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Ytterbium Perfluorooctanesulfonate–Catalyzed Synthesis of 1,5-Benzodiazepine Derivatives in Fluorous Solvents

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Abstract: Ytterbium perfluorooctanesulfonate [$Yb(OPf)_3$] catalyses the highly efficient synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines in fluorous solvents. By simple separation of the fluorous phase containing only the catalyst, the reaction can be repeated several times.

Keywords: 2,3-dihydro-1*H*-1,5-benzodiazepines, fluorous biphasic catalysis, ytterbium perfluorooctanesulfonate

INTRODUCTION

Benzodiazepines are very important compounds, widely used in past decades as anticonvulsant, antianxiety, antitumor, psychosis, hypnotic, and antipyretic agents.[1] Some benzodiazepine derivatives are also used in industry, such as light-sensitive material,[2] and also as anti-inflammatory agents.[3] 1,5-Benzodiazepines are also used for preparation of some fused-ring benzodiazepine derivatives, such as triazol[4] and oxadiazol.[5]

Because of their wide range of pharmacological activity and industrial and synthetic applications, many methods for their preparation are reported in the literature. These include condensation reactions of *o*-phenylenediamine with α,β-unsaturated carbonyl compounds,[2,6] β-haloketones,[7] β-aminoketones,[8]

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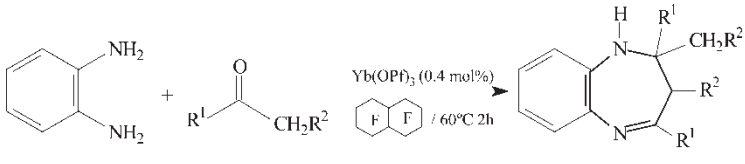
or ketones in the presence of BF_3-etherate,[9] $NaBH_4$,[10] polyphosphoric acid,[11] SiO_2,[11] MgO and $POCl_3$,[12] cerium (III) chloride/sodium iodide,[13] zirconia,[14] acetic acid,[15] and low-valent titanium.[16] However, all of these methods have problems, including drastic reaction conditions, low yields, and severe side reactions. Giri et al. reported a reusable and efficient heterogeneous catalyst, monoammonium salt of 12-tungstophosphoric acid $[(NH_4)H_2PW_{12}O_{40}]$, for the synthesis of 1,5-benzodiazepines.[17] Wu et al.[18] and Curini et al.[19] reported that ytterbium trichloride ($YbCl_3$) and ytterbium triflate [$Yb(OTf)_3$] respectively can catalyze the formation of 1,5-benzodiazepines from *o*-phenylenediamine and ketones in good to excellent yields. However, reusing these catalysts required tedious workup procedures such as filtration, purification, and drying.

Recently, a new kind of Lewis acid of rare earth (III) perfluorooctanesulfonates ($RE(OSO_2C_8F_{17})_3$, $RE(OPf)_3$, RE = Sc,Y, La∼Lu) has been of special interest because they have characteristic features such as low hygroscopicity, ease of handling, robustness for recycling, and high solubility in fluorous solvent.[20] On the other hand, perfluorocarbon solvents, especially perfluoroalkanes, have some unique properties that make them attractive alternatives for conventional organic solvents.[21] The compounds functionalized with perfluorinated groups often dissolve preferentially in fluorous solvents, and this property can be used to extract fluorous components from reaction mixtures.[22] As a part of our studies to explore the utility of lanthanide perfluorooctanesulfonate–catalyzed reactions in fluorous solvents,[23] we decided to investigate $Yb(OPf)_3$-catalyzed synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines by condensation of *o*-phenylenediamine with ketones (Scheme 1).

RESULTS AND DISCUSSION

$Yb(OPf)_3$ was capable of producing quantitive yields of 2,2,4-trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine by condensation of *o*-phenylenediamine with acetone in perfluorodecalin ($C_{10}F_{18}$, *cis* and *trans*-mixture). When using perfluorotoluene (C_7F_8) and perfluoromethylcyclohexane (C_7F_{14}) as fluorous solvents, the condensation also proceeded smoothly to give the desired product. However, perfluorotoluene is in fact miscible with reaction substrates such as acetone at room temperature. Thus, it is impossible to



Scheme 1.

recover the fluorous phase by phase separation. In addition, during repeated condensation reactions, the loss of fluorous solvent is very serious when using perfluoromethylcyclohexane (C_7F_{14}) as a fluorous solvent because it is very volatile (bp 76°C).

Thus, the use of the catalytic systems $Yb(OPf)_3/C_{10}F_{18}$ was extended to the synthesis of other 1,5-benzodiazepine derivatives as summarized in Table 1. As shown in Table 1, both acyclic and cyclic ketones react to give the corresponding 2,3-dihydro-1*H*-1,5-benzodiazepines in nearly quantitative yield. The reaction products were isolated and identified as 1,5-benzodiazepines, and no side reactions were observed. It is interesting to note that when using unsymmetrical ketones such as 2-butanone or 2-pentanone as substrates, the ring closure occurs selectively from only one side of the carbon skeleton, giving a single product. In addition, we found that a catalyst loading of only 0.4% was required when using fluorous phase technology, which is more effective than the 5% of $Yb(OTf)_3$ required to catalyze the condensation. When the reaction was finished, the reaction mixture was cooled to room temperature. The fluorous phase with $Yb(OPf)_3$ catalysts can separate from the organic layer and return to the bottom layer. Based on gas chromatography-mass spectrography (GC-MS) data, no loss of fluorous solvent to the organic phase can be detected. By simple phase separation, the separated fluorous phase containing only catalyst could be reused for the next reaction without any treatment and without any loss of activity. The condensations of *o*-phenylenediamine with acetone under the conditions mentioned previously were run for five consecutive cycles, furnishing the corresponding **1** with 99, 98, 99, 97, and 97% isolated yields.

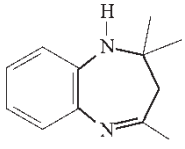
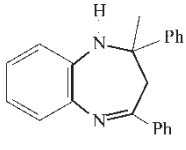
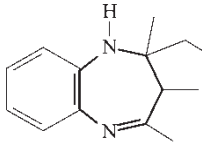
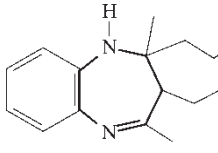
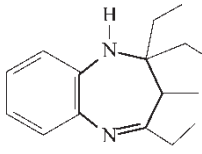
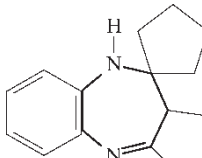
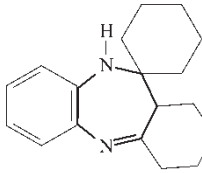
In conclusion, the use of $Yb(OPf)_3$ as catalyst in properly chosen fluorous solvents for preparation of 1,5-benzodiazepines can be considered an interesting new alternative to existing heterogeneous catalysts. The simple procedures as well as easy recovery and reuse of this novel catalytic system are expected to contribute to the development of more benign synthesis of benzodiazepines.

EXPERIMENTAL

Typical Procedure for Condensation of *o*-Phenylenediamine with Acetone

A mixture of $Yb(OPf)_3$ (67 mg, 0.04 mmol), *o*-phenylenediamine (1.08 g, 10 mmol), acetone (3.5 mL, 30 mmol), and perfluorodecalin ($C_{10}F_{18}$, *cis* and *trans*-mixture, 1.5 mL) was stirred at 60°C for 2 h. When the reaction was finished, the reaction mixture was cooled to room temperature. The fluorous layer on the bottom was separated for the next condensation. The upper organic phase was washed with water (10 mL), 10% $NaHCO_3$ solution (10 mL), and water (10 mL × 2) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on a silica-gel column (eluent: CH_2Cl_2/

Table 1. Yb(OPf)$_3$-catalyzed synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines in $C_{10}F_{18}$

Reactant	Product	Yield (%)[a]	Mp (°C)
Acetone	 **1**	99 (99[b], 98[c])	124–125 (lit.[8] 126)
Acetophenone	 **2**	99	150–151 (lit.[12] 151–152)
2-Butanone	 **3**	96	137–138 (lit.[12] 137–138)
2-Pentanone	 **4**	94	139–140
3-Pentanone	 **5**	95	142–143 (lit.[12] 144–145)
Cyclopentanone	 **6**	99	134–135 (lit.[8] 134)
Cyclohexanone	 **7**	92	137–138 (lit.[12] 137–139)

[a]Yields of pure isolated products, characterized by IR, GC-MS, ^{1}H NMR, and ^{13}C NMR.
[b,c]Perfluorotoluene and perfluoromethylcyclohexane as fluorous solvents respectively.

MeOH = 90/10) to give the condensation product. All the condensation products were adequately characterized by IR, ^{1}H NMR, ^{13}C NMR, and GC-MS. The products **1**, **2**, **3**, **5**, **6**, and **7** have been reported earlier.

Data

2,2,4-Trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine 1: white solid; mp 124–125°C; IR (KBr): ν 3290 (NH), 1642 (C═N), 1592 (Ar) cm^{-1}; ^{1}H NMR (300 MHz, TMS, $CDCl_3$) δ 1.34 (s, 6H, 2-CH_3), 2.20 (s, 2H, -CH_2), 2.36 (s, 3H, -CH_3), 3.45 (br, 1H, -NH), 6.62–7.21 (m, 4H, Ar); ^{13}C NMR (300 MHz, TMS, $CDCl_3$) δ 171.6, 140.4, 138.0, 126.9, 125.3, 121.8, 121.6, 68.1, 45.4, 30.6, 29.5, 29.5; GC/MS: $M^+ = 188$.

2,4-Diphenyl-2-methyl-2,3-dihydro-1*H*-1,5-benzodiazepine 2: yellow solid; mp 150–151°C; IR (KBr): ν 3342 (NH), 1635 (C═N), 1588 (Ar) cm^{-1}; ^{1}H NMR (300 MHz, TMS, $CDCl_3$) δ 1.76 (s, 3H, CH_3), 2.93 (d, 2H, -CH_2, $J = 0.17$ Hz), 3.10 (d, 2H, -CH_2, $J = 0.17$ Hz), 3.36 (br, 1H, -NH), 6.80–7.71 (m, 14H, Ar); ^{13}C NMR (50 MHz, TMS, $CDCl_3$) δ 167.4, 146.6, 140.2, 139.5, 138.2, 129.9, 128.6, 128.4, 128.1, 127.2, 127.2, 126.4, 125.7, 121.7, 121.6, 74.1, 43.0, 29.9; GC/MS: $M^+ = 312$.

2,3,4-Trimethyl-2-ethyl-2,3-dihydro-1*H*-1,5-benzodiazepine 3: yellow solid; mp 137–138°C; IR (KBr): ν 3338 (NH), 1637 (C═N), 1590 (Ar) cm^{-1}; ^{1}H NMR (300 MHz, TMS, $CDCl_3$) δ 0.98 (t, 3H, CH_3, $J = 7.0$ Hz), 1.24 (t, 3H, CH_3, $J = 7.1$ Hz), 1.69 (q, 2H, CH_2, $J = 7.0$ Hz), 2.16 (m, 2H, -CH_2), 2.34 (s, 3H, -CH_3), 2.69 (q, 2H, -CH_2, $J = 7.1$ Hz), 3.29 (br, 1H, -NH), 6.80–7.31 (m, 4H, Ar); ^{13}C NMR (50 MHz, TMS, $CDCl_3$) δ 175.6, 140.6, 138.1, 127.0, 126.2, 125.3, 121.6, 70.8, 42.1, 35.6, 35.6, 26.8, 10.6, 8.4; GC/MS: $M^+ = 216$.

2,4-Dimethyl-3-ethyl-2-(*n*-propyl)-2,3-dihydro-1*H*-1,5-benzodiazepine 4: yellow solid; mp 139–140°C; IR (KBr): ν 3336 (NH), 1640 (C═N), 1589 (Ar) cm^{-1}; ^{1}H NMR (300 MHz, TMS, $CDCl_3$) δ 0.76–1.48 (m, 13H), 2.38 (s, 3H, CH_3), 2.89 (q, 1H, CH, $J = 7.0$ Hz), 3.70 (br, 1H, -NH), 6.68–7.43 (m, 4H, Ar); ^{13}C NMR (50 MHz, TMS, $CDCl_3$) δ 173.8, 142.2, 139.6, 132.7, 126.8, 118.1, 117.3, 68.2, 45.9, 30.4, 28.3, 28.0, 12.2, 11.6, 7.8, 7.3; GC/MS: $M^+ = 244$.

2,2,4-Triethyl-3-methyl-2,3-dihydro-1*H*-1,5-benzodiazepine 5: yellow solid; mp 142–143°C; IR (KBr): ν 3330 (NH), 1639 (C═N), 1586 (Ar) cm^{-1}; ^{1}H NMR (300 MHz, TMS, $CDCl_3$) δ 0.80–1.52 (m, 14H), 2.33 (m, 2H, CH_2), 2.91 (q, 1H, CH, $J = 7.0$ Hz), 3.69 (br, 1H, -NH), 6.66–7.40 (m, 4H, Ar); ^{13}C NMR (50 MHz, TMS, $CDCl_3$) δ 173.8, 142.0, 139.6, 132.7, 126.8, 118.0, 117.4, 68.3, 46.2, 35.4, 28.3, 28.0, 12.2, 11.6, 7.8, 7.3; GC/MS: $M^+ = 244$.

10-Spirocyclopentan-1,2,3,9,10,10a-hexahydrobenzo[b]-cyclopenta[e][1,4] diazepine 6: yellow solid; mp 134–135°C; IR (KBr): ν 3334 (NH), 1658

(C═N), 1600 (Ar) cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$) δ 1.01–2.24 (m, 13H), 3.26 (m, 2H, CH_2), 3.72 (br, 1H, -NH), 6.58–7.23 (m, 4H, Ar); ^{13}C NMR (50 MHz, TMS, $CDCl_3$) δ 178.0, 143.2, 139.6, 132.2, 126.8, 119.1, 118.6, 68.0, 54.3, 39.2, 38.4, 33.3, 28.9, 24.2, 24.0, 23.6; GC/MS: $M^+ = 240$.

10-Spirocyclohexan-2,3,4,10,11,11a-hexahydro-*1H*-dibenzo[b,e][1,4]diazepine 7: yellow solid; mp 137–138°C; IR (KBr): ν 3300 (NH), 1642 (C═N), 1600 (Ar) cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$) δ 0.96–2.36 (m, 17H), 3.24 (m, 2H, CH_2), 3.70 (br, 1H, -NH), 6.56–7.18 (m, 4H, Ar); ^{13}C NMR (50 MHz, TMS, $CDCl_3$) δ 178.4, 142.7, 138.0, 129.4, 126.5, 121.4, 121.2, 63.0, 52.8, 40.6, 39.2, 34.3, 33.3, 25.4, 24.3, 23.2, 21.7, 21.7; GC/MS: $M^+ = 268$.

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