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Bicyclic 1,2,3-Triazolium Ionic Liquids: Synthesis, Characterization, and Application to Rutaecarpine Synthesis

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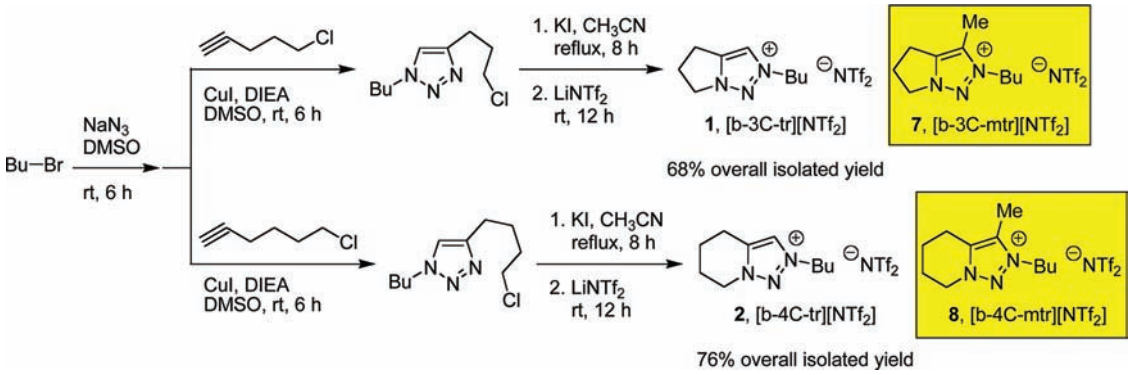
ABSTRACT



Starting with commercial reagents, bicyclic 1,2,3-triazolium ionic liquids [b-3C-tr][NTf_2] (1) and [b-4C-tr][NTf_2] (2) were synthesized in four steps with high overall isolated yields of 68% and 76%, respectively. Since the C-5 hydrogen is acidic, under basic condition ionic liquids 1 and 2 were readily methylated with methyl iodide to afford chemically stable ionic liquids 7 and 8 at room temperature (88% and 82%, respectively). Ionic liquid 1 was used as the ionic solvent to demonstrate its usefulness for the synthesis of rutaecarpine, a natural product.

This paper reports the development of a bicyclic 1,2,3-triazolium ionic liquid system based on the Huisgen [3 + 2] cycloaddition of azides and alkynes (click reaction)[1] with specific aims to study its chemical stability and usefulness as reaction medium for organic synthesis. Ionic liquids are low-melting molten salts composed entirely of ions, and many of them are liquid at room temperature.[2] Ionic liquids carry numerous desirable properties such as wide liquid range, thermal stability, excellent solubility with many small molecules, attractive recyclability, and negligible vapor pressure that are well suited for a myriad of applications, including electrolytes for solar cells and solvents for organic synthesis.[2]

Today, the research on ionic liquids continues to be dominated by imidazolium salts with fluorine-containing anions.[2] Studies of 1,2,3-triazolium ionic liquids, however, are most recent.[3] In our laboratory, we have been interested in developing new ionic liquids and have a program to evaluate ionic liquids as novel and stable media for

(1) For recent reviews on click chemistry, see: (a) Kappe, C. O.; Van der Eycken, E. *Chem. Soc. Rev.* **2010**, *39*, 1280. (b) Baskin, J. M.; Bertozzi, C. R. *Aldrichim. Acta* **2010**, *43*, 15. (c) Angell, Y. L.; Burgess, K. *Chem. Soc. Rev.* **2007**, *36*, 1674. (d) Wu, P.; Fokin, V. V. *Aldrichim. Acta* **2007**, *40*, 7. (e) Binder, W. H.; Kluger, C. *Curr. Org. Chem.* **2006**, *10*, 1791. (f) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249.

(2) For recent reviews on ionic liquids, see: (a) Giernoth, R. *Angew. Chem., Int. Ed.* **2010**, *49*, 2834. (b) Coleman, D.; Gathergood, N. *Chem. Soc. Rev.* **2010**, *39*, 600. (c) Huo, C.; Chan, T. H. *Chem. Soc. Rev.* **2010**, *39*, 2977. (d) Sowmiah, S.; Srinivasadesikan, V.; Tseng, M.-C.; Chu, Y.-H. *Molecules* **2009**, *14*, 3780. (e) Plechkova, N. V.; Seddon, K. R. *Chem. Soc. Rev.* **2008**, *37*, 123.

(3) (a) Jeong, Y.; Kim, D.-Y.; Choi, Y.; Ryu, J.-S. *Org. Biomol. Chem.* **2011**, *9*, 374. (b) Jeong, Y.; Ryu, J.-S. *J. Org. Chem.* **2010**, *75*, 4183. (c) Fletcher, J. T.; Keeney, M. E.; Walz, S. E. *Synthesis* **2010**, 3339. (d) Khan, S. S.; Hanelt, S.; Liebscher, J. *ARKIVOC* **2009**, *xii*, 193. (e) Hanelt, S.; Liebscher, J. *Synlett*. **2008**, 1058.

(4) (a) Chen, C.-W.; Tseng, M.-C.; Hsiao, S.-K.; Chen, W.-H.; Chu, Y.-H. *Org. Biomol. Chem.* **2011**, *9*, 4188. (b) Tseng, M.-C.; Chu, Y.-H. *Chem. Commun.* **2010**, *46*, 2983. (c) Tseng, M.-C.; Tseng, M.-J.; Chu, Y.-H. *Chem. Commun.* **2009**, 7503. (d) Tseng, M.-C.; Kan, H.-C.; Chu, Y.-H. *Tetrahedron Lett.* **2007**, *48*, 9085. (e) Lin, Y.-L.; Kan, H.-C.; Chu, Y.-H. *Tetrahedron* **2007**, *63*, 10949. (f) Kan, H.-C.; Tseng, M.-C.; Chu, Y.-H. *Tetrahedron* **2007**, *63*, 1644. (g) Cheng, J.-Y.; Chu, Y.-H. *Tetrahedron Lett.* **2006**, *47*, 1575.

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chemical and biochemical applications.[2d,4] Since 1,2,3-triazoles are reported to be chemically stable and nearly impossible to oxidize or reduce and, also, from our own experience on bicyclic imidazolium-based ionic liquids such as [b-3C-im][NTf_2] and [b-4C-im][NTf_2],[4a−c,f,g] we decided to investigate bicyclic triazolium ionic liquids as we believed that these ionic liquids would potentially provide the needed chemical stability as useful media for organic synthesis and the desired property for biochemical applications.

We recently reported the synthesis of [b-3C-im][NTf_2] and [b-4C-im][NTf_2] and found that both ionic liquids are far more chemically stable than the common [bmim][PF_6], [bdmim][PF_6], and [bdmim][NTf_2].[4f,g] Because of this intriguing property, we went further to explore other bicyclic ionic liquids, and herein, we present [b-3C-tr][NTf_2] (**1**) and [b-4C-tr][NTf_2] (**2**), a novel class of room temperature

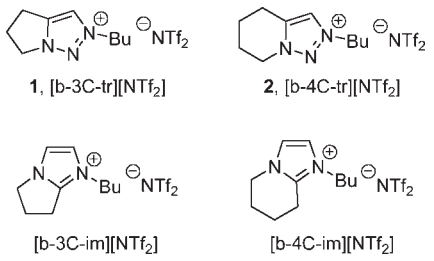


Figure 1. Bicyclic ionic liquids.

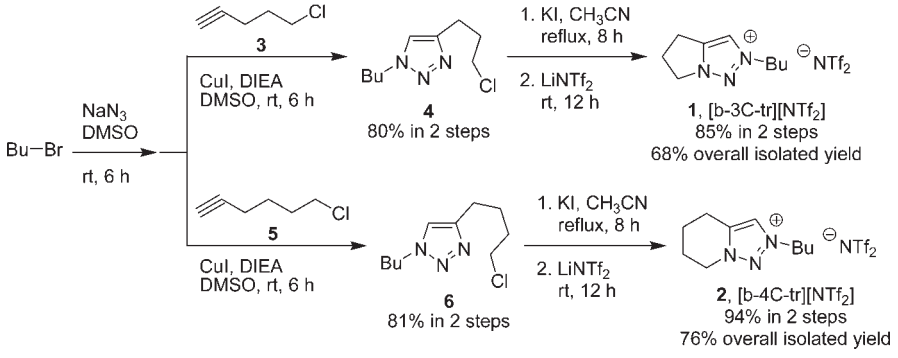
ionic liquids, for use as alternatives to molecular solvents in reactions.

Liebscher and co-workers reported first the synthesis of 1,3,4-trisubstituted 1,2,3-triazolium salts by making use of the click reaction.[3d,e] Our synthesis of bicyclic triazolium ionic liquids (**1** and **2**) is outlined in Scheme 1. First, a two-step, one-pot reaction process involved in situ formation of 1-butyl azide from 1-butyl bromide reaction with sodium azide, followed by the Cu-catalyzed Huisgen [3 + 2] 1,3-dipolar cycloaddition with 5-chloropentyne **3** or 6-chlorohexyne **5** to yield the 1,2,3-triazoles **4** or **6**, respectively. These tandem reactions needed no harsh conditions, avoided the isolation of potentially hazardous organic azide, and proceeded smoothly in DMSO at ambient temperature. Both reactions furnished in 6 h each with high isolated yields (80% for **4** and 81% for **6** over two steps, respectively). The next reaction sequence proceeded with an intramolecular *N*-alkylation of the 1,2,3-triazoles **4** or **6** under the condition of the Finkelstein cyclization (KI in refluxed CH_3CN) for 8 h to form cleanly the corresponding triazolium iodide salts, followed by metathesis with $LiNTf_2$ at ambient temperature for 12 h to finally afford the desired ionic liquid product **1** or **2** with high isolated yields in two steps (85% for **1** and 94% for **2**, respectively). Starting from butyl bromide, the overall isolated yields for this four-step synthesis of [b-3C-tr][NTf_2] (**1**) and [b-4C-tr][NTf_2] (**2**) ionic liquids were 68% and 76%, respectively.

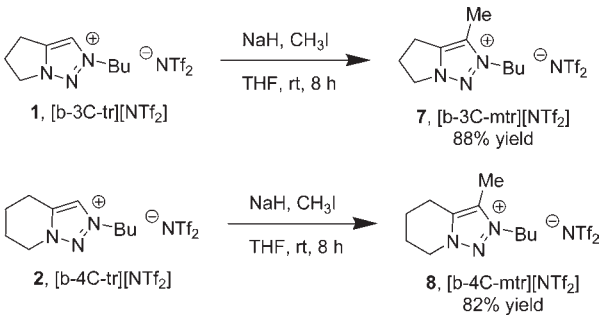
Both bicyclic ionic liquids **1** and **2** are pale yellow liquids at room temperature. We were interested in incorporating low-melting, hydrophobic [NTf_2] anion for ionic liquids mainly because of its water inmiscibility and very low water content; that is, they could be used directly as substitutes to molecular solvents for organic synthesis. Moreover, the conformationally constrained and nonplanar structure of bicyclic ionic liquids further ensured their liquid state at room temperature. In addition to its immiscibility with water, ionic liquids **1** and **2** are readily miscible with polar organic solvents such as methanol, ethanol, acetone, dichloromethane, chloroform, tetrahydrofuran, ethyl acetate, acetonitrile, DMSO, and DMF but practically insoluble in less polar solvents including diethyl ether, hexane, benzene, and toluene.

On first glance, 1,2,3-triazolium ionic liquids **1** and **2** lack the acidic hydrogens at position 2, which prevents imidazolium ionic liquids such as [bmim][PF_6] from being innocent solvents by deprotonation and carbene formation under basic conditions.[2d] Accordingly, the problems associated with acidic C-2 hydrogens in [bmim]-based ionic liquids could be totally avoided in our ionic liquids **1** and **2**. It has been shown in the literature, however, that the aryl hydrogens on 1,2,3-triazolium salts are acidic and can be rapidly deprotonated by bases, and the resulting triazolium anions have been reported to react with various electrophilic reagents.[5] Moreover, 1,2,3-triazolium salts

Scheme 1. Synthesis of Bicyclic 1,2,3-Triazolium Ionic Liquids [b-3C-tr][NTf_2] (**1**) and [b-4C-tr][NTf_2] (**2**)



Scheme 2. Synthesis of [b-3C-mtr][NTf_2] (**7**) and [b-4C-mtr]-[NTf_2] (**8**)



were recently reported as abnormal N-heterocyclic carbene (NHC) precursors that could form complexes, via C-5 hydrogen, with transition metals.[6] All these aforementioned results prompted us to synthesize C-5 methylated ionic liquids **7** and **8** (Scheme 2) and systematically investigate the susceptibility of all bicyclic 1,2,3-triazolium ionic liquids **1**, **2**, **7**, and **8** to solvent deuterium isotope exchange by ^{1}H NMR.

Scheme 2 illustrates the preparation of ionic liquids **7** and **8**. At ambient temperature, both ionic liquids **7** and **8** could be readily achieved with high isolated yields from **1** and **2** (88% and 82%, respectively) by substitution of hydrogen with methyl group at C-5 position using methyl iodide and sodium hydride (Scheme 2). Our ^{1}H NMR study of solvent deuterium isotope exchanges with ionic liquids **1**, **2**, **7** and **8** clearly indicated that, as expected, both

Table 1. Study of Chemical Stability of Ionic Liquids **1**, **2**, **7**, and **8** in Neutral and Basic Conditions by ^{1}H NMR[a]

		conversion (%) of H/D exchange at C-5					
		neutral conditions			basic conditions		
entry	ionic liquid	3 min	24 h	1 wk	3 min	24 h	1 wk
1	**1**	[b]	[b]	75	100	100	100
2	**2**	[b]	[b]	11	100	100	100
3	**7**	[b]	[b]	[b]	[b]	[b]	8[b]
4	**8**	[b]	[b]	[b]	[b]	[b]	5[b]

[a] Experimental conditions: ionic liquid (0.1 M) in CD_3OD/D_2O (7:3, v/v, 0.5 mL) or in CD_3OD/D_2O (7:3, v/v, 0.5 mL) containing 0.1 M KOD. The progress of deuterium exchange could be readily monitored by ^{1}H NMR. [b] Not detectable by ^{1}H NMR.

1 and **2** were chemically reactive and exchanged with deuterium solvents (entries 1 and 2, Table 1).

The solvent deuterium isotope exchanges were measured under two (neutral and strongly basic) experimental conditions by observing the changes in the ^{1}H NMR integrals of the C-5 position hydrogens (i.e., H for **1** and **2**, CH_3 for **7** and **8**) to that of the terminal methyl hydrogens (a nonexchangeable position) on the butyl group. Results from Table 1 showed that, under strongly basic conditions (0.1 M KOD in the 7:3 mixture of CD_3OD and D_2O), ionic liquids **7** and **8** were practically resistant to deuterium isotope exchanges and chemically stable for up to 1 week (only 8% and 5% exchanged, respectively) while ionic liquids **1** and **2** were completely exchanged immediately after mixing with the deuterium solvent (i.e., within 3 min).

Under neutral conditions (CD_3OD/D_2O = 7:3, v/v), all ionic liquids studied proceeded no solvent deuterium isotope exchanges and were chemically stable for 24 h at ambient temperature (entries 1–4, Table 1). Ionic liquids **1** and **2**, however, exchanged slowly with deuterium solvent (75% and 11%, respectively) and ionic liquids **7** and **8** gave no detectable exchanges for up to 1 week. We reasoned that the nonplanar, constrained fused tetrahydropyridinotriazolium ring structure in ionic liquids **2** and **8** appears to make the hydrogen and CH_3 group at C-5 less accessible than those of the dihydropyrrolotriazolium ring in ionic liquids **1** and **7** for solvent exchange; that is, ionic liquids **2** and **8** are more chemically stable than **1** and **7**, respectively. The results of solvent deuterium isotope exchange experiments demonstrate that the C-5 position of bicyclic triazolium ionic liquids can be made less acidic by simply replacing the hydrogen with a methyl group. Table 1 summarizes exchange rates of all ionic liquids studied in deuterium solvents under neutral and basic conditions. In comparison with bicyclic [b-3C-im][NTf_2] and [b-4C-im][NTf_2] ionic liquids previously reported (Figure 1), both **7** and **8** developed in this work are far more superior in chemical stability.[7]

The success of the development of bicyclic 1,2,3-triazolium ionic liquids prompted us to initiate a preliminary program to investigate its usefulness as ionic solvents for synthesis of natural products. We chose rutaecarpine (**9**) as our initial synthetic target on which to test and support our design that synthesis of natural products could be promoted in these ionic liquids. Rutaecarpine **9**, a cytotoxic alkaloid first isolated in 1915 from the dried fruit of the plant *Evodia rutaecarpa*,[8] exhibits important biological activities[9] and, for exactly this reason, has been the subject of a number of total syntheses and bioactivity investigations.[10,11] Scheme 3 illustrates our initial success of rutaecarpine synthesis of which the middle CD rings were concomitantly assembled from an

(5) (a) Begtrup, M. *J. Chem. Soc., Chem. Commun.* **1975**, 334. (b) Begtrup, M. *Acta Chem. Scand. B* **1975**, *29*, 141.

(6) Mathew, P.; Neels, A.; Albrecht, M. *J. Am. Chem. Soc.* **2008**, *130*, 13534.

(7) Under the same basic conditions, the times required at 50% deuterium exchange ($t_{1/2}$) for [b-3C-im][NTf_2] and [b-4C-im][NTf_2] were 140 and 28 h, respectively.[4f] These results clearly indicate that ionic liquids **7** and **8** are far more chemically stable: only 8% and 5% exchanged, respectively, after 168 h (1 week).

(8) This plant has a history of use in Chinese medicine for gastrointestinal disorders, postpartum hemorrhage, and migraine.

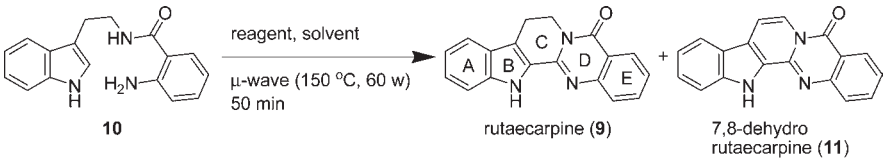
(9) For a recent review on biological activities of rutaecarpine, see: Jia, S.; Hu, C. *Molecules* **2010**, *15*, 1873.

(10) For a recent review on rutaecarpine synthesis, see: Lee, S. H.; Son, J.-K.; Jeong, B. S.; Jeong, T.-C.; Chang, H. W.; Lee, E.-S.; Jahng, Y. *Molecules* **2008**, *13*, 272.

(11) Since its discovery, there have been 146 publications (SciFinder on June 29, 2011) on the synthesis of rutaecarpine. For selected examples of recent syntheses of rutaecarpine, see: (a) Zhang, C.; De, C. K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416. (b) Hamid, A.; Elomri, A.; Daich, A. *Tetrahedron Lett.* **2006**, *47*, 1777.

(12) The starting 2-aminobenzamide **10** could be readily prepared in high isolated yield (90%) from the reaction of tryptamine with isatoic anhydride in DMF for 30 min at ambient temperature.

Scheme 3. Synthesis of Rutaecarpine in Molecular and Ionic Solvents



entry	reagent	solvent	isolated yield (**9** + **11**)	**9**/**11** ratio
1	Vilsmeier reagent	ionic liquid **1**	68%	100:0
2	DMF	ionic liquid **1**	13%	77:23
3	Vilsmeier reagent	DMF	58%	66:34
4	DMF	DMF	no reaction	-

2-aminobenzamide **10**[12] reaction with the Vilsmeier reagent (*N*,*N*-dimethylformiminium chloride) in ionic liquid **1**.

We envisaged that this concurrent formation of CD rings, if formed, would be challenging to assemble due primarily to the harsher reactions likely required to drive the reaction to completion. We therefore decided to employ microwaves to deliberately promote such double cyclization reaction. In our hands, after several initial trials in screening experimental conditions, it was quickly revealed that microwave irradiation (60 W) with temperature controlled at 150 °C produced best results.

With microwaves, reaction of **10** in ionic liquid **1** with the Vilsmeier reagent for 50 min cleanly furnished the desired natural product **9** with 68% isolated yield after column chromatography (entry 1, Scheme 3). In our hand, this ionic solvent appeared to be thermally stable under the experimental condition. If performed in DMF molecular solvent, lower yield with significant contamination of a fully aromatized 7,8-dehydrorutaecarpine (**11**)[10] was obtained (entry 3). Albeit the less reactive DMF could replace the Vilsmeier reagent for the synthesis of **9**, poor yield along with contamination of **11** was observed (entry 2). This result of the reaction formation of **9** and **11** with DMF in ionic liquid **1** is consistent with our recent report on the weak Lewis acidic nature of ionic liquid, which likely activates DMF.[4a] Moreover, under identical experimental conditions, a microwave reaction of **10** with DMF in DMF solvent gave no trace of **9** or **11** (entry 4, Scheme 3). Scheme S1 (Supporting Information) illustrates a plausible mechanism for the synthesis of rutaecarpine **9**.

In summary, we have developed a novel class of room-temperature, bicyclic 1,2,3-triazolium ionic liquids **1**, **2**, **7**, and **8** that appear to fulfill practical requirement as solvents for chemical reactions such as rutaecarpine synthesis. Further studies to evaluate its reaction scope under various conditions are in progress. Moreover, these new ionic liquids may open exciting perspectives for use in various synthetic applications of natural and non-natural products of biological significance.

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Supporting Information Available. Scheme S1, experimental procedures, and ^{1}H and ^{13}C NMR data and spectra of all ionic liquids (**1**, **2**, **7**, and **8**) and rutaecarpine **9**. This material is available free of charge via the Internet at http://pubs.acs.org.