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Ytterbium triflate promoted synthesis of 1,5-benzodiazepine derivatives

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Abstract—2,3-Dihydro-1*H*-1,5 benzodiazepines have been synthetized in very good yield in solvent-free conditions from *o*-phenylendiamine and ketones in the presence of $Yb(OTf)_3$ as catalyst. The method is applicable to both cyclic or acyclic ketones without significant differences.

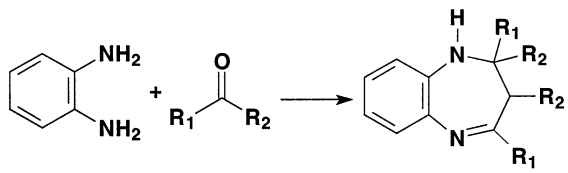
Benzodiazepines are very important compounds, widely used in the last decades as anticonvulsant, antianxiety and hypnotic agents. In addition to the well known pharmacological profile of 1,4-benzodiazepines, it has been shown that also some 1,5-benzodiazepines exert a biological activity, similar to 1,4-derivatives.[1] Moreover, 1,5-benzodiazepines are valuable synthons used for the preparation of other fused ring compounds such as triazolo-[2] or oxadiazolo-benzodiazepines.[3]

Although 1,5-benzodiazepines are interesting compounds from a pharmacological, industrial and synthetic point of view, few methods for their preparation are reported in the literature. These include condensation reactions of *o*-phenylendiamine, as free base or hydrochloride, with α,β-unsaturated carbonyl compounds,[4] β-haloketones[5] or ketones in the presence of BF_3–etherate,[6] $NaBH_4$,[7] polyphosphoric acid,[8] SiO_2,[8] MgO and $POCl_3$.[9] Unfortunately, many of these processes suffer major or minor limitations, such as drastic reaction conditions, low yields, tedious work-up procedures and co-occurrence of several side reactions.

During the last decade rare earth metal triflates have been found as unique Lewis acids in that they are water tolerant reusable catalysts and they can effectively promote several carbon–carbon bond formation reactions in good yield.[10] As a part of our studies to explore the utility of lanthanide triflates catalyzed reactions in solvent-free conditions, we decided to investigate the use of $Yb(OTf)_3$ as a catalyst for the preparation of substituted 2,4-dihydro-1*H*-1,5-benzodiazepines by condensation of ketones with *o*-phenylendiamine (Scheme 1).

The reaction was carried out neat at room temperature for 4 h, using ketone (2.1 mmol) and *o*-phenylendiamine (1 mmol) in the presence of $Yb(OTf)_3$. The results are summarized in Table 1.

As shown in Table 1, both acyclic and cyclic ketones react without any significant difference to give the corresponding 2,4-dihydro-1*H*-1,5-benzodiazepines in nearly quantitative yield. It is noteworthy that, starting from unsymmetrical ketones such as 2-butanone or 6-methyl-5-hepten-2-one, the ring closure occurs selectively only from one side of the carbon skeleton giving a single product. Best results were obtained using 0.05 equivalents of $Yb(OTf)_3$, lower loading resulted in lower yields, while upper loading did not increase reaction times significantly. The catalyst, recovered by filtration from the reaction media can be reused several times without any loss of activity.[11] In addition, it is interesting to note that other lanthanide triflates, used



Scheme 1.

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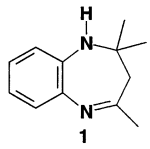
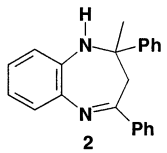
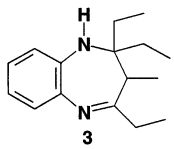
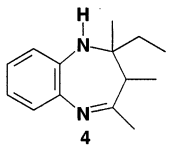
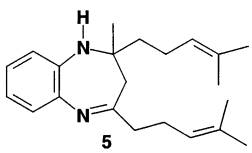
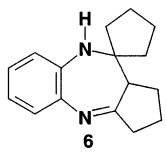
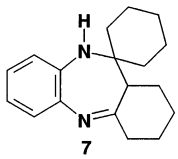
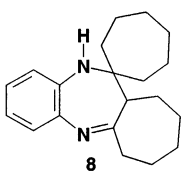
Table 1. $Yb(OTf)_3$ catalyzed formation of 2,3-dihydro-1*H*-1,5 benzodiazepines

Reactant	Product	Yield %[a]
Acetone	 1	96
Acetophenone	 2	99
3-Pentanone	 3	95
2-Butanone	 4	93
6-Methyl-5-hepten-2-one	 5	99
Cyclopentanone	 6	99
Cyclohexanone	 7	89
Cycloheptanone	 8	88

[a]Yields of pure isolated products, characterized by IR, GC-MS, ^{1}H NMR and ^{13}C NMR.

as catalysts in the same reaction conditions, namely $La(OTf)_3$ or $Eu(OTf)_3$, yielded a complex mixture of products. The mechanism of the reaction probably involves an intramolecular imine–enamine cyclisation promoted by $Yb(OTf)_3$, as already reported by Jung and coworkers by using polyphosphoric acid or SiO_2.[8]

In summary, a simple work-up procedure, mild reaction conditions, selectivity and very good yields make our methodology a valid contribution to the existing processes in the field of 1,5-benzodiazepine derivatives synthesis.

Experimental

Typical procedure: A mixture of *o*-phenylenediamine (1 mmol) and ketone (2.1 mmol) was well stirred with $Yb(OTf)_3$ (0.05 mmol) at room temperature for 4 h. CH_2Cl_2 (2 ml) was added to crystallize $Yb(OTf)_3$; the catalyst was removed under reduced pressure and the residue was purified by SiO_2 gel column chromatography using CH_2Cl_2/MeOH 95:5 as eluent.

2,2,4-Trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine (1): yellow solid; mp 137–139°C; IR; ^{1}H NMR;[9] ^{13}C NMR;[7] GC/MS: $M^+ = 188$.

2-Methyl-2,4-diphenyl-2,3-dihydro-1*H*-1,5-benzodiazepine (2): yellow solid; mp 151–152°C; IR 3330 (s br), 1635 (s) cm^{-1}; ^1H NMR;[8] ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.5, 146.6, 140.1, 139.5, 138.2, 129.8, 128.6, 128.4, 128.1, 127.1, 127.1, 126.4, 125.5, 121.7, 121.5, 73.9, 43.0, 29.9; GC/MS: $M^+=312$.

2,2,4-Triethyl-3-methyl-2,3-dihydro-1*H*-1,5-benzodiazepine (3): yellow solid; mp 144–145°C; IR 3330 (s br), 1638 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.76–1.48 (m, 13H), 1.61 (s, 3H), 2.87 (q, 1H, $J=7.0$ Hz), 3.75 (s br, 1H), 6.65–7.40 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.8, 142.4, 139.0, 132.7, 126.7, 118.0, 117.5, 68.7, 46.2, 35.6, 28.4, 28.0, 12.2, 11.5, 7.8, 7.3; GC/MS: $M^+=244$.

2,4-Diethyl-2-methyl-2,3-dihydro-1*H*-1,5-benzodiazepine (4): yellow solid; mp 137–138°C; IR 3330 (s br), 1637 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.98 (t, 3H, $J=7.0$ Hz), 1.26 (t, 3H, $J=7.1$ Hz), 1.69 (q, 2H, $J=7.0$ Hz), 2.12 (m, 2H), 2.35 (s, 3H), 2.69 (q, 2H, $J=7.1$ Hz), 3.25 (s br, 1H), 6.75–7.30 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.4, 140.8, 137.9, 127.0, 126.1, 125.3, 121.8, 70.6, 42.1, 35.6, 35.6, 26.9, 10.6, 8.5; GC/MS: $M^+=216$.

2-Methyl-2,4-di(4-methyl-3-pentenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine (5): yellow solid; mp 158–160°C; IR 3330 (s br), 1638 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.66 (s, 3H), 1.68 (s, 3H), 1.73 (s, 3H), 1.74 (s, 3H), 2.01–2.70 (m, 10H), 3.15 (s br, 1H), 5.03–5.24 (m, 2H), 6.67–7.19 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.7, 140.6, 137.9, 132.2, 131.9, 127.0, 125.48, 123.8, 123.4, 121.8, 121.7, 70.6, 43.0, 42.9, 42.7, 27.5, 25.7, 25.7, 25.1, 23.0, 17.7, 17.7; GC/MS: $M^+=324$.

10-Spirocyclopentan-1,2,3,9,10,10a-hexahydrobenzo[*b*]-cyclopenta[*e*][1,4]diazepine (6): yellow solid; mp 138–139°C; IR; ^1H NMR;[6] ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.1, 143.4, 139.1, 132.0, 126.9, 119.3, 118.6, 67.2, 54.3, 39.2, 38.3, 33.3, 28.9, 24.2, 24.0, 23.4; GC/MS: $M^+=240$.

10-Spirocyclohexan-2,3,4,10,11,11a-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepine (7): yellow solid; mp 137–139°C; IR; ^1H NMR;[6] ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.6, 142.7, 138.0, 129.4, 126.3, 121.4, 121.2, 63.0, 52.5, 40.5, 39.2, 34.3, 33.1, 25.3, 24.3, 23.2, 21.7, 21.7; GC/MS: $M^+=268$.

10-Spirocycloheptan-6,7,8,9,10,10a,11,12-octahydrobenzo[*b*]cyclohepta[*e*][1,4]diazepine (8): yellow solid; mp 136–137°C; IR; ^1H NMR;[6] ^{13}C NMR;[7] GC/MS: $M^+=296$.

Acknowledgements

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11. The reaction to yield compound **1** has been repeated five times, through the catalyst washed with dichloromethane and dried for 2 h at 70°C with the following yields: 96, 95, 96, 93, 93%.