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Room temperature ionic liquid promoted synthesis of 1,5-benzodiazepine derivatives under ambient conditions

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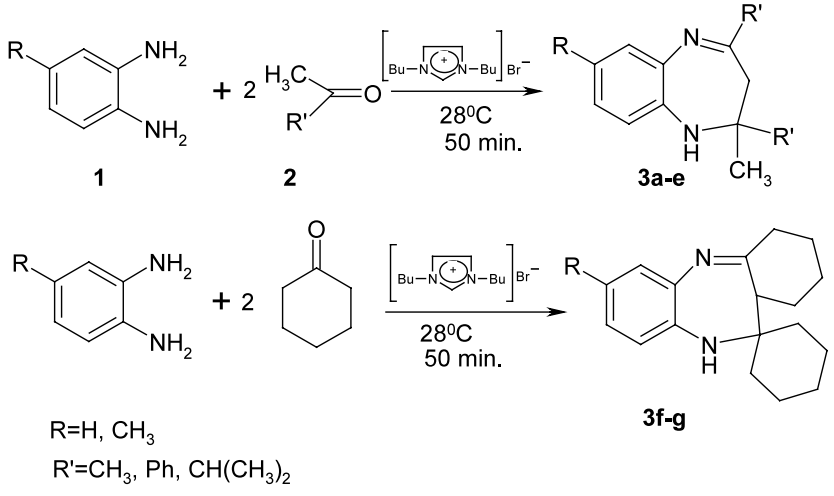
Abstract—The reaction of *o*-phenylenediamines with both acyclic and cyclic ketones in the ionic liquid 1,3-di-*n*-butylimidazolium bromide afforded 1,5-benzodiazepines in excellent isolated yields in the absence of a catalyst at ambient temperature.

Benzodiazepines are an important class of pharmacologically active compounds finding application as anticonvulsant, antianxiety and hypnotic agents.[1,2] Benzodiazepine derivatives also find commercial use as dyes for acrylic fibers[3] and as anti-inflammatory agents.[4] Moreover, they are key intermediates for the preparation of other fused ring compounds such as triazolo-,[5] oxazino-,[6] oxadiazolo-,[7] or furano-benzodiazepines.[8] The literature methods for the synthesis of 1,5-benzodiazepines many of which have been reported recently, include condensation reactions of *o*-phenylenediamines with α,β-unsaturated carbonyl compounds,[9] β-haloketones,[10] or with ketones in the presence of BF_3–etherate,[11] $NaBH_4$,[12] polyphosphoric acid or SiO_2,[13] $MgO/POCl_3$,[14] $Yb(OTf)_3$,[15] Al_2O_3/P_2O_5 or AcOH under microwave irradiation (MW).[16,17] Many of these processes suffer from one or other limitations such as requiring harsh conditions, expensive reagents, low to moderate yields, relatively long reaction times and occurrence of several side reactions. Almost all of them make use of an acid catalyst giving rise to tedious work-up procedures for their separation and recycling or disposal problems.

In recent years, the use of room temperature ionic



Scheme 1.

Keywords: benzodiazepines; ionic liquid; *o*-phenylenediamines; green solvent.

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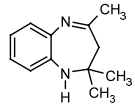
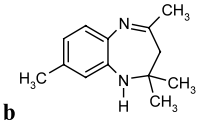
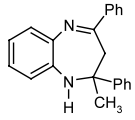
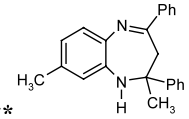
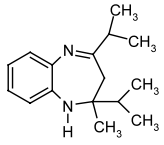
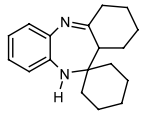
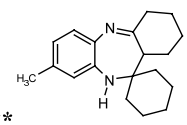
liquids (I.L.s) as 'green' solvents in organic synthetic processes has gained considerable importance due to their solvating ability, negligible vapor pressure, easy recyclability and reusability.[18] Very recently, we have reported the use of 1,3-di-*n*-butylimidazolium salts as newer I.L.s as solvents for promoting the sonochemical Heck and Suzuki reactions under ambient conditions.[19] In continuation of our investigations of organic transformations in ionic liquids acting both as media and promoters, this communication reports for the first time a regioselective synthesis of 1,5-benzodiazepine derivatives in excellent isolated yields and in relatively short reaction times using the I.L., 1,3-*n*-dibutylimidazolium bromide ([bbim]Br), at ambient temperature in the absence of any added catalyst.

ortho-Phenylenediamine (OPD) and substituted OPD's were reacted with both acyclic and cyclic ketones in the I.L. [bbim]Br at 28°C in the absence of any added catalyst (Scheme 1).[20]

The results are summarized in Table 1. As is evident, the reactions in I.L. gave rise to excellent isolated yields of the 1,5-benzodiazepines in a relatively short reaction time (50 min). The isolated benzodiazepines **3** were completely characterized by IR, ^{1}H and ^{13}C NMR analyses, and their melting points.[21] The elemental analyses were in agreement with their structures. The benzodiazepines **3** were the only products obtained and the rest of the material was essentially starting material. The I.L. could be recovered and recycled at least three times for the reaction of the OPD with acetone without incurring any loss in yield of the benzodiazepine **3a**.

No reaction was observed when OPD was reacted with acetone under similar conditions in the absence of the I.L., thus highlighting the role of the I.L. as a promoter. It was also ascertained that a minimum of an equimolar proportion of the I.L. with respect to the OPD is needed to achieve optimum conversion. Any excess of I.L. beyond this proportion did not show any further increase in conversion and yield.

Table 1. Synthesis of benzodiazepines **3** in [bbim]Br

Reactants		Benzodiazepines **3**	Yield* (%)
o-phenylenediamine (OPD)	Acetone	 **a**	93
4-methyl OPD	Acetone	 **b**	95
OPD	Acetophenone	 **c**	96
4-methyl OPD	Acetophenone	 **d****	91
OPD	3-methyl-2-butanone	 **e****	96
OPD	Cyclohexanone	 **f**	90
4-methyl OPD	Cyclohexanone	 **g****	87

* Isolated yields after column chromatography.

** New compounds.

The reaction of OPD with acetone when performed under similar conditions in the I.L. *n*-Butyl pyridinium tetrafluoroborate showed no conversion whereas the I.L. ethyl ammonium nitrate showed only 53% conversion. The use of [bbim]BF_4 and [bmim]Br gave similar results as for [bbim]Br.

The enhanced reactivity for the synthesis of the benzodiazepines in the imidazolium I.L. even in the absence of a catalyst may be attributed to the inherent Brønsted and Lewis acidities of the ring hydrogens H2, H4 and H5 of the imidazolium cation in [bbim]Br. Previous studies involving multi-nuclear NMR spectroscopy and conductivity measurements for the imidazolium ions correlating their acidity characteristics support the above observations.[22–24] Further work is in progress to enhance the acidities of such I.L.s by incorporating weakly coordinating anions and to study their efficacy in promoting similar reactions.

In conclusion, we have developed a new and efficient method for the regioselective synthesis of 1,5-benzodiazepines in excellent isolated yields in short reaction times using a room temperature ionic liquid viz. [bbim]Br as a reaction medium for the first time. Importantly, the I.L. not only acts as a solvating medium but also as a promoter for the reaction giving rise to twin advantages of ambient temperature conditions and the non-requirement of a catalyst. The easy work-up procedures, the absence of a catalyst and recyclability of the non-volatile I.L. used as the reaction medium makes the method amenable for scale-up operations.

Acknowledgements

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References

1. (a) Schultz, H. *Benzodiazepines*; Springer: Heidelberg, 1982; (b) Smalley, R. K. In *Comprehensive Organic Chemistry*; Barton, D.; Ollis, W. D., Eds.; Pergamon: Oxford, 1979; Vol. 4, p. 600; (c) Landquist, J. K. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 1, p. 166, 170.
2. Randall, L. O.; Kappel, B. In *Benzodiazepines*; Garattini, S.; Mussini, E.; Randall, L. O., Eds.; Raven Press: New York, 1973; p. 27 and references cited therein.
3. Harris, R. C.; Straley, J. M.; US Patent 1,537,757, 1968; *Chem. Abstr*. **1970**, *73*, 100054w.
4. De Baun, J. R.; Pallos, F. M.; Baker, D. R.; US Patent 3,978,227, **1976**; *Chem. Abstr*. **1977**, *86*, 5498d.
5. Essaber, M.; Baouid, A.; Hasnaoui, A.; Benharreb, A.; Lavergne, J. P. *Synth. Commun*. **2000**, *28*, 4097–4105.
6. El-Sayed, A. M.; Abdel-Ghany, H.; El-Saghier, A. M. M. *Synth. Commun*. **1999**, *29*, 3561–3572.
7. (a) Xu, J. X.; Wu, H. T.; Jin, S. *Chin. J. Chem*. **1999**, *17*, 84–91; (b) Zhang, X. Y.; Xu, J. X.; Jin, S. *Chin. J. Chem*. **1999**, *17*, 404–410.
8. Reddy, K. V. V.; Rao, P. S.; Ashok, D. *Synth. Commun*. **2000**, *30*, 1825–1836.
9. Stahlofen, P.; Ried, W. *Chem. Ber*. **1957**, *90*, 815–824.
10. Ried, W.; Torinus, E. *Chem. Ber*. **1959**, *92*, 2902–2916.
11. Herbert, J. A. L.; Suschitzky, H. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2657–2661.
12. Morales, H. R.; Bulbarela, A.; Contreras, R. *Heterocycles* **1986**, *24*, 135–139.
13. Jung, D. I.; Choi, T. W.; Kim, Y. Y.; Kim, I. S.; Park, Y. M.; Lee, Y. G.; Jung, D. H. *Synth. Commun*. **1999**, *29*, 1941–1951.
14. Balakrishna, M. S.; Kaboudin, B. *Tetrahedron Lett*. **2001**, *42*, 1127–1129.
15. Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Tetrahedron Lett*. **2001**, *42*, 3193–3195.
16. Kaboudin, B.; Navace, K. *Heterocycles* **2001**, *55*, 1443–1446.
17. Minothora, P.; Julia, S.-S.; Constantinos, A. *Tetrahedron Lett*. **2002**, *43*, 1755–1758.
18. (a) Welton, T. *Chem. Rev*. **1999**, *99*, 2071–2083; (b) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed. Engl*. **2000**, *39*, 3772–3789; (c) Earle, M. J.; Seddon, K. R. *Pure Appl. Chem*. **2000**, *72*, 1391–1398; (d) Gordon, C. M. *Appl. Catal. A: General* **2001**, *222*, 101–117; (e) Sheldon, R. *Chem. Commun*. **2001**, 2399–2407.
19. (a) Deshmukh, R. R.; Rajagopal, R.; Srinivasan, K. V. *Chem. Commun*. **2001**, 1544–1545; (b) Rajagopal, R.; Jarikote, A.; Dilip, V.; Srinivasan, K. V. *Chem. Commun*. **2002**, 616–617.
20. **Typical procedure**:
The I.L. [bbim]Br was prepared as per the reported procedure.[19]
A solution of OPD/substituted OPD **1** (4.62 mmol) and the ketone **2** (9.72 mmol) in [bbim]Br (4.62 mmol) was stirred at 28°C for 50 min. The completion of reaction was followed by TLC using 30% EtOAc in petroleum ether as eluent. After completion, the reaction mixture was diluted with water (25 ml) and extracted with EtOAc (2×15 ml). The combined organic layer was separated, dried over anhydrous sodium sulphate and the solvent evaporated under reduced pressure to afford the 1,5-benzodiazepines. The products, thus isolated, were pure (single spot on TLC). They were subjected to further purification by chromatography through a column of silica-gel using 20% EtOAc in petroleum ether as eluent and fully characterized. The aqueous layer consisting of the I.L. was subjected to distillation (80°C at 10 mmHg) for 2 h to remove water, leaving behind the I.L. [bbim] Br (recovery 98%), which could be recycled.
21. Selected data for the new compounds **3d**, **3e**, **3g**:
3d. Mp 92°C (found C, 84.53; H, 6.85; N, 8.62. $C_{23}H_{22}N_2$ requires C, 84.63; H, 6.79; N, 8.58%); IR (cm^{-1}) 3275 (NH), 1659 (C=N); ^1H NMR (200 MHz, $CDCl_3$) δ 1.8 (s, 3H, CH_3), 2.41 (s, 3H, Ar-CH_3), 2.98–3.03 (d, 1H, $J=13$, CH_2^a), 3.13–3.17 (d, 1H, $J=13$, CH_2^b), 3.5 (br s, 1H, NH), 6.70–7.69 (m, 13H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.6, 136.9, 134.0, 131.2, 130.8, 129.0, 128.6, 128.5, 128.3, 128.2, 127.4, 126.3, 125.7, 123.5, 113.5, 51.0, 45.9, 28.7, 20.9.
3e. Mp 119°C (found C, 78.54; H, 9.95; N 11.51. $C_{16}H_{24}N_2$ requires C, 78.64, H, 9.90; N, 11.46%); IR

(cm^{-1}) 3268 (NH), 1665 (C=N); ^1H NMR (200 MHz, $CDCl_3$) δ 0.94 (d, 6H, $J=7.8$, CH (CH_3)$_2$), 1.12 (s, 3H, CH_3), 1.42 (d, 6H, $J=7.2$, N=C-CH (CH_3)$_2$), 1.85 (m, 1H, C*H* (CH_3)$_2$), 2.1 (m, 1H, C*H* (CH_3)$_2$), 2.47–2.55 (d, 1H, $J=15.5$, CH_2[a]), 2.57–2.64 (d, 1H, $J=16$, CH_2[b]), 3.67 (br s, 1H, NH), 6.64–7.35 (m, 4H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.6, 137.0, 132.8, 127.8, 122.8, 118.2, 113.6, 40.4, 36.1, 29.2, 23.8, 16.5, 14.7

3g. (Found C, 80.71; H, 9.32; N, 9.97 $C_{19}H_{26}N_2$ requires C, 80.80; H, 9.28; N, 9.92%); IR (cm^{-1}) 3260 (NH), 1665 (C=N); ^1H NMR (200 MHz, $CDCl_3$) δ 1.96–2.75 (m, 19H, 8×CH_2 and Ar-CH_3), 2.95–3.29 (m, 3H, N=C-C*H* and N=C-CH_2), 4.99 (br s, 1H, NH), 7.00–7.50 (m, 3H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.6, 134.0, 132.7, 128.5, 127.4,123.5, 113.5, 47.8, 43.7, 34.9, 33.0, 27.4, 26.7, 23.8, 20.9, 20.1.

22. Avent, A. G.; Chaloner, P. A.; Day, M. P.; Seddon, K. R.; Welton, T. *J. Chem. Soc., Dalton Trans*. **1994**, 3405–3413.
23. Howarth, J.; Hanlon, K.; Fayne, D.; McCormac, P. *Tetrahedron Lett*. **1997**, *38*, 3097–3100.
24. (a) Arduengo, A. J.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc*. **1991**, *113*, 361–363; (b) Arduengo, A. J.; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc*. **1992**, *114*, 5530–5534.