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Ionic liquid accelerated intramolecular hetero-Diels–Alder reactions: a protocol for the synthesis of octahydroacridines

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Abstract—2-Azadienes derived in situ from arylamines and (*R*)-(+)-citronellal/3-methylcitronellal undergo intramolecular [4+2] hetero-Diels–Alder reactions in the air and moisture stable ionic liquid [bmim]BF_4 in the absence of any acid catalyst to afford 1,2,3,4,4a,9,9a,10-octahydroacridine derivatives in high to quantitative yields.

The aza-Diels–Alder reaction is becoming a mainstay for heterocycle and natural product synthesis.[1,2] The imino-Diels–Alder reaction between arylimines and electron-rich dienophiles is a useful synthetic tool for constructing *N*-containing six-membered heterocycles such as tetrahydroquinolines and dihydro-4-pyridones.[3] In particular, the intramolecular imino-Diels–Alder reaction provides a simple route for the stereoselective synthesis of octahydroacridines, tetrahydrochromanoquinolines and furo-pyranoquinolines.[4] Among these, octahydroacridines are an important class of bioactive molecules in the field of drugs and pharmaceuticals and are inhibitors of gastric acid secretion.[5] The simplest and the most straightforward method for the synthesis of octahydroacridines involves acid catalyzed intramolecular cyclization of aryl amines with non-activated olefins tethered to the diene system.[6] Many of these procedures cannot be operated in a single-step with a carbonyl compound having a non-activated olefin and an arylamine because the amines and water that exist during imine formation can decompose or deactivate the Lewis acids. Furthermore, most of the imines are hygroscopic, unstable at high temperatures and difficult to purify either by distillation or by column chromatography. To circumvent some of these problems, one-pot procedures have been developed for this transformation.[7] In fact, these procedures do not require the isolation of unstable imines prior to the reactions, but they require either a long reaction time[7a] or microwave activation[7b] and in addition they demand routine aqueous work-up for the catalyst separation, recycling and disposal.

Recently, ionic liquids have emerged as alternative reaction media for the immobilization of transition metal based catalysts, Lewis acids and enzymes.[8] They are also being used as solvents to carry out various functional group transformations.[9]

Ionic liquids provide an ideal medium for reactions that involve reactive ionic intermediates. Due to the stabilization of charged intermediates by ionic liquids, they can promote enhanced selectivities and reaction rates and are finding increasing applications in organic synthesis.[10]

In this report, we wish to describe the use of ionic liquids (Fig. 1) as solvents for the intramolecular aza-Diels–Alder reaction of arylimines derived from arylamines and

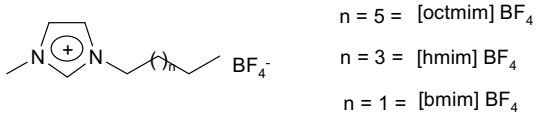

Figure 1. Chemical structure of representative ionic liquids.

Keywords: Ionic liquids (ILs); Aza-dienes; Octahydroacridines.
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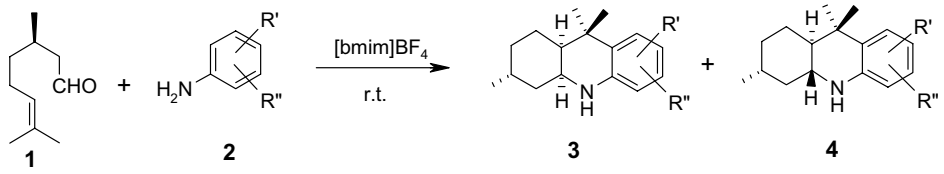


Scheme 1.

(*R*)-(+)-citronellal or 3-methylcitronellal to afford octahydroacridine derivatives in excellent yields under mild and neutral conditions (Scheme 1).

Treatment of (*R*)-(+)-citronellal with aniline in 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) at room temperature over a period of 1 h resulted in the formation of 3,9,9-trimethyl-1,2,3,4,4a,9,9a,10-octahydroacridine in 95% yield. The reaction proceeded efficiently at room temperature without the need for any additional acid catalyst. The product was obtained as a mixture of **3** *cis*- and **4** *trans*-isomers. In product **3a**, the small value of 3.2 Hz for $J_{9aH-4aH}$ indicates *cis*-fusion of the rings B and C with *S*-configuration at C9a and C4a. The ring C adopts a[9a] C_3 conformation, which was further confirmed by NOEs between 3Ha–1Ha and 2Ha–4Ha (Fig. 2).

In product **4a** the value of J_{9a-4a} = 10.5 Hz, which indicates a *trans*-fusion of the rings B and C. The *cis*- and *trans*-isomers could be easily separated by column chromatography. The ratio of products was determined by ^{1}H NMR spectroscopy of the crude products and also by comparison after purification. Encouraged by the results obtained with aniline, we turned our attention towards various substituted anilines. Interestingly, a wide range of arylamines reacted smoothly with (*R*)-(+)-citronellal under similar reaction conditions to give the corresponding 1,2,3,4,4a,9,9a,10-octahydroacridine derivatives. However, the reaction did not proceed with 2,6-disubstituted arylamines such as 2,6-dimethyl- and 2,6-dichloroaniline. 3-Methylcitronellal and aniline gave the corresponding cycloadduct **5k** in 97% yield with high *trans*-selectivity. Compared to (*R*)-(+)-citronellal, the reactions are faster with 3-methylcitronellal and complete within 15 min to 3.5 h. In the case of 3-methylcitronellal, the corresponding products were obtained exclusively as the *trans*-isomers (Table 1, entries **5k**–**o**). Furthermore, aromatic diamines having two amino groups on the same aromatic system were studied. *para*-Phenylenediamine underwent cyclization very rapidly with 2 equiv of 3-methylcitronellal in [bmim]BF_4 to afford a *trans*-biscyclization product (Table 1, entry **5o**). Treatment of 4,4′-oxydianiline with (*R*)-(+)-citronellal gave a mixture of products **6p** and **7p** in the ratio 1:1.2 (Table 2, entries **6p** and **7p**, Scheme 2). Treatment of 4,4′-oxydianiline with 3-methylcitronellal in [bmim]BF_4 gave the *trans*-bisadduct (Table 2, entry **7q**) whereas 4,4′-methylenedianiline afforded the corresponding *trans*-bisadduct (Table 2, entry **7r**).

The presence of a single set of peaks for both halves of the structure of **6p** implies a twofold molecular symmetry and is consistent with the proposed structure in Figure 3. The structure of the dimer **6p** is very similar to that of the monomer **3a** as indicated by very similar couplings as well as NOE's between the protons. Similarly **7p** results in one set of peaks in the NMR spectra with $J_{9aH-4aH}$ = 10.5 Hz, thus *trans* fusion at rings B and C is amply supported. Virtually identical NMR data for **7q** and **7r** implies exclusive formation of the *trans–trans* adduct. In all cases, the reactions proceeded smoothly and rapidly at room temperature with high efficiency. In the absence of an ionic liquid, the desired products were not obtained even after a long reaction time (8–12 h). As a solvent for this reaction, the efficiency of the ionic liquid was strongly influenced by the nature of the counter anion. The reaction of arylamines with (*R*)-(+)-citronellal/3-methyl citronellal was studied in both hydrophilic [bmim]BF_4 and hydrophobic [bmim]PF_6 ionic liquids and [bmim]BF_4 was found to be more effective in terms of conversion and reaction rates. Arylimines, formed in situ from anilines and (*R*)-(+)-citronellal or 3-methyl citronellal, exhibit enhanced reactivity in the ionic liquid thereby reducing the reaction times and improving the yields significantly. For instance, treatment of 3-methylcitronellal with aniline in [bmim]BF_4 afforded the corresponding acridine

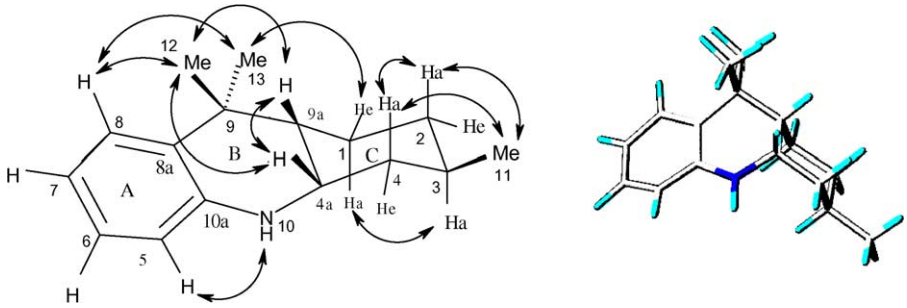
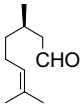
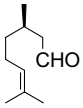
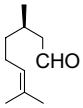
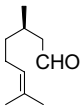
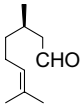
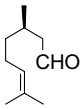
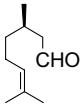
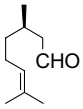
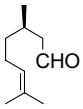
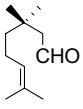
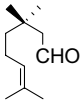
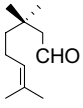
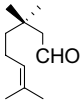


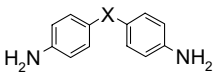
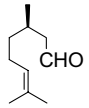
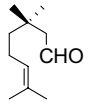
Figure 2. Observed NOEs and energy minimized structure of **3a**.

Table 1.

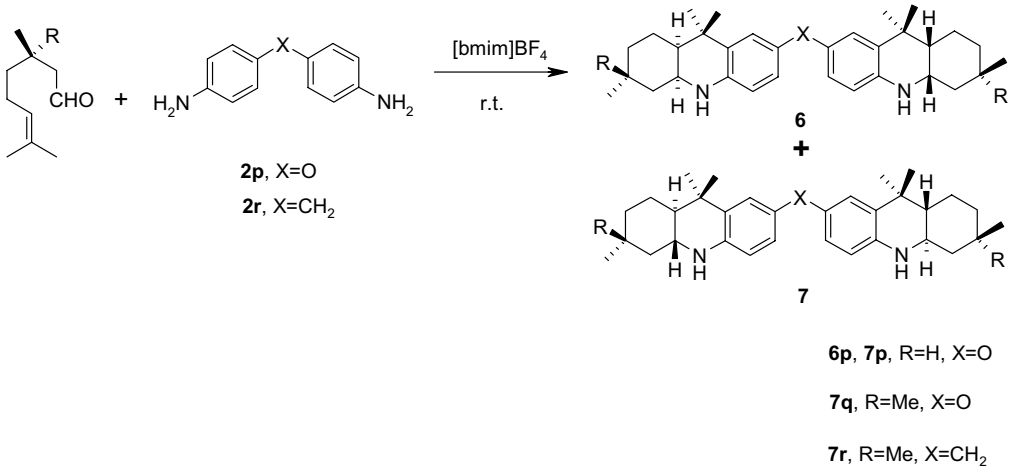
Aldehyde	Arylamine	Product[a]	Conversion[b]	Time (h)	Yield[c] (%)	Ratio (**3**:**4**)[d]
	$C_6H_4NH_2$ (**2a**)	**3a/4a**	100	1.0	95	1:1
	2-Me–$C_6H_4NH_2$ (**2b**)	**3b/4b**	99	1.5	92	1:3
	4-F–$C_6H_4NH_2$ (**2c**)	**3c/4c**	98	1.0	90	1:2
	4-CI–$C_6H_4NH_2$ (**2d**)	**3d/4d**	100	1.5	93	1:2
	2-Br–4-Me–$C_6H_3NH_2$ (**2e**)	**3e/4e**	97	2.0	86	1:1.5
	α-Naphthylamine (**2f**)	**3f/4f**	99	1.5	94	1:4
	4-MeO–$C_6H_4NH_2$ (**2g**)	**3g/4g**	97	3.5	89	1:1.2
	4-EtO–$C_6H_4NH_2$ (**2h**)	**3h/4h**	95	3.0	87	1:1.5
	4-Me–$C_6H_4NH_2$ (**2i**)	**3i/4i**	100	1.0	95	1:2
	2,6-$(CH_3)_2$–$C_6H_3NH_2$ (**2j**)	**3j/4j**	No reaction	5.0	—	—
	$C_6H_5NH_2$ (**2a**)	**5k**	100	15 min	97	*trans*
	2-Me–$C_6H_4NH_2$ (**2b**)	**5l**	100	20 min	95	*trans*
	2-CF_3–$C_6H_4NH_2$ (**2k**)	**5m**	98	15 min	89	*trans*
	4-NO_2–$C_6H_4NH_2$ (**2l**)	**5n**	93	3.5	70	*trans*
	4-NH_2–$C_6H_4NH_2$ (**2m**)	**5o**[e]	100	20 min	94	*trans*

[a] All the products have been reported previously in the literature.[6,7]
[b] Conversions were determined by TLC and GLC analysis.
[c] Yield refers to pure products after chromatography.
[d] Ratio was determined by ^{1}HNMR spectroscopy of the crude products and by comparison after purification.
[e] Bisadduct was isolated when 2 equiv of 3-methylcitronellal was used.

Table 2.

		Product[a]	Conversion[b]	Time	Yield[c] (%)	Ratio (6:7)[d]
	X = O (**2p**)	**6p/7p**	100	1.5 h	87	1:1.2
	X = O (**2p**) X = CH_2 (**2r**)	**7q** **7r**	100 99	20 min 35 min	92 90	*trans–trans* *trans–trans*

[a] All the products have been reported previously in the literature.[6,7]
[b] Conversions were determined by TLC and GLC analysis.
[c] Yield refers to pure products after chromatography.
[d] Ratio was determined by ^{1}HNMR spectroscopy of the crude products and by comparison after purification.



Scheme 2.

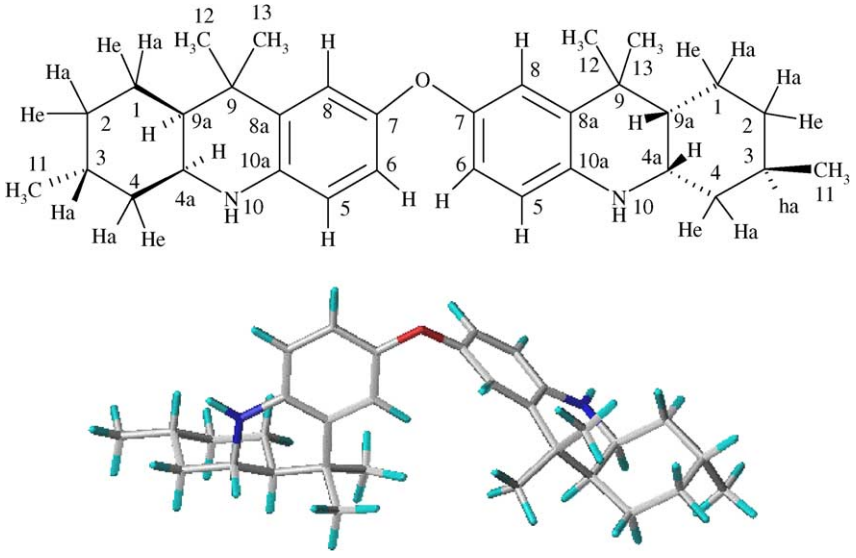


Figure 3. Schematic representation and energy minimized structure of **6p**.

5k in 97% yield within 15 min whereas the same reaction in the absence of acid catalyst in commonly used organic solvents such as acetonitrile or methanol gave the intermediate imine after 3 h but with no further cyclization.

In addition, the ionic liquid was easily recovered after the reaction and reused several times without loss of activity, even after a fourth cycle, the product **5k** was obtained with similar yield and purity to that obtained in the first cycle. The use of ionic liquids as reaction media for this transformation helps to avoid the neccessity for moisture sensitive reagents or heavy metal Lewis acids as promoters thereby minimizing the production of toxic waste during work-up. The scope and generality of this method is illustrated with respect to (*R*)-(+)-citronellal/3-methylcitronellal and a wide range of amines and the results are presented in Tables 1 and 2.[11] Similar results were also obtained with ionic liquids having longer alkyl chains such as 1-hexyl-3-methylimidazolium tetrafluoroborate [hmim]BF_4 and 1-octyl-3-methylimidazolium tetrafluoroborate [octmim]BF_4.

In summary, we have described a one-pot procedure for the synthesis of octahydroacridines via an intramolecular imino-Diels–Alder reaction of *N*-arylamines with (*R*)-(+)-citronellal/3-methyl citronellal using an ionic liquid as the solvent under mild and neutral conditions. The ionic liquid plays the dual role of solvent and promoter in this conversion.

Acknowledgements

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11. *General procedure for the synthesis of octahydroacridines*: A mixture of (*R*)-(+)-citronellal/3-methylcitronellal (1 mmol) and arylamine (1 mmol) in 1-butyl-3-methylimidazolium tetrafluoroborate (3 mL) was stirred at room temperature for the appropriate time (Tables 1 and 2). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with diethyl ether (3×10 mL). The combined ether extracts were concentrated in vacuo and the resulting product was directly charged onto a small silica gel column and eluted with a mixture of ethyl acetate and hexane to afford pure octahydroacridine. The recovered ionic liquid was washed with ether and reused several times without further purification. The products thus obtained were characterized by comparison of their NMR, IR, MS, TLC, mixed TLC analysis and physical data with authentic samples. The spectral data of all the products were identical with those of authentic samples.[5,6] Commercially available ionic liquids were used for this study. They have also been prepared in our laboratory from the readily available and inexpensive *N*-methylimidazole, 1-chlorobutane and hexafluorophosphoric acid or sodium tetrafluoroborate[12] and their purity was determined by comparing their ^{1}H NMR spectra with commercial samples. 3-Methyl citronellal was prepared according to the procedure reported in literature.[13] Spectral data for selected products: **3a**: *cis*-isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 (dd, $J_{7H-8H} = 7.5$ Hz, $J_{8H-6H} = 1.6$ Hz, 1H, H8), 6.95 (ddd, $J_{6H-5H} = 7.5$ Hz, $J_{6H-7H} = 7.5$ Hz, $J_{6H-8H} = 1.6$ Hz 1H, H6), 6.58 (dt, $J = 7.5$ Hz, $J_{7H-5H} = 1.6$ Hz, 1H, H7), 6.32 (dd, $J_{5H-6H} = 7.5$ Hz, $J_{5H-7H} = 1.6$ Hz, 1H, H5), 3.83 (q, $J = 3.2$ Hz, 1H, 4aH), 3.47 (br s, 1H, H10), 1.76 (m, 1H, 3Ha), 1.71 (m, 1H, 4He), 1.65 (m, 1H, 2He), 1.58 (dq, $J = 3.2$ Hz, $J_{1He-1Ha} = 12.8$ Hz, 1H, 1He), 1.31 (s, 3H, Me-13), 1.29 (dt, $J = 3.2$ Hz, $J_{1Ha-9aH} = 12.8$ Hz, 1H, 9aH), 1.24 (dt, $J_{4Ha-4aH} = 3.2$ Hz, $J = 12.8$ Hz, 1H, 4Ha), 1.21 (s, 3H, Me-12), 1.04 (dq, $J = 12.8$ Hz, $J_{1Ha-2He} = 3.2$ Hz, 1H, 1Ha), 0.90 (ddt, $J = 12.8$ Hz, $J_{2Ha-2He} = 11.3$ Hz, $J_{2Ha-1He} = 3.2$ Hz, 1H, 2Ha), 0.88 (d, $J = 6.7$ Hz, 3H, Me-11). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.1, 128.1, 126.5, 126.1, 116.2, 112.8, 46.8, 44.5, 41.2, 35.5, 34.8, 34.1, 26.1, 25.5, 22.9, 22.2. Compound **4a**: *trans*-isomer: ^{1}H NMR (500 MHz. $CDCl_3$): δ 7.17 (dd, $J_{7H-8H} = 7.5$ Hz, $J_{8H-6H} = 1.6$ Hz, 1H, H8), 6.86 (ddd, $J_{5H-6H} = 7.5$ Hz, $J_{6H-7H} = 7.5$ Hz, $J_{6H-8H} = 1.6$ Hz, 1H, H6), 6.54 (dt, $J = 7.5$ Hz, $J_{7H-5H} = 1.6$ Hz, 1H, H7), 6.33 (dd, $J_{5H-6\ H} = 7.5$ Hz, $J_{5H-7H} = 1.6$ Hz, 1H, H5), 3.51 (br s, 1H, H10), 3.05 (dt, $J_{4He-4aH} = 3.7$ Hz, $J = 10.5$ Hz, 1H, 4aH), 1.88 (m, 1H), 1.84 (m, 1H), 1.76 (m, 1H), 1.53 (m, 1H), 1.3 (s, 3H, Me-13), 1.27 (m, 1H), 1.25 (m, 1H), 1.17 (m, 1H), 1.07 (s, 3H, Me-12), 1.01 (m, 1H), 0.95 (d, $J = 6.4$ Hz, 3H, Me-11). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.1, 130.2, 129.1, 128.8, 114.3, 107.5, 46.8, 44.0, 41.0, 35.8, 34.6, 33.7, 25.9, 25.5, 22.9, 22.1. Compound **6p**: *cis–cis*-isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (d, $J_{6H-8H} = 2.4$ Hz, 2H, H8), 7.01 (dd, $J_{5H-6H} = 8.4$ Hz, $J_{6H-8H} = 2.4$ Hz, 2H, H6), 6.29 (d, $J_{5H-6H} = 8.4$ Hz, 2H, H5), 3.80 (q, $J = 3.2$ Hz, 2H, 4aH), 3.59 (br s, 2H, H10), 1.74 (m, 2H, 3Ha), 1.72 (m, 2H, 4He), 1.67 (m, 2H, 2He), 1.58 (dq, $J = 3.2$ Hz,

$J_{1He-1\ Ha}$ = 13.0 Hz, 2H, 1He), 1.29 (s, 6H, Me-13), 1.25 (ddd, $J_{4Ha-4aH}$ = 3.2 Hz, $J_{4Ha-3Ha}$ = 13.0 Hz, $J_{4Ha-4He}$ = 13.0 Hz, 1H, 4Ha), 1.19 (s, 6H, Me-12), 0.94 (dq, $J_{1Ha-2He}$ = 3.2 Hz, J = 13.0 Hz, 2H, 1Ha), 0.92 (dq, $J_{2Ha-1He}$ = 3.2 Hz, J = 13.0 Hz, 2H, 2Ha), 0.88 (d, J = 6.4 Hz, 6H, Me-11). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.1, 130.3, 129.2, 128.8, 114.3, 107.6, 46.8, 44.0, 41.0, 35.9, 34.6, 33.8, 25.9, 25.5, 22.9, 22.1.

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