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NOTE

Phosphonium Ionic Liquid Promoted Synthesis of 1,5-Benzodiazepines under Ambient Conditions

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The development of an environmentally benign green methodology for the synthesis of benzodiazepines using new phosphonium-based ionic liquids without any added catalyst. *o*-Phenylenediamine undergo condensation with different type of ketone in phosphonium based ionic liquids under mild conditions to afford 1,5-benzodiazepines, yield of the products are excellent.

Key Words: Phosphonium ionic liqids, *o*-Phenylenediamine, Benzodiazepine.

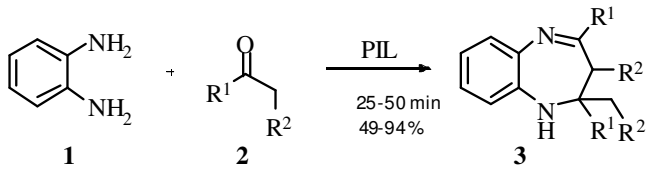
Benzodiazepines are potentially important class of medicinally active compounds and have been extensively used as antibacterial, anticonvulsant, antianxiety, hypnotic and antiinflammatory agents[1,2]. These are also used against viral infections, cardiovascular disorders[3] and in viral disease, *e.g.* AIDS[4]. This nucleus has also been exploited commercially, as dyes for acrylic fiber[5] in photography.

1,5-Benzodiazepines have been successfully utilized in the synthesis of fused ring benzodiazepine class of compounds[6-8] such as oxadiazolo, oxazino, triazolo and furanobenzodiazepine systems.

Due to the wide range of applications of 1,5-benzodiazepines, their synthesis have received a special attention. The relevant literature survey reveals that the synthetic methodology for this ring system include the condensation of *o*-phenylenediamine with α,β-unsaturated carbonyl compounds, β-haloketones or with ketones in the presence of BF_3-etherate,[9] polyphosphoric acid[10], SiO_2, MgO-$POCl_3$[11], $NaBH_4$[12], Yb(OTf)[13] and ionic liquids (ILs)[14]. Many of these methodologies are associated with several shortcomings such as long reaction times, expensive reagents, harsh reaction conditions, low-product yields, occurrence of several side products, *etc*. A surge in activity has recently been noticed to develop environmentally benign procedures involving such chemicals/solvents that avoid or at least minimize these effects.

Recently, phosphonium ionic liquids (PILs), which differ from the well known imidazolium ionic liquids, have been introduced in organic reactions. Phosphonium ionic liquids are much more thermally stable than the corresponding imidazolium salts. This is very important for processes, which operate at temperatures higher than 100 ºC. In addition to being less thermally stable, in addition, imidazolium-based ionic liquids contains protons, which are not innocent. Phosphonium ionic liquids, on the other hand, have no such acidic protons and are easily recoverable by using three phase system (hexane/ionic liquid/water).

In the current strategy the reaction of *o*-phenylenediamine (OPD) with acyclic or cyclic ketones in a phosphonium ionic liquid was carried out at ambient temperature without addition of any extra catalyst to yield 1,5-benzodiazepines (**Scheme-I**).



1 **2** **3**

Scheme-I Synthesis of 1,5-benzodiazepines

NMR spectra were recorded on a Bruker MSL-300 spectrometer operation at 300 MHz for ^1H and 75 MHz for ^{13}C and Bruker AV-200 spectrometer operation at 200 MHz for ^1H and 50 MHz for ^{13}C. Spectra were obtained at 25 ºC in $CDCl_3$, solution and were referenced to the $CHCl_3$ peak (δ 7.26), for ^1H or to the center line of the $CDCl_3$, at δ 77, for ^{13}C, all chemical shifts are given as d values (ppm) relative to TMS. IR spectra were recorded on Perkin-Elmer FT-IR instrument. Melting points were determined by using a Yanco micro melting point apparatus and were uncorrected.

Column chromatography was carried out using 60-80 mesh silica gel. *o*-Phenylenediamine, cyclohexanone and ketones were purchased from Aldrich and were used without purification.

General procedure of benzodiazepine synthesis: *Ortho*-phenylenediamine (499 mg, 4.62 mmol) and ketone (9.72 mmol) in ionic liquid (3 mL) were stirred at ambient temperature. After completion of reaction the reaction mixture was diluted with water. Hexane-EtOAc (95:05) was added to establish the three-phase system and the products were extracted into the hexane layer. The hexane layer was separated, dried and concentrated under reduced pressure. It was further subjected to purification by column chromatography through silica-gel subjected to using 20 % EtOAc in petroleum ether as eluent and fully characterized. The ionic liquid layer separated and reused for the next run without noticeable effect on the product yield.

The reactions were performed in four different phosphonium ionic liquids (Fig. 1). The isolated yields of 1,5-benzodiazepines were excellent in relatively short reaction time (25-50 min). The results are summarized in Table-1. The products were characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. These spectral data and physical constants were comparable to those reported in the literature. The phosphonium ionic liquid could be recovered by three phase system, dried on high vacuum and recycled at least three times without incurring any loss in product yield.

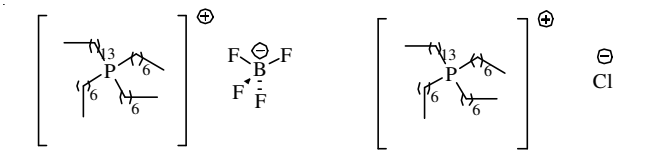


Fig. 1. Structures of various phosphonium ionic liquids

TABLE-1
SYNTHESIS OF 1,5-BENZADIAZOPINE FROM *o*-PHENYLENEDIAMINE

Compound	Ketone		Yield of 1,5-benzadiazopine (%)*/time (min)			
	R^1	R^2	PIL-1	PIL-2	PIL-3	PIL-4
3a	CH_3	H	58/40	79/25	54/40	59/45
3b	CH_3	CH_3	76/45	92/30	63/40	66/50
3c	Ph	H	73/50	88/30	76/45	69/50
3d	4-MePh	H	75/30	94/25	71/35	76/40
3e	3-NO_2Ph	H	43/50	56/35	49/50	44/45
3f	Cyclohexanone		74/45	78/40	50/50	56/50

*Isolated yield after column chromatography, PIL = Phosphonium ionic liquid.

It was found that PIL-2 and PIL-4 afforded the best results. Interestingly, cyclic ketones such as cyclohexanone also reacted well and equally efficiently with similar success to afford fused ring 1,5-benzodiazepines in high yields. It was also found that ketone having electron withdrawing group reduced the product yield. (Table-1, Entry 5).

Under similar conditions there was no reaction of acetone with *o*-phenylenediamine in the absence of phosphonium ionic liquid even after 8 h (Table-2, Entry 1), but an equimolar proportion of phosphonium ionic liquid yielded 98 % product in just 1 h. Thus highlighting the role of the phosphonium ionic liquid as a promoter (Table-2, Entry 4). Any excess of phosphonium ionic liquid beyond this proportion did not show any further increase in conversion and yield.

TABLE-2
CATALYTIC STUDY OF PIL-2 FOR THE SYNTHESIS OF BENZODIAZEPINE **3a** IN ACETONITRILE

Entry	Mol % of IL	Time (h)	Yield (%)
1	0	8	Nil
2	10	6	32
3	20	4	45
4	100	1	98

Conclusion

Catalytic property of new phosphonium-based ionic liquids chacked for the synthesis of 1,5-benzodiazepines. Phosphonium ionic liquids, which not only afforded the product in excellent yields but also avoid the problems associated with catalyst cost, handling, safety and pollution.

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