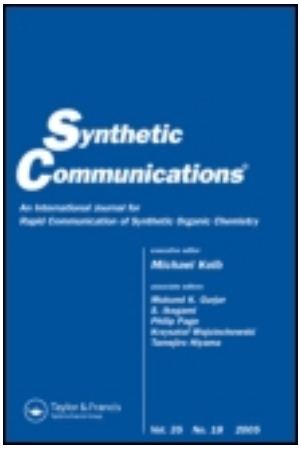

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$SbCl_3$-Al_2O_3-Catalyzed, Solvent-Free, One-Pot Synthesis of Benzo[b]1,4-diazepines

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$SbCl_3$-Al_2O_3–Catalyzed, Solvent-Free, One-Pot Synthesis of Benzo[b]1,4-diazepines

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Abstract: This article explores the use of antimony(III) chloride adsorbed on neutral alumina as an efficient catalyst for the one-pot synthesis of benzo[b]1,4-diazepines (83–94%) under solvent-free conditions. The process is easy, efficient, ecofriendly, and economical.

Keywords: Antimony(III) chloride, benzo[b]1,4-diazepines, solid-supported reagents, sun rays

INTRODUCTION

Considerable interest has been focused on the synthesis of benzodiazepines because of their wide range of biological activities and therapeutic uses.[1a,1b] In addition to their well-known anxiolytic, anticonvulsant, sedative, and muscle-relaxant activities found in therapeutics,[2] benzodiazepines also exhibit activities as antibiotics[3a,3b] anti-HIV agents,[4a,4b] and farnesyltransferase inhibitors.[5] Because of their rich therapeutic value, efficient methods for their preparation are continually being developed. However, the most commonly employed methods involve the cyclocondensation of 1,2-diamines with ketones,[6] enones,[7] or β-haloketones[8] in the presence of acid catalysts such as BF_3-etherate,[9] $NaBH_4$,[10] polyphosphroic acid-SiO_2,[11] MgO-$POCl_3$,[12] Yb(OTf),[13] Al_2O_3-P_2O_5,[14] AcOH,[15] SO_4^{2-}-ZrO_2,[16] $Ag_3PW_{12}O_{40}$,[17] Zn [L-proline]$_2$,[18] and ionic liquids.[19]

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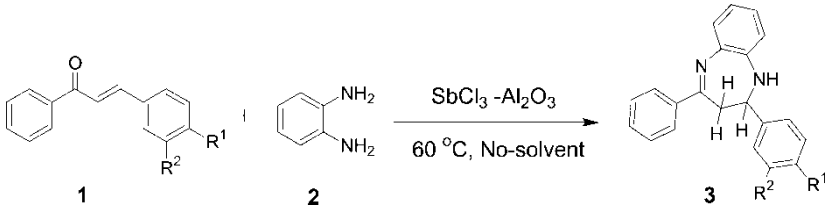
In our earlier communication,[20] $SbCl_3$-Al_2O_3 was used as an efficient catalyst for the synthesis of several dimeric quinazolines in solvent-free conditions. In view of the advantages associated with solvent-free reactions[21] such as easy handling, simple equipment, less environmentally hazardous reactions, time and energy efficiency, and low capital outlay for scaling, we thought to explore the usage of $SbCl_3$-Al_2O_3 as a catalyst to synthesize benzo[b]1,4-diazepines from o-phenylene diamine and benzylidene acetophenones under solvent-free conditions. When a mixture of o-phenylene diamine and various benzylidene acetophenones (Table 1) and 1.6 mol% of $SbCl_3$ as $SbCl_3$-Al_2O_3 was heated at 60°C in an oil bath under solvent-free conditions, the formation of the desired products was observed, which was supported by the spectroscopic data, particularly the ^{1}H NMR spectra of 3a–g, by the indicative appearance of the ABM–spin system with characteristic geminal and vicinal coupling constant for the methylene group resonances ($^2J = 9$–11 Hz, $^3J = 4$–5.5 Hz, $^3J = 9$–11 Hz) and the vicinal coupling constants for methine resonances ($^3J = 5$–5.5 Hz, ^{3}J = 9–11 Hz). The IR spectra and HRMS of compounds 3a–g are also in agreement with the structures envisaged. Similar product formation was observed in about 45 min when the previously mentioned mixture was exposed to sun rays. Although the yields of the products were comparable to that in the oil bath at 60°C, we did not pursue it further, keeping in view the impracticality of the procedure because the sun rays cannot be delivered/diverted to the reaction place in the laboratory. However, when this reaction was carried out in the dark at room temperature, only 30% conversion to the product benzo[b]1,4-diazepine was noticed after 24 h. No formation of the products occured

Table 1. $SbCl_3$-Al_2O_3–catalyzed solvent-free one-pot formation of benzo[b]1,4-diazepines



1 2 3

Entry	R^1	R^2	Product 3	Time (min)	Yield (%)
1	H	H	a	120	94
2	Cl	H	b	90	92
3	OCH_3	H	c	120	85
4	H	Cl	d	100	90
5	F	H	e	80	88
6	Br	H	f	110	83
7	CH_3	H	g	70	84

when the reaction was carried out with $SbCl_3$ or Al_2O_3 alone as catalysts either in solvent-free conditions or in the presence of a solvent ($CHCl_3$). Here the role of sun rays seems to be providing the heat energy to the reaction.

The substrates benzylidene acetophenones 1a–1 g were prepared by the well-known Claisen–Schmidt condensation process.[22] The substrates 1a–1 g were allowed to react with o-phenylene diamine using Sb(III) chloride–Al_2O_3 as catalyst at 60°C in an oil bath without any solvent. The resulting products 3a–3 g were obtained in good yields (83–94%) after simple workup followed by purification by column chromatography.

In conclusion, an efficient, simple, one-pot, solvent-free synthesis of benzo[b]1,4-diazepines has been accomplished from o-phenylene diamine and benzylidene acetophenones in the presence of $SbCl_3$-Al_2O_3.

EXPERIMENTAL

Melting points were measured in open capillaries on a Perfit melting-point apparatus and are uncorrected. IR spectra on KBr were recorded on Brucker-4800 infrared spectrometer. ^{1}H NMR and HRMS spectra were recorded on Brucker Ac-200 (200-MHz) spectrometer and JEOL D-300 mass spectrometer at 70 eV respectively. The progress of the reaction was monitored by TLC (0.5-mm-thick plates using BDH silica gel G as adsorbent). The plates were developed with ceric ammonium sulfate in H_2SO_4, and the compounds were observed as black spots without heating. Development of plates with Draggendroff reagent resulted in orange spots. All solvents were distilled before use. Column chromatography was performed on silica gel (100–200 mesh), and compounds were eluted with graded solvent systems of petroleum ether (40–60) and ethylacetate. Recrystallization was achieved with a $CHCl_3$–petroleum ether (40–60) solvent system.

Synthesis of Catalyst

The catalyst was prepared by the same procedure as described in our earlier communication.[20]

General Procedure for Synthesis of 3a–3 g

The benzylidene acetophenone derivatives 1a–1 g (10 mmol), o-phenylene diamine (10 mmol), and $SbCl_3$-Al_2O_3 catalyst (3.17 g) were thoroughly ground in a pestle-mortar and transferred to a round-bottom flask. This round-bottom flask was heated in an oil bath at 60°C until the completion of the reaction (TLC). Ethylacetate (50 ml) was added to the reaction mixture after cooling to room temperature, and the resultant heterogeneous solution was stirred for 5 min and filtered to remove the insoluble materials.

The filterate was dried over anhydrous Na_2SO_4. The solvent was removed, and the residue was column chromatographed to obtain solid products, which were further recrystallized (83–94% yield).

2,4-Diphenyl-1H,2H,3H-benzo [b]1,4-diazepine 3a: Yellowish needles (94%), mp 130–131°C. IR (ν, cm^{-1}): 3440, 3350, 3067, 2890, 1604, 1508, 1466, 1210, 834, 770. ^{1}H NMR ($CDCl_3$): δ 7.8–6.8 (m, 14H aromatic), 5.1 (dd, 1H, $J = 4$ and 8 Hz), 3.9 (brs, 1 × NH, D_2O exchangeable), 3.1 (dd, 1H, $J = 4$ and 10 Hz), 3.0 (dd, 1H, $J = 8$ and 10 Hz). HRMS: m/z at 298.3794 (M^+) 100% (calc. for $C_{21}H_{18}N_2$, 298.3896).

2-(4-Chlorophenyl)-4-phenyl-1H,2H,3H-benzo[b]1,4-diazepine 3b: Yellow crystal (92%), mp 110–112°C. IR (ν, cm^{-1}): 3455, 3367, 3045, 2900, 1609, 1516, 1470, 1204, 840, 777. ^{1}H NMR ($CDCl_3$): δ 7.9– 6.75 (m, 13H aromatic), 5.2 (dd, 1H, $J = 4.5$ and 9 Hz), 3.6 (brs, 1 × NH, D_2O exchangeable), 3.2 (dd, 1H, $J = 4.5$ and 11 Hz), 3.1 (dd, 1H, $J = 9$ and 11 Hz). HRMS: m/z at 332.8341 (M^+) 100% (calc. for $C_{21}H_{17}ClN_2$, 332.8344).

2-(4-Methoxyphenyl)-4-phenyl-1H,2H,3H-benzo[b]1,4-diazepine 3c: Yellow solid (85%), mp 64–65°C. IR (ν, cm^{-1}): 3433, 3328, 2872, 1600, 1514, 1454, 1200, 872, 758. ^{1}H NMR ($CDCl_3$): δ 7.8–6.7 (m, 13H aromatic) 5.3 (dd, 1H, $J = 4.2$ and 8 Hz), 3.8 (brs, 1 × NH, D_2O exchangeable), 3.4 (s, 3H), 3.2 (dd, 1H, $J = 4.2$ and 10 Hz) 3.0 (dd, 1H, $J = 8$ and 10 Hz). HRMS: m/z at 328.4158 (M^+) 100% (calc. for $C_{22}H_{20}N_2O$, 328.4160).

2-(3-Chlorophenyl)-4-phenyl-1H,2H,3H-benzo[b]1,4-diazepine 3d: White powder (90%), mp 112–114°C. IR (ν, cm^{-1}): 3452, 3360, 3045, 2898, 1608, 1510, 1468, 1205, 840, 772. ^{1}H NMR ($CDCl_3$): δ 7.9–6.7 (m, 13H aromatic), 5.2 (dd, 1H, $J = 4.4$ and 9.1 Hz), 3.4 (brs, 1 × NH, D_2O exchangeable), 3.2 (dd, 1H, $J = 4.4$ and 11.2 Hz), 3.0 (dd, 1H, $J = 9.1$ and 11.2 Hz). HRMS: m/z at 332.8342 (M^+) 100% (calc. for $C_{21}H_{17}ClN_2$, 332.8344).

2-(4-Fluorophenyl)-4-phenyl-1H,2H,3H-benzo[b]1,4-diazepine 3e: Shining light yellow crystals (88%), mp 84–85°C. IR (ν, cm^{-1}): 3461, 3362, 3074, 2904, 1610, 1508, 1470, 1210, 840, 774. ^{1}H NMR ($CDCl_3$): δ 7.8–6.75 (m, 13H aromatic), 5.3 (dd, 1H, $J = 5$ and 10 Hz), 3.9 (brs, 1 × NH, D_2O exchangeable), 3.2 (dd, 1H, $J = 5$ and 12 Hz), 3.3 (dd, 1H, $J = 10$ and 12 Hz). HRMS: m/z at 316.3793 (M^+) 100% (calc. for $C_{21}H_{17}FN_2$, 316.3800).

2-(4-Bromophenyl)-4-phenyl-1H,2H,3H-benzo[b]1,4-diazepine 3f: White Solid (83%), m.p. 103–104°C IR (ν, cm^{-1}): 3432, 3340, 2872, 1602, 1504, 1450, 1202, 834, 766. ^{1}H NMR ($CDCl_3$): δ 7.7–6.75 (m, 13H aromatic) 5.1 (dd, 1H, $J = 4$ and 8 Hz), 3.8 (brs, 1 × NH, D_2O exchangeable) 3.0 (dd, 1H, $J = 4$ and 10 Hz), 2.9 (dd, 1H, 8 and 10 Hz) HRMS: m/z at 376.0424/378.0301 (M^+) (calc. for $C_{21}H_{17}BrN_2$, 376. 0569/378.0549).

2-(4-Methylphenyl)-4-phenyl-1H,2H,3H-benzo[b]1,4-diazepine 3 g: Yellow crystals (84%), m.p. 78–80°C. IR (ν, cm^{-1}) 3452, 3358, 3040, 2892, 1602,

1502, 1466, 1212, 832, 756. ^{1}H NMR ($CDCl_3$): δ 7.9–6.7 (m, 13H aromatic) 5.0 (dd, 1H, $J = 4.2$ and 8 Hz), 3.6 (brs, 1 × NH, D_2O exchangeable) 2.4 (s, 3H) 3.1 (dd, 1H, $J = 4.2$ and 10.2 Hz), 3.0 (dd, 1H, $J = 8$ and 10.2 Hz). HRMS: m/z at 312.4164 (M^+) 100% (calc. for $C_{22}H_{20}N_2$, 312.4166).

REFERENCES

1. (a) Landquist, J. K. *Comprehensive Heterocyclic Chemistry*; Kalritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 1, 166–170; (b) Schutz, H. *Benzodiazepines*. Springer: Heidelberg, 1982.
2. Strenbach, L. H. *J. Med. Chem.* **1979**, *22*, 1.
3. (a) Leimgruber, W.; Stefanovic, V.; Schenker, F.; Karr, A.; Berger, J. *J. Am. Chem. Soc.* **1965**, *87*, 5791; (b) Leimgruber, W.; Batcho, A. D.; Schenker, F. *J. Am. Chem. Soc.* **1965**, *87*, 5793.
4. (a) Kukla, M. J.; Breslin, H. J.; Diamond, C. J.; Grous, P. P.; Ho, C. Y.; Mirands, M.; Rodgers, J. D.; Sherrill, R. G.; De Clercq, E.; Pauwels, R.; Andries, K.; Moens, L. J.; Janssen, M. A. C.; Janssen, P. A. J. *J. Med. Chem.* **1991**, *34*, 3187; (b) Parker, K. A.; Coburn, C. A. *J. Org. Chem.* **1992**, *57*, 97.
5. Ding, C. Z.; Batorsky, R.; Bhide, R.; Chao, H. J.; Cho, Y.; Chong, S.; Gullo-Brown, J.; Guo, P.; Kin, S. H.; Lee, F.; Leftthеris, K.; Miller, A.; Mitt, T.; Patel, M. Penchallow, B. A.; Ricca, C.; Rose, W. C.; Schmidt, R.; Sulsarchyk, W. A.; Vite, G.; Yan, N.; Manne, V.; Hunt, J. T. *J. Med. Chem.* **1999**, *42*, 5241.
6. Balakrishan, M. S.; Kaboudin, B. *Tetrahedron Lett.* **2001**, *42*, 1127.
7. Stahlofen, P.; Ried, W. *Chem. Ber.* **1957**, *90*, 815–824.
8. Ried, W.; Torinus, E. *Chem. Ber.* **1959**, *92*, 2902–2916.
9. Herbert, J. A. L.; Suschitzky, H. J. *J. Chem. Soc., Perkin Trans. 1.* **1974**, 2657–2661.
10. Morals, H. R.; Bulbarela, A.; Contreras, R. *Heterocycles* **1986**, *24*, 135–139.
11. Jung, D. I.; Choi, T. W.; Kim, Y. Y.; Kim, I. S.; Park, Y. M.; Lee, Y. G.; Jug, D. H. *Synth. Commun.* **1999**, *29*, 1941–1951.
12. Balakrishan, M. S.; Kaboudin, B. *Tetrahedron Lett.* **2001**, *42*, 1127–1129.
13. Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Tetrahedron Lett.* **2001**, *42*, 3193–3195.
14. Kaboudin, B.; Navace, B. *Heterocycles* **2001**, *55*, 1443–1446.
15. Minothora, P.; Julia, S. S.; Constatinos, A. T. *Tetrahedron Lett.* **2002**, *43*, 1755–1758.
16. Reddy, B. M.; Sreekanth, P. M. *Tetrahedron Lett.* **2003**, *44*, 4447–4449.
17. Yadav, J. S.; Reddy, B. V. S.; Kumar, P. S.; Nagarah, K.; Ungauah, N.; Saiprasad, S. P. *Synthesis* **2004**, *6*, 901–904.
18. Srivamurugan, V.; Deepa, K.; Palanichamy, M.; Murugesan, V. *Synth Commun.* **2004**, *34*, 3833–3846.
19. Jarikote, D. V.; Siddiqui, S. A.; Rajagopal, R.; Thomas, D.; Lahoti, R. J.; Srinivasan, K. V. *Tetrahedron Lett.* **2003**, *44*, 1835–1838.
20. Ganai, B. A.; Koul, S.; Razdan, T. K.; Andotra, C. S. *Synth. Commun.* **2004**, *34*, 1823.
21. Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Chem. Commun.* **2001**, 2159.
22. Furniss, B. S.; Hannaford, A. J.; Smith, P. W.G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*; Addison Wesley Longman: Harlow, UK, 1998; Chapter 6.12, p. 1033.