Reports

Ionic Liquid Phase Synthesis of Tetrahydropyrano- and Tetrahydrofuranoquinolines under Microwave Irradiation

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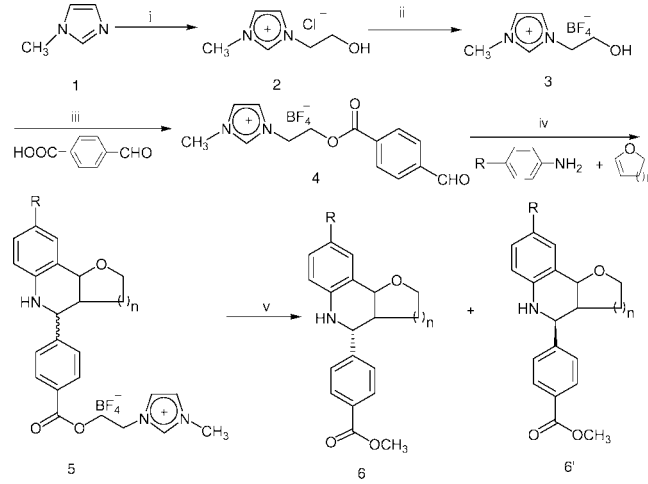
Received March 22, 2007

The tetrahydroquinoline derivatives are an important class of the natural products and exhibit biological activities in various fields,[1] such as antiallergenic, psychotropic, anti-inflammatory, and estrogenic activity. Moreover, they are useful derivatives as pesticides, antioxidants, and corrosion inhibitors.[2] Therefore, a variety of approaches have been developed for their synthesis.[3] Among them, the aza-Diels–Alder reaction of electron-rich dienophiles with *N*-aryl aldimines to obtain the tetrahydroquinolines is one of the most powerful methods, and it has been reported to improve the reaction by using various metal catalysts and different acids.[3]

To our knowledge, Kiselyov et al.[4] reported the solid-phase synthesis of tetrahydroquinoline derivatives, and Wang et al.[5] reported the PEG-supported liquid-phase synthesis of them. However, solid-phase synthesis still exhibits several shortcomings such as the nature of heterogeneous reaction, using a large excess of reagents, and difficulties in reaction monitoring. At the same time, there is a main limitation of low loading capacity in the use of soluble polymer supports.

Bazureau was the first to propose the use of ionic liquid as a soluble support for the synthesis of small organic molecules.[6,7] It has recently been extended by Miao and Chan who have shown it to be compatible with Suzuki coupling and oligopeptide synthesis.[8] As the soluble support in liquid-phase organic synthesis, the functionalized ionic liquids have attracted more attention owing to the advantages of the nature of homogeneous reaction, high loading capacity, a wide range of solvent compatibility, the easy reaction monitoring method, and especially the capability of preparing a wide number of biologically active heterocycles.[9–16] Significantly,

Scheme 1. Regents and Conditions of the Reaction[a]



[a] (i) Chloroethanol (1 equiv), N_2, MV, 200 W, refluxing for 3min; (ii) $NaBF_4$ (1 equiv), CH_3CN, 80°C, 24 h; (iii) DCCI (1 equiv), DMAP (5%), dry CH_3CN, rt, 24 h; (iv) cat. 2%TFA/CH_3CN, MV, 400 W, refluxing for 5 min; (v) sodium methoxide–methanol, MV, 400 W, refluxing for 10 min.

the three reagents were added in equal amount in the reaction, to allow standard analytical methods (^{1}H NMR, thin-layer chromatography (TLC)) to monitor reaction progress. To our knowledge, this ionic liquid supported synthesis of tetrahydroquinoline derivatives have not been reported and provided a complimentary synthetic method to the conventional solution phase synthesis.

Deetlefts and Seddon[17] reported that microwave irradiation could accelerate synthetic reaction for the preparations of ionic liquids. Hoffmann et al.[18] found that ionic liquids could efficiently absorb microwave energy by which the reaction rate could be accelerated remarkably. Recently, Legeay et al.[19] refered to the fact that ionic liquid phase technology is applied for the three-component synthesis of Hantzsch 1,4-dihydro-pyridines and Biginelli 3,4-dihydropyrimidin-2(1*H*)-ones under a microwave dielectric heating condition.

Herein, we report the application of functionalized ionic liquid as the soluble support in the synthesis of tetrapyrano- and tetrafuranoquinolines under microwave irradiation. The efficient preparation of the functionalized 1-[2-(4-benzoyloxy)ethyl]-3-methylimidazolium tetrafluoroborate-bound aldehyde **4** (Scheme 1) was realized by the reaction of an ionic liquid (IL), 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate ([2-hydemim] [BF_4]) **3**, and 4-formylbenzoic acid in dry CH_3CN with dicyclo-hexylcarbodiimide (DCCI) and 5% dimethylamino pyridine (DMAP) as catalysts, and this reaction lastly afforded the functionalized IL-bound benzaldehyde **4** in high yields.[19] With the IL-bound benzaldehyde **4** in hands, it was studied that the application of IL-bound benzaldehyde **4** in the one-pot three-component aza-Diels–Alder reaction under microwave irradiation.[20] In this work, 2% TFA–CH_3CN was chosen for this reaction.[5] As

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10.1021/cc070052l CCC: $37.00
Published on Web 08/21/2007

indicated by ^{1}H NMR monitoring, the above reaction was nearly complete in only 5 min. In contrast, it would take 12 h without microwave irradiation.[5] After the removal of acetonitrile, deionized water (10 mL) was added to the mixture. The IL-bound cycloadduct **5** was collected by filtration and purified by washing with diethyl ether. Finally, the IL-bound cycloadduct **5** was treated with sodium methoxide in methanol reflux for about 10 min under microwave irradiation to cleave the IL-bound support to obtain the product. In contrast, it would take 6 h by conventional heating. After the cleavage, the methanol in the reaction mixture was removed in vacuum, and the product was extracted from the residue with dichloromethane. After the removal of dichloromethane, a mixture of trans and cis isomers of tetrahydroquinolines with high diastereoselectivity were obtained. Then, *trans*-**6a** and *cis*-**6a′** were separated by column chromatography over silica gel using ethyl acetate/*n*-hexane (1:8 v/v) as eluent.. The ratio of the isomers produced in the reaction was determined by the ^{1}H NMR spectrum of the crude product or by silica gel column chromatography, and the structures of the products were established from the spectral data[21] of the pure compounds (^{1}H NMR and MS). In particular, the ^{1}H NMR data were in agreement with earlier observation.[22]

To recover the hydroxyl-functionalized ionic liquid [2-hydemim][BF_4], the extracted residue was washed three times with dichloromethane and then acetone was added. The precipitate was removed, the IL phase **3** ([2-hydemim][BF_4]) could be typically recovered and reused with no appreciable decrease in yields and reaction rates after the workup as described in the literature.[10] The IL-bound benzaldehyde **4** was synthesized in the same way by using recovered [2-hydemim] [BF_4] and employed in the next cycle.

Five kinds of anilines were investigated for this synthetic strategy. As shown in Table 1, the desired compounds were obtained in good yields and purities with high diastereoselectivity. From Table 1, for the aryl amines bearing the similar steric hindrance groups, employing the aryl amines with the electron-withdrawing group would increase the amount of trans isomers. Moreover, the yields were almost the same with both olefins. Nevertheless, the selectivity of 3,4-dihydropyran was better than that of 2,3-dihydrofuran while reacting with the same aniline.

In conclusion, we have developed the use of hydroxyl-functionalized ionic liquids as soluble supports in the liquid-phase synthesis of tetrahydroquinoline. This methodology exemplifies the importance of functionalized ionic liquid phase combinatorial synthesis for lead optimization and offers easy access to compound collections containing this crucial heterocycle. Also, it offers several advantages: First, the IL-bound cycloadduct **5** and mixture of trans and cis isomers of **6** can be obtained in good yields and purified by simple washing and filtration, and the reaction was almost complete in 5 min. Second, the two steps of cyclocondensation and cleavage completed in only about 15 min under microwave irradiation. Third, higher loading capacity is achieved due to the lower molecular weight of the functionalized ionic liquid. Fourth, the recovered ionic liquid after cleavage can be reused in another cycle without losing its activity. This new and effective methodology is associated with the benefits derived from both multicomponent coupling and ionic liquid phase synthesis. We feel the present protocol will find important applications for the synthesis of tetrahydropyrano- and tetrahydrofuranoquinolines.

Table 1. Ionic Liquid-Phase Synthesis of Tetrahydroquinolines[d]

Entry	R	Olefins	MS[M+H]$^+$	Yields(%)[a]	*Trans/cis*
a	H		324.1	89	90 : 10[b]
b	CH_3		338.2	92	73 : 27[b]
c	CH_3O		354.1	90	75 : 25[b]
d	Cl		358.6	85	85 : 15[b]
e	F		342.0	87	90 : 10[b]
f	H		310.0	91	77 : 23[c]
g	CH_3		324.1	87	74 : 26[b]
h	CH_3O		340.1	91	79 : 21[b]
i	Cl		344.6	89	86 : 14[b]
j	F		328.0	83	91 : 9[b]

[a] Isolated and unoptimized yield. [b] Trans/cis isomers were separated by the silica gel column chromatography. [c] Trans/cis isomers were determined from the ^{1}H NMR spectra of the crude product. [d] All products showed the satisfactory ^{1}H NMR, MS, and IR data.

Acknowledgment. This work was financially supported by the National Key Project for Basic Research (2003CB114400), the National Natural Science Foundation of China (No. 20572057), and the Natural Science Foundation of Shandong Province (No. Y2006B11).

Supporting Information Available. Details of experimental procedures, analytical data (^{1}H, ^{13}C NMR, MS, and IR), and elemental analysis for all compounds. This material is available free of charge via the Internet at http: //pubs.acs.org.

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(20) Typical procedure for the synthesis of **6a** and **6a′**: The newly synthesized IL-bound benzaldehyde **4** (2 mmol), aniline (2 mmol), and 3,4-dihydropyran (2 mmol) were added to 2% TFA–CH_3CN (25 mL). The mixture was heated under microwave irradiation of 400 W for 5 min (see Scheme 1). After the removal of acetonitrile, the IL-bound cycloadduct **5a** was purified by washing with deionized water (10 mL) and diethyl ether (3 × 10 mL). Then, it was treated with 20 mL 0.1 M MeONa in MeOH reflux for about 10 min under microwave irradiation of 400 W to cleave the IL-bound support to obtain the product. After the cleavage, the methanol in the reaction mixture was removed in vacuum, and the mixture of *trans*-**6a** and *cis*-**6a′** was extracted from the residue with dichloromethane (3 × 10 mL). After the removal of dichloromethane, *trans*-**6a** and *cis*-**6a′** were separated by column chromatography over silica gel using ethyl acetate/*n*-hexane (1:8 v/v) as eluent. The ratio of *trans*-**6a** and *cis*-**6a′** is 90:10.

(21) Typical spectral data for compound **6a**: IR (KBr): 3371, 1710 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.28–1.90$ (m, 4H), 2.13 (m, 1H), 3.74 (m, 1H), 3.96 (s, 3H), 4.11 (m, 2H), 4.42 (d, $J = 2.6$ Hz, 1H), 4.80 (d, $J = 10.6$ Hz, 1H), 6.58–8.08 (m, 8H, Ar-H). For compound **6a′**: IR (KBr): 3349, 1716 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.26$ (m, 2H), 1.55 (m, 2H), 2.15 (m, 1H), 3.44 (m, 1H), 3.58 (m, 1H), 3.77 (s, 1H), 3.93 (s, 3H), 4.76 (s, 1H), 5.33 (d, $J = 5.2$ Hz, 1H), 6.62–8.06 (m, 8H, Ar-H).

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CC070052L