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Scandium(III) triflate as an efficient and reusable catalyst for synthesis of 1,5-benzodiazepine derivatives

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Abstract—2,3-Dihydro-1*H*-1,5-benzodiazepines have been synthesized in solvent-free conditions in excellent yield from *o*-phenylenediamines and ketones in the presence of a catalytic amount of $Sc(OTf)_3$. This method is a very easy, rapid, and high yielding reaction for the synthesis of 1,5-benzodiazepine derivatives.

Benzodiazepines are very important compounds because of their pharmacological properties. Most of the members of this family have wide applications in medicinal chemistry such as tranquilizing, anticonvulsant, antianxiety, and hypnotic agents.[1] In addition, 1,5-benzodiazepines are valuable synthons used for the preparation of other fused ring compounds such as triazolo,[2] oxazino or furano-benzodiazepines.[3] Benzodiazepine derivatives also find commercial use in photography[4] (as dyes for acrylic fibers) and also as anti-inflammatory agents.[5]

Despite their importance from a pharmacological, industrial, and synthetic point of view, comparatively few methods for the preparation of 1,5-benzodiazepines have been reported. These include condensation reaction of *o*-phenylenediamines with α,β-unsaturated carbonyl compounds,[6] β-haloketones[7] or ketones in the presence of BF_3–OEt_2,[8] $NaBH_4$,[9] polyphosphoric acid,[10] SiO_2,[10] MgO and $POCl_3$,[11] AcOH under microwave irradiation,[12] and ionic liquid.[13] Unfortunately, many of these processes suffer from one or other limitations such as drastic reaction conditions, low yields, tedious work-up procedures, relatively long reaction times, and co-occurrence of several side reactions. Moreover, the main disadvantage of almost all existing methods is that the catalysts are destroyed in the work-up procedure and cannot be recovered or reused. Therefore, the search continues for a better catalyst for the synthesis of 1,5-benzodiazepines in terms of operational simplicity, reusability, economic viability, and greater selectivity.

In recent years, scandium triflate has received considerable attention as a mild Lewis acid for an array of organic transformations[14] because the catalyst is quite stable in water and is reusable. The catalyst scandium triflate [$Sc(OTf)_3$] is commercially available and can be used for the preparation of 1,5-benzodiazepines from *o*-phenylenediamines and ketones. In continuation of our work to develop new synthetic methodologies,[15] we report herein a facile method for the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines by the condensation of *o*-phenylenediamine with ketones in the presence of a catalytic amount of $Sc(OTf)_3$ under solvent-free conditions.

The reactions were carried out in neat at room temperature for 3 h by taking a 1:2.2 mol ratio mixture of *o*-phenylenediamine and the ketone in the presence of 5 mol % $Sc(OTf)_3$ to give the desired products (Scheme 1) in excellent yield.[16,17] 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 good yield. It is noteworthy that starting from unsymmetrical ketone such as 2-butanone (entry 3), the ring closure occurs selectively only from one side of carbon skeleton yielding a single product. Among the various metal triflates such as $Cu(OTf)_2$, $La(OTf)_3$, $Lu(OTf)_3$, $Nd(OTf)_3$, and $Ce(OTf)_3$ studied for this reaction, $Sc(OTf)_3$ was found to be the most effective catalyst in terms of conversion and reaction rates. The scope and generality of this process is

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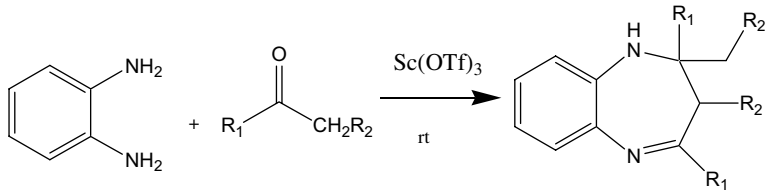
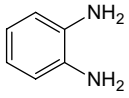
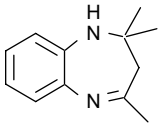
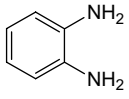
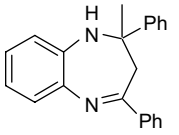
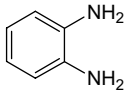
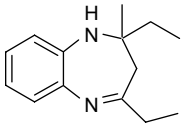
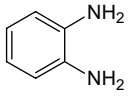
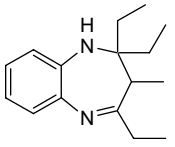
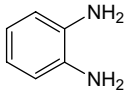
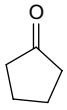
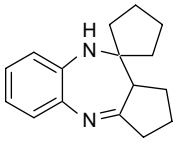
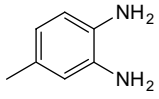
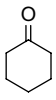
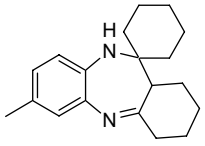
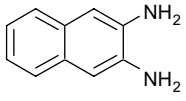
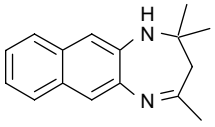
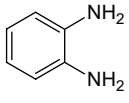
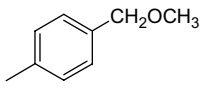
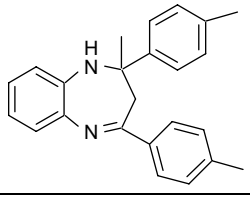


Scheme 1.

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

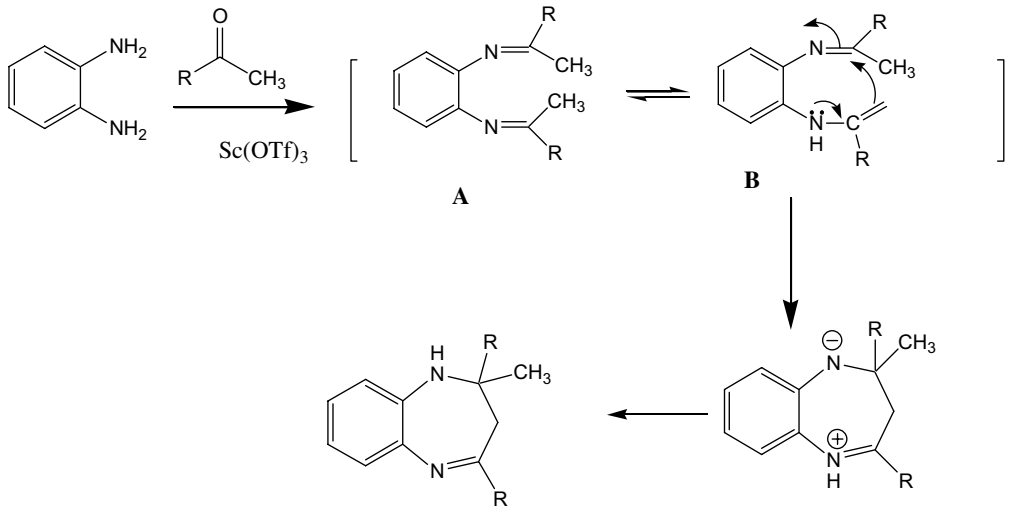
Entry	Substrate	Ketone	Product	Yield[a] (%)
1		CH_3COCH_3		96
2		$PhCOCH_3$		93
3		$CH_3COCH_2CH_3$		90
4		$CH_3CH_2COCH_2CH_3$		89
5				87
6				91
7		CH_3COCH_3		81
8				84

[a] Yields refer to isolated pure products and were characterized by NMR and MS spectra.

illustrated with respect to various cyclic and acyclic ketones and the results are summarized in Table 1.

The mechanism of the reaction[6–13] probably involves an intramolecular imine–enamine cyclization promoted by $Sc(OTf)_3$ as shown in Scheme 2. Amine of *o*-phenylenediamine attacks carbonyl group of ketone giving the intermediate diimine **A**. A 1,3-shift of the hydrogen attached methyl group then occurs to form an isomeric enamine **B**, which cyclizes to afford seven-membered ring.

In conclusion, we describe a mild and efficient method for the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines. The easy work-up procedure, recyclable catalyst,



Scheme 2.

short reaction times, selectivity, and very good yields make this method a valid contribution to the existing methodologies.

References and notes

1. (a) Schutz, H. In *Benzodiazepines*; Springer: Heidelberg, 1982; Vol. 2, p 240; (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., Ress, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 1, p 166.
2. Aversa, M. C.; Ferlazzo, A.; Giannetto, P.; Kohnke, F. H. *Synthesis* **1986**, 230.
3. Chimirri, A.; Grasso, S.; Ottana, R.; Romeo, G.; Zappala, M. *J. Heterocycl. Chem.* **1990**, *27*, 371.
4. Harris, R. C.; Straley, J. M. U.S. Patent 1,537,757, 1968; *Chem. Abstr*. **1970**, *73*, 100,054w.
5. De Baun, J. R.; Pallos, F. M.; Baker, D. R. U.S. Patent 3,978.227, 1976; *Chem. Abstr*. **1977**, *86*, 5498d.
6. Stahlofen, P.; Ried, W. *Chem. Ber.* **1957**, *90*, 815.
7. Ried, W.; Torinus, E. *Chem. Ber.* **1959**, *92*, 2902.
8. Herbert, J. A. L.; Suschitzky, H. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2657.
9. Morales, H. R.; Bulbarela, A.; Contreras, R. *Heterocycles* **1986**, *24*, 135.
10. 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.
11. Balakrishna, M. S.; Kaboudin, B. *Tetrahedron Lett.* **2001**, *42*, 1127.
12. Minothora, P.; Julia, S. S.; Constantinos, A. T. *Tetrahedron Lett.* **2002**, *43*, 1755.
13. Jarikote, D. V.; Siddiqui, S. A.; Rajagopal, R.; Thomas, D.; Lahoti, R. J.; Srinivasan, K. V. *Tetrahedron Lett.* **2003**, *44*, 1835.
14. (a) Kobayashi, S. *Eur. J. Org. Chem.* **1999**, *73*, 4961; (b) Kobayashi, S.; Siguira, M.; Kitagawa, H.; Lam, W. W. *Chem. Rev.* **2002**, *102*, 2227.
15. (a) De, S. K. *Tetrahedron Lett.* **2003**, *44*, 9055; (b) De, S. K. *Tetrahedron Lett.* **2004**, *45*, 1035; (c) De, S. K. *Tetrahedron Lett.* **2004**, *45*, 2339; (d) De, S. K. *Tetrahedron Lett.* **2004**, *45*, 2919; (e) De, S. K.; Gibbs, R. A. *Tetrahedron Lett.* **2004**, *45*, 7407; (f) De, S. K.; Gibbs, R. A. *Tetrahedron Lett.* **2004**, *45*, 8141.
16. General procedure: a mixture of *o*-phenylenediamine (5 mmol) and ketone (11 mmol) was stirred at room temperature in the presence of $Sc(OTf)_3$ (5 mol %) for 3 h. After completion of the reaction (TLC), the reaction mixture was diluted with ethyl acetate (40 mL), washed with water (15 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by silica gel column chromatography (15% ethyl acetate in hexane) to afford the pure product. All reactions were completed within 3 h. All products were characterized by comparison of their mp, ^1H NMR spectra with those of authentic samples. The aqueous layer containing the catalyst could be evaporated under reduced pressure to give a white solid. The IR spectrum of the recovered catalyst was identical to that of the commercially available catalyst (Aldrich), which could be reused for the next reaction with only a modest loss in activity. The catalyst has been recovered and reused for four times (reaction yields 96%, 92%, 83%, 74%).
17. Selected data: *2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine* (entry 1): ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 6H), 2.26 (s, 2H), 2.34 (s, 3H), 3.46 (br s, 1H), 6.61–7.28 (m, 4H); EIMS *m/z* 188 (M^+). *2,4-Diethyl-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine* (entry 3): ^1H NMR (300 MHz, $CDCl_3$): δ 0.97 (t, $J = 7.2$ Hz, 3H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.69 (q, $J = 7.2$ Hz, 2H), 2.14 (m, 2H), 2.34 (s, 3H), 2.69 (q, $J = 7.1$ Hz, 2H), 3.28 (br s, 1H), 6.73–7.32 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.6, 10.5, 26.8, 35.5, 35.6, 42.1, 70.6, 121.8, 125.4, 126.1, 127.0, 137.8, 140.8, 175.5; MS *m/z* 216 (M^+).