Tetrahedron Letters 51 (2010) 54–56

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Facile ring-closure cyclization of arenes by nucleophilic C-alkylation reaction in ionic liquid

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ARTICLE INFO

Article history:
Received 19 August 2009
Revised 14 October 2009
Accepted 15 October 2009
Available online 20 October 2009

ABSTRACT

A novel synthetic method using an ionic liquid (IL) for a six-membered ring-closure cyclization is described. The ring-closure cyclization by nucleophilic C-alkylation was achieved with various halo- and alkanesulfonyloxyalkyl aromatic compounds in high yields with minimal byproducts using ILs as the reaction media in the absence of any catalyst. For example, the cyclization of 2-(3-methanesulfonyloxy-propoxy)naphthalene (**1a**) to 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran (**2**) in IL [bmim][PF_6] proceeded selectively at 150 °C for 24 h in 85% yield.

Compounds bearing the chromane moiety are widespread in nature and have received much interest given their physiological properties.[1] As shown in Figure 1, ring-closure cyclizations by C-alkylation of phenyl ethers (Path A)[2] or O-alkylation of alkyl phenols (Path B)[3] are the typical synthetic strategies for the preparation of chromanes.[4] Although O-alkylation is much more adept than C-alkylation, this strategy is less attractive given the difficulty in preparation of the alkyl phenol substrates.[3] Thus, much attention has been focused on facile ring-closure cyclization via C–C bond formation of phenyl ethers to chromanes on account of the ease of preparation of the phenyl ether substrates.[2] Ring-closure cyclization by Friedel–Crafts approach is the most common method for these purposes. However, these reactions generally require vigorous reaction conditions in the presence of a strong Lewis acid catalyst.[2,5]

Over the past decade, room temperature ILs have been extensively investigated as eco-friendly alternative reaction media to replace volatile organic solvents in various chemical processes on account of their intrinsic physical and chemical properties.[6] In particular, it has been reported that ILs containing imidazolium cations and their counteranions (Fig. 2) can act as powerful reaction media in nucleophilic substitution-type reactions for acceleration of the reaction rate, as well as for improvement of selectivity. Such examples of nucleophilic substitutions include: Friedel–Crafts reaction;[7] fluorination with alkali metal salts;[8] hydroxylation using water;[9] dealkylation of ethers to phenols;[10] and C-alkylation of pyrrole.[11] Herein the successful use of ILs such as [bmim][X][12] as a solvent for the significant rate enhancement of ring-closure cyclizations of halo- or alkanesulfonyloxyalkyl benzenes into cyclic compounds via an intra C–C bond formation in the absence of any kind of Lewis acid or other catalyst is reported.

As shown in Scheme 1, the intracyclization of 2-(3-bromopropoxy)naphthalene (**1d**) in the IL [bmim][BF_4] at 150 °C proceeded in the absence of any kind of catalyst, affording 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran (**2**) in 54% yield. However, a naphthol byproduct **3** was formed in 29% yield because of the generation of HBr from cleavage of the ether to phenol, due to dealkylation in the IL[9] during the cyclization reaction process. The HBr acts as an effective nucleophile and acid catalyst. To remove this in situ generated HBr and maintain neutral or basic reaction conditions, $NaHCO_3$ was used as a scavenger to provide chromane product **2** in a yield (52%) similar to the reaction in the absence of $NaHCO_3$, along with 27% of alcohol byproduct **4** on account of hydroxylation by the water generated from the reaction process. These results show that the IL

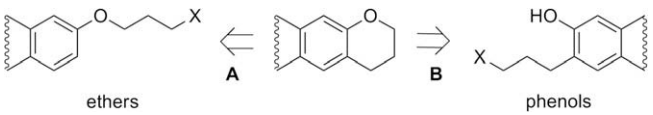
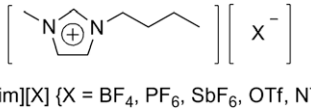


Figure 1. Two different synthetic paths to benzopyrans.



[bmim][X] {X = BF_4, PF_6, SbF_6, OTf, NTf_2}

Figure 2. Structure of ILs.

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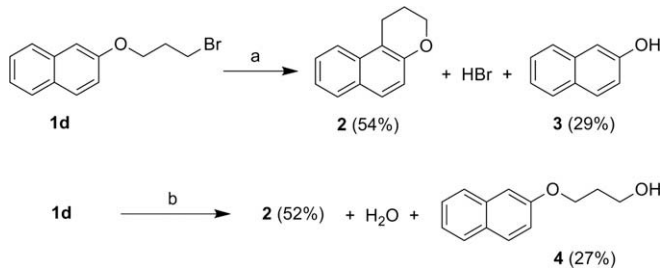
doi:10.1016/j.tetlet.2009.10.065

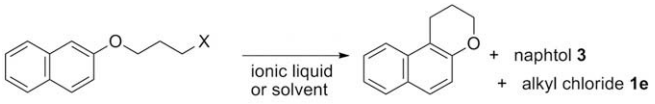


Scheme 1. Intramolecular cycloalkylation via C–C bond formation using IL [bmim][BF_4] as a solvent. Reagents and conditions: (a) [bmim][BF_4], 150 °C, 12 h; (b) [bmim][BF_4], $NaHCO_3$ as a HBr scavenger, 150 °C, 24 h.

media system could allow intracyclization by nucleophilic C-alkylation to proceed in the absence of any kind of catalyst.

Table 1 concerns the cyclization reactions of various halo- and alkanesulfonyloxypropoxynaphthalenes to chromane product **2** under various reaction conditions. As entries 1–5 demonstrate, in order to determine the optimal IL, cyclization of model compound 2-(3-methanesulfonyloxypropoxy)naphthalene (**1a**), of which mesylate is a good leaving group but not become a nucleophile caused the dealkylation as a side reaction, was carried out in various imidazolium-based ILs, such as [bmim][X] (X = BF_4, OTf, PF_6, SbF_6, and NTf_2). Among the various ILs, [bmim][PF_6] showed the best performance (entry 3). In particular, a comparison of entries 3 and 6 showed that [bmim][PF_6] enhanced the reaction rate significantly compared with organic solvents. Where the cyclization of mesylate **1a** in organic solvents such as DMF at 150 °C (in a pressure vial) hardly occurred, even after 48 h (entry 6), the same reaction in [bmim][PF_6] was complete within 24 h, affording cyclic-product **2** in 85% yield (entry 3). Entry 7 shows that a Friedel–Crafts-type alkylation using $ZnCl_2$ as a Lewis acid catalyst for the cyclization, which afforded the desired product **2** in only 27% yield together with chlorocompound **1e** as a byproduct, was inefficient compared to the nucleophilic C-alkylation using the IL. The desired cyclic-product **2** was also produced in good yield by the cyclization of tosylate **1b** with [bmim][PF_6] (entry 8). Next, the cyclization of fluoro-, chloro-, bromo-, and iodo-substrate in the optimal IL [bmim][PF_6] was carried out. Interestingly, nucleophilic cyclization of iodo- and bromo-substrates (**1c** and **1d**) using [bmim][PF_6] proceeded selectively to afford cyclic-product **2** in high yield (79% and 75%, entries 9 and 10, respectively), almost without any ether cleavage side reaction to naphthol **3**; compare this with the same reaction using [bmim][BF_4] in Scheme 1. However, chloro- and fluoro-substrates (**1e** and **1f**) were hardly converted to the desired cyclic-product under the same reaction conditions, even after 48 h (entries 11 and 12). The halide reaction order is the obvious one expected; the reaction rates follow the order: I > Br ≫ Cl > F.

Table 1
Cyclization under various reaction conditions[a]

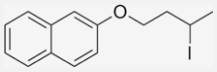
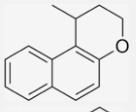
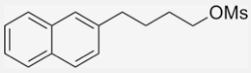
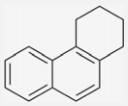
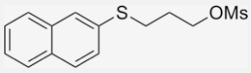
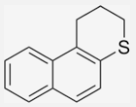
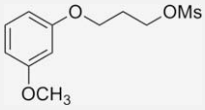
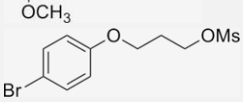
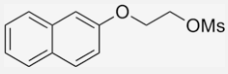


1a: X = OMs, **1b**: X = OTs, **1c**: X = I, **1d**: X = Br, **1e**: X = Cl, **1f**: X = F

Entry	IL or solvent	X	Time (h)	Yield of product[b] (%)		
				1	**2**	**3**
1	[bmim][BF_4]	OMs	48	Trace	75	—
2	[bmim][OTf]	OMs	24	Trace	71	—
3	[bmim][PF_6]	OMs	24	Trace	85	—
4	[bmim][SbF_6]	OMs	36	—	59	—
5	[bmim][NTf_2]	OMs	36	Trace	75	—
6	DMF	OMs	48	90	—	—
7[c]	1,4-Dioxane/$ZnCl_2$	OMs	24	Trace	27	56[d]
8	[bmim][PF_6]	OTs	24	—	71	—
9	[bmim][PF_6]	I	20	—	79	Trace
10	[bmim][PF_6]	Br	48	—	75	Trace
11	[bmim][PF_6]	Cl	48	99	Trace	—
12	[bmim][PF_6]	F	48	100	—	—

[a] All reactions were carried out on a 1.0 mmol reaction scale of starting material using 3.0 mL of IL at 150 °C.
[b] Isolated yield.
[c] 3.0 equiv of $ZnCl_2$ as a Lewis acid was used in 1,4-dioxane (4.5 mL) at reflux condition.
[d] 2-(3-Chloropropoxy)naphthalene (**1e**) was formed in 56% yield as a byproduct.

Table 2
Cyclization of Various Substrates in [bmim][PF_6][a]

Entry	Compound	Time (h)	Yield[b] (%)	Product
1		18	70	
2		7 days	71	
3		48	9	
4		48	65	7-Methoxychromane (50%) 5-Methoxychromane (15%)
5		48	—	No reaction
6		48	—	No reaction

[a] Unless otherwise noted, all reactions were carried out under the same condition as entry 3 in Table 1.
[b] Isolated yield.

Table 2 illustrates further characteristics of this ring-closure cyclization reaction with various substrates in [bmim][PF_6], in the absence of any kind of catalyst and under the reaction conditions described previously (Table 1, entry 3). The cyclization of a secondary iodoalkane (entry 1) proceeded smoothly within 18 h, affording the corresponding chromane in 70% yield, with 1,2,3,4-tetrahydrophenanthrene produced in high yield by cyclization of 2-(4-mesyloxybutyl)naphthalene (entry 2). However, thiochromane was obtained in poor yield (9%) with the corresponding sulfane under the same reaction conditions. A comparison of entries 4 and 5 shows that cyclization of the methoxybenzene substrate containing the electron-donating group proceeded smoothly, providing methoxychromane in 65% yield, whereas the same reaction of the bromobenzene substrate containing electron-withdrawing groups did not proceed at all. The dihydrobenzofuran compound also could not be obtained through a five-membered ring-closure cyclization by nucleophilic C-alkylation.

In summary, a novel method for the ring-closure cyclization of select primary and secondary halo- and alkanesulfonyloxyalkyl aromatic systems to the corresponding cyclic compounds in ILs such as [bmim][PF_6] has been described. The ILs act as an important driving force and reaction medium in the intramolecular cycloalkylation via C–C bond formation without any kind of catalyst. Further studies on more efficient green protocols (shorter reaction times, lower reaction temperatures) for these cyclizations using ILs, as well as polymer-supported ionic liquids (PSIL),[13] are in progress in our laboratories.

Acknowledgments

This work was supported by research funds of Chonbuk National University in 2009, Nuclear Research and Development Program of the Korea Science and Engineering Foundation (KOSEF) grant funded by the Korean government (MEST) (Grant code: 2009-0078422 to D.W.K), and the conversing Research center program through the National Research Foundation of Korea (NRF) funded by MEST (Grant code: 2009-0081956).

Supplementary data

Supplementary data (experimental section, characterization, and ^1H and ^{13}C NMR spectra of all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.065.

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