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Zirconyl(IV) chloride: a novel and efficient reagent for the rapid synthesis of 1,5-benzodiazepines under solvent-free conditions

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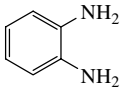
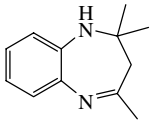
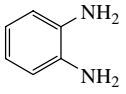
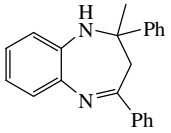
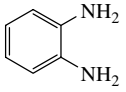
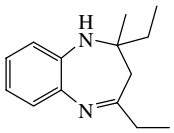
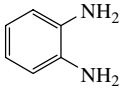
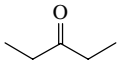
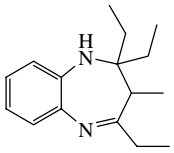
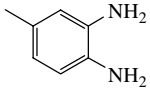
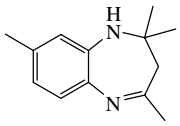
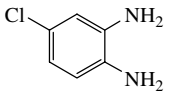
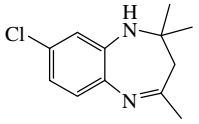
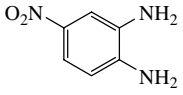
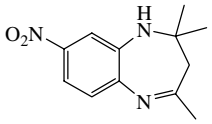
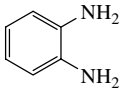
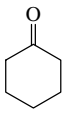
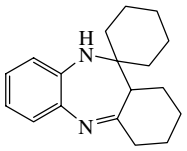
o-Phenylenediamines undergo rapid condensation with ketones having hydrogens at the α-position in the presence of 10 mol% zirconyl(IV) chloride under extremely mild reaction conditions to afford the corresponding 1,5-benzodiazepines in excellent yields with high selectivity. This method works well for both electron-rich as well as electron-deficient *o*-phenylenediamines.

Benzodiazepines are very important compounds in the manufacture of drugs and pharmaceuticals.[1] Many diazepines are widely used as anticonvulsants, antianxiety, analgesics, sedative, antidepressive and hypnotic agents.[2] Benzodiazepine derivatives also find commercial use as dyes for acrylic fibers[3] and as anti-inflammatory agents.[4] In addition, 1,5-benzodiazepines are key intermediates for the synthesis of various fused ring compounds such as triazolo, oxadiazolo, oxazino or furanobenzodiazepines.[5] Consequently, numerous methods have been reported for the preparation of benzodiazepines.[6] The acid catalysed condensation of *o*-phenylenediamines with ketones is one of the simplest and straightforward approaches to the synthesis of benzodiazepines.[7] Reagents such as $BF_3{\cdot}OEt_2$, $NaBH_4$, polyphosphoric acid–SiO_2, MgO–$POCl_3$, $Yb(OTf)_3$, $InBr_3$, Al_2O_3–P_2O_5, HOAc-microwave, SO_4^{2-}–ZrO_2 and 1-butyl-3-methylimidazolium bromide ([bmim]Br) have been employed to accomplish this transformation.[7–9] However, many of these methods involve the use of strong acids, high temperature conditions and extended

Table 1 Zirconyl(IV) chloride-promoted synthesis of 1,5-benzodiazepines.

Entry	Diamine	Ketone	Product	Yield (reported yield)[9] (%)	Time (reported time)[9]/min	mp (reported mp)[9]/°C
1				95 (91)	45 (90)	134–136 (136–138)
2				92 (89)	90 (150)	151–153 (150–152)
3				94 (91)	50 (90)	138–139 (137–139)
4				96 (94)	75 (120)	142–143 (143–144)
5				95 (96)	45 (90)	128–129 (127–129)
6				94 (93)	80 (120)	91–92 (90–92)
7				90 (85)	120 (180)	112–113 (113–114)
8				88 (85)	105 (180)	134–136 (136–137)

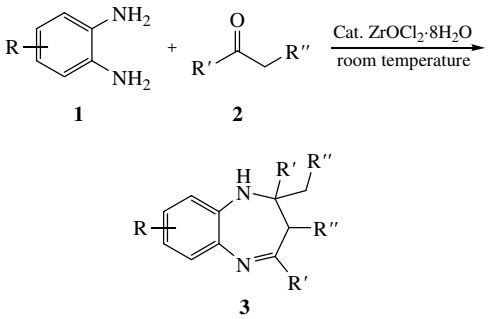
reaction times, and also entail several side reactions resulting in low yields of products. Due to their wide range of biological, industrial and synthetic applications, the synthesis of benzodiazepines has recently received renewed interest of researchers for the discovery of improved protocols and still awaits further developments towards milder and high-yielding approaches.

Zirconyl(IV) chloride is a moisture stable, readily available and inexpensive oxy salt of zirconium, which is not much explored in synthetic organic chemistry as a mild and versatile Lewis acid catalyst. Compared to conventional Lewis acids, zirconyl(IV) chloride has advantages of low catalyst loading, moisture stability and catalyst recycling. However, there are no examples of the use of zirconyl(IV) chloride as a catalyst for the preparation of benzodiazepines.

Here, we describe a novel protocol for the rapid synthesis of a variety of biologically significant 1,5-benzodiazepines using a catalytic amount of zirconyl(IV) chloride under extremely mild conditions (Scheme 1).†

For instance, the treatment of *o*-phenylenediamine with acetone in the presence of 10 mol% zirconyl(IV) chloride for 45 min afforded 2,3-dihydro-2,2,4-trimethyl-1*H*-1,5-benzo[*b*]-[1,4]diazepine in 95% yield. Ketones such as acetophenone, butan-2-one and pentan-3-one reacted smoothly with *o*-phenylenediamines under similar reaction conditions to give corresponding 1,5-benzodiazepines in 85–96% yields. Several pharmacologically relevant 1,5-benzodiazepines were prepared using this procedure (Table 1). This method is effective for the preparation of benzodiazepines from electron-deficient *o*-phenylenediamines (Table 1, entries 6 and 7). Interestingly, a cyclic ketone such as cyclohexanone also worked well with similar success to afford fused ring 1,5-benzodiazepine in a high yield (Table 1, entry 8, Scheme 2).

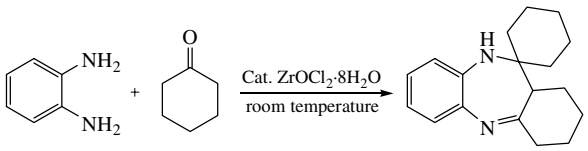
In all cases, the reactions are clean and are completed within 45–120 min with good yields (85–96%) in comparison with a reported method,[9] where the time required is around 90–180 min (Table 1). The reactions proceeded well at room temperature



1 **2**

3

Scheme 1



Scheme 2

under solvent-free conditions. The crude products were purified by recrystallization from diethyl ether–hexane or by silica gel column chromatography. All of the products were characterised by ^{1}H NMR, ^{13}C NMR and IR spectroscopy; mass spectrometry; elemental analysis and melting point measurements. The scope and generality of this procedure are illustrated with respect to various *o*-phenylenediamines and a wide range of ketones and the results are presented in Table 1. This method offers several advantages such as high conversions, shorter reaction times, cleaner reaction profiles, high regioselectivity in the case of unsymmetrical ketones, solvent-free conditions, simple experimental and work-up procedures.

† Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer. Chemical shifts δ (ppm) relative to TMS as an internal standard are reported. Electron spray ionization mass spectra (ES-MS) were recorded on a Water-Micromass Quattro-II spectrometer. IR spectra were recorded on a Varian spectrometer. All of the reagents used were of AR grade and used without further purification. Column chromatography employed silica gel of 60–120 mesh.

General procedure for the preparation of 2,3-dihydro-1,5-benzodiazepines. A mixture of *o*-phenylenediamines (1 mmol), a ketone (2.5 mmol) and $ZrOCl_2 \cdot 8H_2O$ (0.1 mmol) was stirred at room temperature for an appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water and extracted with ethyl acetate (3×10 ml). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford a crude compound. The crude compounds were purified by recrystallization with diethyl ether–hexane or by silica gel column chromatography to afford pure desired compounds.

The zirconyl(IV) chloride catalyst (Aldrich) was used; it could also be synthesised conveniently from $ZrCl_4$ and Cl_2O.[10]

*2,3-Dihydro-2,2,4-trimethyl-1*H*-1,5-benzo[*b*][1,4]diazepine* **3a** (R = = R″ = H, R′ = Me): ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.35 (s, 6H), 2.20 (s, 2H), 2.35 (s, 3H), 2.95 (br. s, 1H, NH), 6.65–7.30 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 29.5, 30.6, 44.9, 67.9, 121.4, 122.2, 125.1, 126.8, 137.5, 140.8, 171.6. IR (KBr, ν/cm^{-1}): 3340, 1650, 1600. ES/MS, *m*/*z*: 189 (M + H, 100%). Found (%): C, 76.29; H, 8.62; N, 14.95. Calc. for $C_{12}H_{16}N_2$ (%): C, 76.56; H, 8.57; N, 14.88.

Thus, we described an efficient protocol for the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines from *o*-phenylenediamines and ketones having hydrogens at the α-position using air- and water-tolerant zirconyl(IV) chloride as a catalyst under solvent-free conditions.

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