Perchloric acid adsorbed on silica gel: an efficient heterogeneous reusable catalyst for synthesis of 1,5-benzodiazepines

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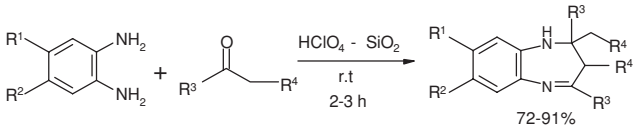
The condensation of *o*-phenylenediamines with both aliphatic (acyclic and cylic) and aromatic ketones has been carried out to produce 1,5-benzodiazepines in high yields using perchloric acid adsorbed on silica gel as a heterogeneous catalyst. The catalyst can be recycled.

Keywords: *o*-phenylenediamine, ketone, benzodiazepine, $HClO_4$–SiO_2, solvent free conditions

Benzodiazepines are a very important class of bioactive compounds having anticonvulsant, analgesic, antidepressive, antiinflamatory, hypnotic and sedative properties.[2] They are also commercially used as dyes for acrylic fibres.[3] Moreover, they are key intermediates for the synthesis of different fused-ring compounds such as triazolo-, oxadiazolo-, oxazino- and furano-benzodiazepines.[4] Due to their wide range of medicinal, commercial and synthetic utilities benzodiazepines have gained a good deal of attention in recent years.

The synthesis of 1,5-benzodiazepines is generally achieved by condensation of *o*-pheylenediamines with ketones in the presence of a catalyst such as BF_3–OEt_2, polyphosphoric acid–SiO_2, MgO / $POCl_3$, $Yb(OTf)_3$, Al_2O_3–P_2O_5, HOAc-microwave, SO_4^{2-}–ZrO_2, $NaBH_4$, $Ag_3PW_{12}O_{40}$ and ionic liquids.[5] However, many of these methods suffer from drawbacks such as harsh reaction conditions, applications of expensive reagents, long reaction times, unsatisfactory yields and tedious experimental procedures.

In continuation of our work[6] on the development of novel synthetic methodologies we have observed that perchloric acid adsorbed on silica gel ($HClO_4$–SiO_2) can efficiently catalyse the condensation of *o*-phenylenediamines with ketones to produce 1,5-benzodiazepines in high yields.



A series of 2,3-dihydro-1*H*-1,5-benzodiazepines were prepared (Table 1) using different *o*-phenylenediamines and ketones. Both aliphatic and aromatic ketones were used. The aliphatic ketones included various acyclic and cyclic compounds and the diamines contained both electron donating and electron withdrawing groups on the aromatic rings. The reaction occured at room temperature and no solvent was added. The yields of 1,5-benzodiazepines were found to be very high in relatively short reaction times (2–3 h). No reaction was observed in the absence of catalyst. The structures of the prepared compounds were determined from their spectral (^{1}H NMR and MS) data.

Perchloric acid adsorbed on silica gel works under heterogeneous conditions.[7] In recent years heterogeneous catalysts have gained importance due to economic and environmental considerations. The present catalyst can easily be prepared[7] from $HClO_4$ and silica gel. It can conveniently be handled and removed from the reaction mixture. The catalyst was recovered and reused three consecutive times with only a small variation in the yields of the products.

In conclusion, we have developed an efficient method for the synthesis of 1,5-benzodiazepines by condensation of *o*-phenylenediamines with ketones in the presence of $HClO_4$–SiO_2 as a heterogeneous catalyst. The mildness of the conversion, the experimental simplicity, the application of inexpensive reagents, high yields and regioselectivity, short reaction times, and reuseability of the catalyst are among the many advantages of the present protocol. We feel the method can be utilised for large scale eco-friendly preparation of 1,5-benzodiazepines.

Experimental

The spectra were recorded with the following instruments: ^{1}H NMR: Varian Gemini 200 MHz and EIMS: VG Micromass 7070H (70eV). The *o*-phenylenediamines and ketones were obtained commercially.

General procedure: A mixture of *o*-phenylenediamine (1 mmol), ketone (2.2 mmol) and $HClO_4$–SiO_2 (25 mg) was stirred at room temperature. The reaction was monitored by TLC. After completion the mixture was washed with EtOAc (5 ml) and filtered to recover the catalyst. The filtrate was concentrated and the residue was subjected to column chromatography over silica gel using EtOAc-hexane (1:4) as eluent to obtain the pure benzodiazepine.

The recovered catalyst was again washed with EtOAc (5 ml), activated by heating at 80°C under vacuum for 2 h and reused.

All the prepared compounds were solid and are known[5f,g,i]. Their spectral (^{1}H NMR and MS) data corresponded well to those reported earlier. The spectral and analytical data of some 1,5-benzodiazepines are given below:

3b: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.70–7.58 (2H, m), 7.32–7.17 (9H, m), 7.02–6.98 (2H, m), 6.74 (1H, d, *J* = 8.0 Hz), 3.45 (1H, brs), 3.12 (1H, d, *J* = 12.0 Hz), 3.02 (1H, d, *J* = 12.0 Hz), 1.65 (3H, s): EIMS: *m/z* 312 ($M^{+\cdot}$). Anal. Calcd for $C_{22}H_{20}N_2$: C, 84.61; H, 6.41; Found: C, 84.52; H, 6.34%.

3c: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.09 (1H, dd, *J* = 8.0, 2.0 Hz), 6.92–6.85 (2H, m), 6.62 (1H, dd, *J* = 8.0, 2.0 Hz), 3.01 (1H, brs), 2.42 (2H, d, *J* =7.0 Hz), 2.24–2.08 (3H, m), 1.72 (1H, m), 1.57–1.43 (2H, m), 1.32 (3H, s), 1.92–1.04 (12H, m): EIMS: *m/z* 272 ($M^{+\cdot}$). Anal. Calcd for $C_{18}H_{28}N_2$: C, 79.41; H, 10.29; Found: C, 79.45; H, 10.35%.

3d: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.70–6.52 (4H, m), 3.86 (1H, brs), 2.53–2.10 (3H, m), 2.01–1.25 (12H, m): EIMS: *m/z* 240 ($M^{+\cdot}$). Anal. Calcd for $C_{16}H_{20}N_2$: C, 80.00; H, 8.33; Found: C, 80.12; H, 8.28%.

3f: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.64–7.36 (4H, m), 7.20–7.15 (7H, m), 6.59 (1H, dd, *J* = 8.0, 2.0Hz), 6.30 (1H, d, *J* = 2.0 Hz), 3.83 (3H, s), 3.59 (1H, brs), 3.19 (1H, d, *J* = 12.0 Hz), 2.98 (1H, d, *J* = 12.0 Hz), 1.78 (3H, s): EIMS: *m/z* 342 ($M^{+\cdot}$). Anal. Calcd for $C_{23}H_{20}$ O N_2: C, 80.70; H, 6.43; Found: C, 80.65; H, 6.41%.

3h: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.64–7.53 (4H, m), 7.25–7.03 (7H, m), 6.59 (1H, s), 3.32 (1H, brs), 3.10 (1H, d, *J* = 12.0 Hz), 2.92 (1H, d, *J* = 12.0 Hz), 2.26 (6H, s), 1.76 (3H, s): EIMS: *m/z* 340 ($M^{+\cdot}$). Anal. Calcd for $C_{24}H_{24}N_2$: C, 84.70; H, 7.05; Found: C, 84.64; H, 7.11%.

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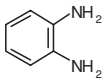
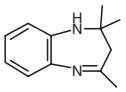
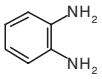
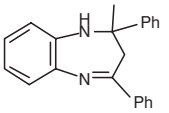
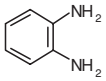
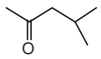
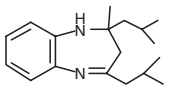
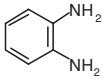
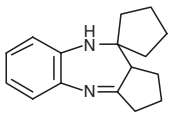
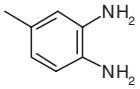
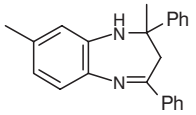
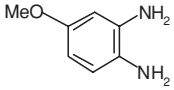
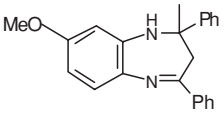
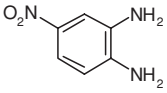
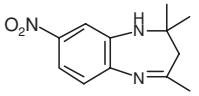
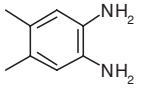
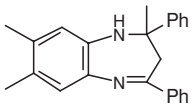
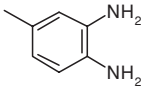
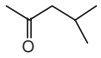
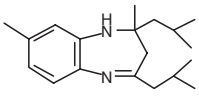
Table 1 $HClO_4$–SiO_2 catalysed synthesis of 1,5-benzodiazepines[a]

Entry	Diamide **1**	Ketone **2**	Product **3**	Time/h	Isolated yield/%	Ref	M.p./°C
a		CH_3COCH_3		2	91	5i	136–138
b		$PhCOCH_3$		2	86	5g	150–152
c				2	89	5i	118–120
d				3	80	5g	137–138
e		$PhCOCH_3$		3	85	5i	91–93
f		$PhCOCH_3$		2	79	5i	121–123
g		CH_3COCH_3		2	72	5i	113–114
h		$PhCOCH_3$		3	81	5f	136–138
i				2	90	5i	124–126

[a]The structures of the 1,5-benzodiazepines prepared were determined from their spectral (^1H NMR and MS) data.

References

1 Part 57 in the series,"Studies on novel synthetic methodologies".

2 (a) L.O. Randall and B. Kappel, *In Benzodiazepines*, S. Garattini, E. Mussini and L.O. Randall, (eds) Raven Press: New York, 1973, 27; (b) H. Schutz, *Benzodiazepines*, Springer: Heidelberg, 1982; (c) J.K. Landquist, In *Comprehensive Heterocyclic Chemistry*, A.R. Katritzky and C.W. Rees, (eds) Pergamon: Oxford, 1984, **11**, 166.

3 R.C. Harris and J.M. Straley, US patent 1, 1968, 757. (*Chem. Abstr*., 1970, **73**, 100054).

4 (a) M. Essabar, A. Baouid, A. Hasnaoui, A. Benharref and J.P. Lavergne, *Synth. Commun*., 1998, **28**, 4097; (b) A.M. El-Sayed, H. Abdel-Ghany and A.M.M. El-Saghier, *Synth. Commun*., 1999, **29**, 3561; (c) K.V.V. Reddy, P.S. Rao and D. Asoke, *Synth. Commun*., 2000, **30**, 1825.

5 (a) J.A. Herbert and H. Suschitzky, *J. Chem. Soc. Perkin Trans 1*, 1974, 2657; (b) H.R. Morales, A. Bulbarela and R. Contreras, *Heterocycles*, 1986, **24**, 135; (c) D.I. Jung, D.W. Choi, Y.Y. Kim, I.S. Kim, Y.M. Park, Y.G. Lee and D.H. Jung, *Synth. Commun*., 1999, **29**, 1941; (d) M.S. Balakrishna and B. Kaboudin, *Tetrahedron Lett.*, 2001, **42**, 1127; (e) M. Curini, F. Epifano, M.C. Marcotullio and O. Rosati, *Tetrahedron Lett*., 2001, **42**, 3193; (f) M. Pozarentzi, J.S. Stephanatou and C.A. Tsoleridis, *Tetrahedron Lett.*, 2002, **43**, 1755; (g) J.S. Yadav, B.V.S. Reddy, B. Eshwaraiah and K. Anuradha, *Green Chem*., 2002, **6**, 592; (h) D.V. Jarikote, S.A. Siddiqui, R. Rajagopal, T. Daniel, R.J. Lahoti and K.V. Srinivasan, *Tetrahedron Lett*., 2003, **44**, 1835; (i) J.S. Yadav, B.V.S. Reddy, S.P. Kumar, K. Nagaiah, N. Lingaiah and P.S. S. Prasad, *Synthesis*, 2004, 901.

6(a) C. Ramesh, G. Mahender, N. Ravindranath and B. Das, *Tetrahedron Lett*., 2003, **44**, 1465; (b) K.V.N.S. Srinivas and B. Das, *J. Org. Chem*., 2003, **68**, 1165; (c) C. Ramesh, J. Banerjee, R. Pal and B. Das, *Adv. Synth. Catal*., 2003, **345**, 557; (d) C. Ramesh, N. Ravindranath and B. Das, *J. Org. Chem*., 2003, **68**, 7101; (e) B. Das, J. Banerjee, N. Ravindranath and B. Venkataiah, *Tetrahedron Lett*., 2004, **45**, 2425; (f) B. Das, H. Holla, G. Mahender, J. Banerjee and M.R. Reddy, *Tetrahedron Lett*., 2004, **45**, 4347.

7 A.K. Chakrabarti and R. Gulhane, *Chem. Commun*., 2003, 1896.