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[HSO_3-pmim][CH_3SO_3] as an Efficient Catalyst for the Synthesis of 1,5-Benzodiazepine Derivatives under Ultrasound Irradiation

CHENG LI[1,2], QING-HONG HAO[3], HAI-YAN LIU[1], CHUN WANG[1], JING-JUN MA[1,*] and WEN-GANG ZHU[1]

[1]Hebei Key Laboratory of Bioinorganic Chemistry, College of Sciences, Agricultural University of Hebei, Baoding 071001, P.R. China
[2]Department of Science and Technology Management, Agricultural University of Hebei, Baoding 071001, P.R. China
[3]College of Life Sciences, Agricultural University of Hebei, Baoding 071001, P.R. China

*Corresponding author: Fax: +86 312 7528292; Tel: +86 312 7528291; E-mail: mjjwjpmartin@sina.com

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1,5-Benzodiazepine derivatives were synthesized in moderate to excellent isolated yields by the condensation reactions of *o*-phenylenediamine and ketones catalyzed by [1-methyl-3-(3-sulphopropyl)imidazolium methyl sulphate] under ultrasound irradiation using *n*-hexane as solvent. This method is simple, effective and gives better yields.

Key Words: 1-Methyl-3-(3-sulphopropyl)imidazolium methyl sulphate, 1,5-Benzodiazepines, *o*-Phenylenediamines, Ultrasound.

INTRODUCTION

Benzodiazepines and their derivatives are very important compounds because of their easy functionalization and potential pharmacological properties[1a]. They are widely used as anticonvulsant[1a], analgesic[1a], hypnotic[1b], sedative[1b] and antidepressive agents[1c]. Besides their biological properties, benzodiazepine derivatives are also used as dyes for acrylic fibers[1c]. In addition, 1,5-benzodiazepines are valuable synthons used for the synthesis of other fused ring compounds such as triazolo-, oxazino-, oxadiazolo- or furano-benzodiazepines[1d-1h]. So the preparation of 1,5-benzodiazepines has received increasingly attention in recent years. But until now, comparatively few methods for their preparation had been reported in the literature[2a]. These include condensation reactions of *o*-phenylenediamine derivatives with α,β-unsaturated carbonyl compounds[2b], β-haloketones or ketones promoted by $BF_3{\cdot}OEt_2$[2c], $NaBH_4$[2d], polyphosphoric acid or SiO_2[2e], ceric ammonium nitrate (CAN)[2f], MgO/$POCl_3$[2g], $Yb(OTf)_3$[2h], Al_2O_3/P_2O_5 or AcOH under microwave conditions[2i,2j], Amberlyst-15 in ionic liquid[2k], $CeCl_3{\cdot}7H_2O$/NaI supported on silica gel[2l], $InBr_3$[2m] and $Sc(OTf)_3$[2a]. However, many of these methodologies have shortcomings, such as long reaction times, low yields of the products, drastic reaction conditions, co-occurrence of several side products and expensive reagents.

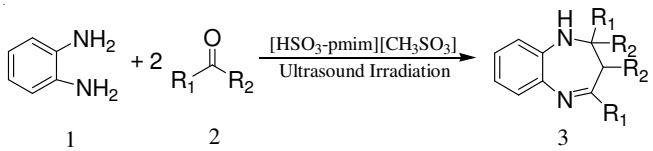
In recent years, ultrasound has increasingly been used in organic synthesis[3a]. As it is known, it can accelerate diverse types of organic reactions and it is established as an important technique in organic synthesis[3b]. Compared with traditional methods, this method is more convenient and easily controlled[3c]. A large number of organic reactions can be carried out with a higher yield, shorter reaction time and environmentally benign approach under ultrasonic irradiation[3d-3g].

Room temperature ionic liquids (RTILs) have received increasingly attention as potential "greener" alternatives to volatile organic solvent and they have been investigated extensively as a solvent or catalyst for many important organic reactions because of their special properties such as their negligible vapour pressure, tunable polarity, high thermal stability, good solvating ability, ease of recyclability and their potential to enhance reaction rates and selectivity[4]. They have also been referred as "designer solvents," as their properties can be altered by the fine-tuning of parameters such as the choice of organic cation, inorganic anion and alkyl chain attached to the organic cation. These structural variations offer flexibility to the chemist to devise the most idealized solvent and catalyst, catering for the needs of a particular process[5].

In continuing our endeavor in green synthesis and using ionic liquids as a recyclable reaction medium to enhance rates and selectivity[6], we report herein a mild and efficient protocol for the preparation of 1,5-benzodiazepine and their derivatives under ultrasound using acidic ionic liquids (1-methyl-3-(3-sulpho-propyl)imidazolium methyl sulphate ([HSO_3-pmim][CH_3SO_3])) as an efficient catalyst (**Scheme-I**).

EXPERIMENTAL

Melting points were recorded on an Electrothermal (Shanghai XRC-1) apparatus and are uncorrected. ^{1}H NMR



1 2 3

Scheme-I

(300 MHz) and ^{13}C NMR (50 MHz) spectra were determined with Bruker AVANCE 300 spectrometer ($CDCl_3$-d_6) using TMS as internal standard. Mass spectra were recorded on a Finnigan Mat 8230MSr operating 70 eV. IR spectra (cm^{-1}) were measured with a Braic WQF-510 spectrometer. Sonication was performed in a Shanghai Kudos CQX ultrasonic cleaner with a frequency of 59 kHz and a nominal power of 200 W. [HSO_3-pmim][CH_3SO_3] was synthesized according to the literature[7].

General procedure: A mixture of *o*-phenylenediamine (5 mmol), ketone (12 mmol) and [HSO_3-pmim][CH_3SO_3] (10 mmol %) in *n*-hexane (5 mL) was stirred rapidly under ultrasound irradiation for a certain period of time (Table-1) to complete the reaction (monitored by TLC). After completion, the reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 mL × 5 mL). The extract was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. Then, the crude product was subjected to column chromatography over silica gel using EtOAc:hexane (1:4) as eluent to afford pure 1,5-benzodiazepine. All the products were fully characterized by IR and ^1H NMR spectroscopy and melting points, which were consistent with the literature data.

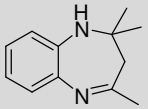
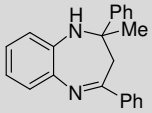
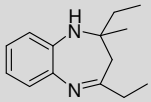
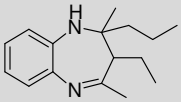
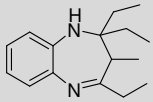
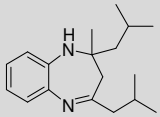
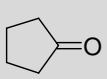
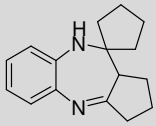
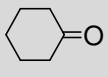
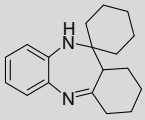
Spectroscopic data for compounds

Entry 3a: ^1H NMR (300 MHz, $CDCl_3$) δ_H: 1.35 (s, 6H), 2.22 (s, 2H), 2.38 (s, 3H), 3.45 (br, 1H), 6.65-7.21 (m, 4H); ^{13}C NMR (^1H-decoupled, 50 MHz, $CDCl_3$) δ_c: 29.8, 30.3, 45.0, 68.0, 121.5, 122.0, 125.3, 126.1, 137.8, 140.6, 171.8; EIMS: m/z (% relative intensity) = 187(100) [M^+], 170(50), 130(15), 105(15), 80(32), 65(20); IR (KBr, ν_{max}, cm^{-1}): 3280, 1650, 1590.

Entry 3b: ^1H NMR (300 MHz, $CDCl_3$) δ_H: 1.72 (s, 3H), 2.95 (d, 2H, *J* = 0.17 Hz), 3.12 (d, 2H, *J* = 0.17 Hz), 3.38 (br, 1H), 6.80-7.72 (m, 14H); ^{13}C NMR (^1H-decoupled, 50 MHz, $CDCl_3$) δ_c: 29.8, 43.3, 73.0, 121.4, 121.5, 125.3, 126.1, 126.8, 127.1, 127.6, 127.9, 128.5, 129.6, 137.8, 138.8, 140.1, 170.1; EIMS: m/z (% relative intensity) = 313(10) [M^+], 300(100), 235(25), 195(30), 105(15), 80(60), 45(80); IR (KBr, ν_{max}, cm^{-1}): 3350, 1645, 1592.

Entry 3c: ^1H NMR (300 MHz, $CDCl_3$) δ_H: 0.99 (t, 3H, *J* = 7.0 Hz), 1.25 (t, 3H, *J* = 7.1 Hz), 1.68 (q, 2H, *J* = 7.0 Hz), 2.14 (m, 2H), 2.32 (s, 3H), 2.70 (q, 2H, *J* = 7.1 Hz), 3.29 (br, 1H), 6.80-7.30 (m, 4H); ^{13}C NMR (^1H-decoupled, 50 MHz, $CDCl_3$) δ_c: 8.8, 10.7, 27.1, 35.3, 35.7, 43.0, 69.0, 121.5, 125.3, 126.1, 127.8, 137.8, 140.6, 175.8; EIMS: m/z (% relative intensity) = 215(15) [M^+], 141(5), 108(100), 80(35), 45(75); IR (KBr, ν_{max}, cm^{-1}): 3348, 1647, 1590.

TABLE-1
[HSO_3-pmim][CH_3SO_3] CATALYZED SYNTHESIS OF 1,5-BENZODIAZEPINES

Entry	Ketone	Product	Time (min)	Yield (%)	m.p. (ºC)	m.p.^{lit} (ºC)
a	CH_3COCH_3		30	95	139-141	137-139[2c,2h]
b	$PhCOCH_3$		60	90	150-151	151-152[2c,2h]
c	$CH_3COCH_2CH_3$		45	90	138-139	137-138[2c,2h]
d	$CH_3COCH_2CH_2CH_3$		50	95	138-140	139-140[8]
e	$CH_3CH_2COCH_2CH_3$		50	85	142-144	144-145[2c,2h]
f	$CH_3COCH_2CH(CH_3)_2$		50	88	118-119	118-120[9]
g			45	83	137-139	138-139[2c,2d,2g]
h			50	81	137-138	137-139[2c]

Entry 3d: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.78-1.48 (m, 13H), 2.40 (s, 3H), 2.89 (q, 1H, *J* = 7.0 Hz), 3.72 (br, 1H), 6.68-7.41 (m, 4H); ^{13}C NMR (^{1}H-decoupled, 50 MHz, $CDCl_3$) δ_c: 7.0, 8.1, 12.1, 13.0, 28.3, 29.6, 30.1, 46.0, 69.0, 117.2, 119.0, 128.1, 132.0, 139.8, 142.6, 175.5; EIMS: m/z (% relative intensity) = 244(30) [M^+], 230(25), 160(15), 215(100); IR (KBr, ν_{max}, cm^{-1}): 3348, 1655, 1592.

Entry 3e: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.83-1.52 (m, 14H), 2.33 (m, 2H), 2.93 (q, 1H, *J* = 7.0 Hz), 3.69 (br, 1H), 6.67-7.41 (m, 4H); ^{13}C NMR (^{1}H-decoupled, 50 MHz, $CDCl_3$) δ_c: 8.0, 9.1, 12.0, 13.5, 29.3, 35.1, 46.0, 69.2, 118.2, 119.0, 127.1, 131.0, 137.8, 142.6, 175.1; EIMS: m/z (% relative intensity) = 245(30) [M^+], 230(25), 160(15), 215(100); IR (KBr, ν_{max}, cm^{-1}): 3340, 1649, 1588.

Entry 3f: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.96-1.05 (m, 12H), 1.30 (s, 3 H), 1.49-1.50 (m, 2 H), 1.67-1.75 (m, 1H), 2.04-2.25 (m, 3 H), 2.24 (d, *J* = 12.7 Hz, 2 H), 6.62-6.65 (m, 1H), 6.85-6.90 (m, 2 H), 7.05-7.13 (m, 1H); ^{13}C NMR (^{1}H-decoupled, 50 MHz, $CDCl_3$) δ_c: 22.5, 22.9, 24.6, 24.8, 25.1, 26.3, 30.1, 44.0, 50.9, 69.2, 121.5, 121.8, 125.3, 127.1, 137.8, 140.6, 174.8; EIMS: m/z (% relative intensity) = 272(10) [M^+], 170(50), 160(15), 140(25), 105(100), 80(50), 55(15); IR (KBr, ν_{max}, cm^{-1}): 3330, 1655, 1589.

Entry 3g: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.02-2.23 (m, 13H), 3.24 (m, 2H), 3.72 (br, 1H), 6.58-7.21 (m, 4H); ^{13}C NMR (^{1}H-decoupled, 50 MHz, $CDCl_3$) δ_c: 23.5, 24.2, 24.6, 28.8, 33.5, 38.1, 40.0, 54.9, 67.2, 120.5, 120.8, 126.3, 131.5, 137.8, 143.6, 177.8; EIMS: m/z (% relative intensity) = 240(30) [M^+]; IR (KBr, ν_{max}, cm^{-1}): 3344, 1659, 1600.

Entry 3h: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.92-2.32 (m, 17H), 3.21 (m, 2H), 3.70 (br, 1H), 6.5-7.16 (m, 4H); ^{13}C NMR (^{1}H-decoupled, 50 MHz, $CDCl_3$) δ_c: 21.5, 21.8, 23.5, 24.6, 26.7, 33.5, 35.2, 38.8, 40.5, 52.9, 64.2, 120.9, 121.8, 126.3, 131.0, 137.0, 142.6, 180.1; EIMS: m/z (% relative intensity) = 270 (25) [M^+]; IR (KBr, ν_{max}, cm^{-1}): 3340, 1648, 1600.

RESULTS AND DISCUSSION

In our initial research, we studied the catalytic properties of [HSO_3-pmim][CH_3SO_3] for the synthesis of 1,5-benzodiazepine using *o*-phenylenediamine and acetone as substrates. The reaction was carried out using 10 mmol % [HSO_3-pmim][CH_3SO_3] in CH_2Cl_2 as solvent under ultrasound irradiation for 6 h to afford the corresponding 1,5-benzodiazepine in 56 % yield. Encouraged by this result, we studied different reaction parameters to optimize the reaction conditions. The reaction was performed in different solvents such as CH_3CN, CH_2Cl_2, C_2H_5OH and *n*-hexane. *n*-Hexane was found to be the best solvent in terms of yields and reaction time. The reaction was also conducted in solvent-free conditions but the yields were poorer compared to the yields obtained in *n*-hexane as solvent. Next, the loading amount of [HSO_3-pmim][CH_3SO_3] was also optimized (Table-2). The results indicated that 10 mmol % of [HSO_3-pmim][CH_3SO_3] is sufficient to promote reaction. The optimum yields of the product were obtained when a 1:2.4 ratio of *o*-phenylenediamine to ketones was used. No products were obtained when *o*-phenylenediamine was reacted with acetone under similar conditions in the absence of the [HSO_3-pmim][CH_3SO_3] even after stirring for 36 h, thus highlighting the role of the [HSO_3-pmim][CH_3SO_3] as a promoter. Any excess of [HSO_3-pmim][CH_3SO_3] beyond this loading did not show any further increase in conversion and yield. Use of less than the required catalyst loading resulted in poor yields.

TABLE-2
YIELD OF REACTIONS ON DIFFERENT QUANTITIES OF CATALYST[a]

Catalyst	0 (mmol %)	2 (mmol %)	5 (mmol %)	7 (mmol %)	10 (mmol %)	15 (mmol %)
Yield (%)	–	12	47	72	95	95

[a]The reaction time was 0.5 h.

Under the optimal reaction conditions, we investigated the reaction of a series of symmetrical and unsymmetrical ketones with *o*-phenylenediamine to get the corresponding 1,5-benzodiazepines (Table-1). In all cases, the reaction could proceed efficiently and complete in 30-60 min with yields ranged in 81-95 %.

Since the recovery and reuse of catalyst and solvent are highly preferable for a green process, so we investigated the reusability and recycling of the ionic liquid. After completion of the reaction, water was added into the reaction mixture and the solid was collected by filtration to give the product. The filtrate containing [HSO_3-pmim][CH_3SO_3] was concentrated under reduced pressure to recover the ionic liquid. The recycled [HSO_3-pmim][CH_3SO_3] was reused in the model reaction of **1** and **2a**. The catalytic activity of [HSO_3-pmim][CH_3SO_3] did not show any significant decrease even after five runs. The results are shown in Table-3. The results also indicate that the ionic liquid employed was stable under the reaction temperature.

TABLE-3
STUDIES ON THE REUSE OF THE [HSO_3-pmim][CH_3SO_3] FOR THE PREPARATION OF **3a**

Round	1	2	3	4	5
Yield (%)	95	93	91	90	87

Conclusion

We have demonstrated here a new and efficient procedure for the synthesis of 1,5-benzodiazepine derivatives catalyzed by [HSO_3-pmim][CH_3SO_3]. The advantages of our protocol are easy work-up, short reaction times, mild reaction condition, good yields which make the method an attractive and a useful contribution to present methodologies. The application studies of the task-specific ionic liquids for other reactions are in progress.

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