. *Org. Lett.* **2011**, *13*, 1706; (c) Qian, B.; Guo, S.; Xia, C.; Huang, H. *Adv. Synth. Catal.* **2010**, *352*, 3195; (d) Qian, B.; Xie, P.; Xie, Y.; Huang, H. *Org. Lett.* **2011**, *13*, 2580; (e) Graves, V. B.; Shaikh, A. *Tetrahedron Lett.* **2013**, *54*, 695; (f) Qian, B.; Guo, S.; Shao, J.; Zhu, Q.; Yang, L.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2010**, *132*, 3650; (g) Qian, B.; Shi, D. J.; Yang, L.; Huang, H. *Adv. Synth. Catal.* **2012**, *354*, 2146; (h) Qian, B.; Yang, L.; Huang, H. *Tetrahedron Lett.* **2013**, *54*, 711; (i) Liu, J. Y.; Niu, H. Y.; Wu, Shan; Qu, G. R.; Guo, H. M. *Chem. Commun.* **2012**, 9723; (j) Yan, Y.; Xu, K.; Fang, Y.; Wang, Z. *J. Org. Chem.* **2011**, *76*, 6849; (k) Rueping, M.; Tolstoluzhsky, N. *Org. Lett.* **2011**, *13*, 1095; (l) Kumar, A.; Gupta, P. L.; Kumar, M. *RSC Adv.* **2013**, *3*, 18771.
4. (a) Wang, F. F.; Luo, C.-P.; Wang, Y.; Deng, G.; Yang, L. *Org. Biomol. Chem.* **2012**, *10*, 8605; (b) Niu, R.; Xiao, J.; Liang, T.; Li, X. *Org. Lett.* **2012**, *14*, 676; (c) Vuppalapati, S. V. N.; Lee, Y. R. *Tetrahedron* **2012**, *68*, 8286; (d) Gao, X.; Zhang, F.; Deng, G.; Yang, L. *Org. Lett.* **2014**, *16*, 3664; (e) Mulla, S. A. R.; Pathan, M. Y.; Chavan, S. S. *RSC Adv.* **2013**, *3*, 20281; (f) Raghua, M.; Rajasekhar, M.; Reddy, B. C. O.; Reddy, C. S.; Reddy, B. V. S. *Tetrahedron Lett.* **2013**, *54*, 3503.
5. (a) Rao, N. N.; Meshram, H. M. *Tetrahedron Lett.* **2013**, *54*, 5087; (b) Rao, N. N.; Meshram, H. M. *Tetrahedron Lett.* **2013**, *54*, 1315; (c) Meshram, H. M.; Rao, N. N.; Rao, L. C.; Kumar, N. S. *Tetrahedron Lett.* **2012**, *53*, 3963; (d) Li, H. Y.; Xing, L. J.; Xu, T.; Wang, P.; Liu, R. H.; Wang, B. *Tetrahedron Lett.* **2013**, *54*, 858.
6. For reviews, see: (a) Gu, Y. L.; Peng, J. J.; Qiao, K.; Yang, H. Z.; Shi, F.; Deng, Y. Q. *Prog. Chem.* **2003**, *3*, 222; (b) Hallett, J. P.; Welton, T. *Chem. Rev.* **2011**, *111*, 3508; (c) Pârvulescu, V. I.; Hardacre, C. *Chem. Rev.* **2007**, *107*, 2615; (d) Welton, T. *Chem. Rev.* **1999**, *99*, 2071; (e) Afonso, C. A. M.; Branco, L. C.; Candeias, N. R.; Gois, P. M. P.; Lourenço, N. M. T.; Mateus, N. M. M.; Rosa, J. N. *Chem. Commun.* **2007**, 2669; (f) Binnemans, K. *Chem. Rev.* **2007**, *107*, 2592; (g) Imperato, G.; König, B.; Chiappe, C. *Eur. J. Org. Chem.* **2007**, 1049; (h) Song, C. E.; Yoon, M. Y.; Choi, D. S. *Bull. Korean Chem. Soc.* **2005**, *26*, 1321; (i) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667; (j) Sheldon, R. *Chem. Commun.* **2001**, 2399; (k) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772.
7. Gu, Y. L.; Zhang, J.; Duan, Z. Y.; Deng, Y. Q. *Adv. Synth. Catal.* **2005**, *347*, 512.
8. Gu, Y.; Shi, F.; Deng, Y. *J. Mol. Catal. A: Chem.* **2004**, *212*, 71.
9. Sahoo, S.; Joseph, T.; Halligudi, S. B. *J. Mol. Catal. A: Chem.* **2006**, *244*, 179.
10. (a) Li, D.-M.; Shi, F.; Peng, J.-J.; Guo, S.; Deng, Y.-Q. *J. Org. Chem.* **2004**, *69*, 3582; (b) Gui, J.-Z.; Deng, Y.-Q.; Hua, Z.-D.; Sun, Z.-L. *Tetrahedron Lett.* **2004**, *45*, 2681; (c) Li, D.-M.; Shi, F.; Guo, S.; Deng, Y.-Q. *Tetrahedron Lett.* **2004**, *45*, 265; (d) Qiao, K.; Yokoyama, C. *Chem. Lett.* **2004**, *33*, 472; (e) Gu, D.-G.; Ji, S.-J.; Jiang, Z.-Q.; Zhou, M.-F.; Loh, T.-P. *Synlett* **2005**, 959; (f) Wang, Z.-L.; Wang, L.; Yan, J.-C. *Synthesis* **2009**, 3744; (g) Kumar, S.; Dixit, S. K.; Awasthi, S. K. *Tetrahedron Lett.* **2014**, *55*, 3208; (h) Smiglak, M.; Kukawka, R.; Lewandowski, P.; Pospieszny, H. *Tetrahedron Lett.* **2014**, *55*, 3565; (i) Chen, Z. K.; Fu, R. Z.; Chai, W.; Zheng, H.; Sun, L.; Lu, Q.; Yuan, R. X. *Tetrahedron* **2014**, *70*, 2237; (j) Chen, Z. W.; Zhu, Q.; Su, W. K. *Tetrahedron Lett.* **2011**, *52*, 2601; (k) Funabiki, K.; Komeda, T.; Kubota, Y.; Matsui, M. *Tetrahedron* **2009**, *65*, 7457; (l) Akbari, J.; Heydari, A. *Tetrahedron Lett.* **2009**, *50*, 4236; (m) Kuroiwa, Y.; Sekine, M.; Tomono, S.; Takahashi, D.; Toshima, K. *Tetrahedron Lett.* **2010**, *51*, 6294; (n) Yamada, C.; Sasaki, K.; Matsumura, S.; Toshima, K. *Tetrahedron Lett.* **2007**, *48*, 4223; (o) Sasaki, K.; Nagai, H.; Matsumura, S.; Toshima, K. *Tetrahedron Lett.* **2003**, *45*, 5605.
11. Huang, B. H.; Li, Z. J.; Shi, N.; Xu, X. L.; Zhang, K.; Fang, Y. X. *Chin. J. Org. Chem.* **2009**, *29*, 770.
12. Huang, B. H.; Li, Z. J.; Wang, Y. F.; Zhang, K.; Fang, Y. X. *Acta Chim. Sinica* **2008**, *66*, 1837.
13. Li, D. M.; Shi, F.; Guo, S.; Deng, Y. Q. *Tetrahedron Lett.* **2004**, *5*, 265.
14. Tao, D.-J.; Wu, J.; Wang, Z.-Z.; Lu, Z.-H.; Yang, Z.; Chen, X.-S. *RSC Adv.* **2014**, *4*, 1.