# A New, Efficient and Environmentally Benign Protocol for the Synthesis of 1,5-Benzodiazepines using Cerium(III) Chloride/Sodium Iodide Supported on Silica Gel†

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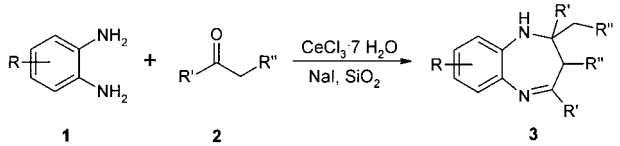
**Abstract:** A novel and green approach has been described for the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines from *o*-phenylenediamines and ketones using cerium(III) chloride/sodium iodide supported on silica gel under mild and heterogeneous conditions. The reactions are carried out at room temperature without using any organic solvent.

**Keywords:** benzodiazepines; cerium(III) chloride; ketones; Lewis acids; *o*-phenylenediamines; silica gel, supported catalysts

Benzodiazepines are an important class of compounds and find many applications as anticonvulsant, anti-inflammatory, anti-anxiety, hypnotic, and anti-depressive agents.[1,2] These derivatives are also used as dyes for acrylic fibres[3] in photography. In addition, benzodiazepines are used as synthons for the preparation of other fused ring systems such as triazolo-, oxadiazolo-, oxazino- or furanobenzodiazepines.[4] Due to their wide range of pharmacological activity, industrial, and synthetic applications, the synthesis of 1,5-benzodiazepines has received more attention and recently many methods have been reported for their synthesis. Generally these compounds are prepared by condensation of *o*-phenylenediamines with α,β-unsaturated carbonyl compounds, β-halo ketones or ketones. Many reagents have been reported for this condensation reaction in the literature which include the use of $BF_3$-etherate,[5] $NaBH_4$,[6] polyphosphoric acid or $SiO_2$,[7] $MgO/POCl_3$,[8] $Yb(OTf)_3$,[9] sulfated zirconia[10] and $Al_2O_3/P_2O_5$ or AcOH[12] under microwave conditions. Recently these condensations have also been reported even in an ionic liquid medium.[12] However, a milder, selective, non-hazardous and inexpensive reagent is still in demand.

In recent years, solid supported catalysts[13] have attracted much interest in organic synthesis because of their high reactivity, stability and selectivity. In particular, among the lanthanide Lewis acids, cerium(III) chloride ($CeCl_3 \cdot 7\,H_2O$) has gained much popularity, owing to its unique reactivity, ease of handling, low toxicity, moisture and air tolerance.[14] Although the use of the $CeCl_3 \cdot 7\,H_2O$ and NaI system without solvent satisfies the demands of environmentally benign "green" chemistry,[15] in some cases the reactions are sluggish and give low yields. Therefore cerium(III) chloride/NaI supported on silica gel has been developed by Bartoli and Marcantoni,[16] to improve its utility in organic synthesis.

In the course of our research on applications of $CeCl_3 \cdot 7\,H_2O$ in various organic transformations,[17] we describe in this report a new, efficient and environmentally benign protocol for the synthesis of 1,5-benzodiazepines using cerium(III) chloride/NaI supported on silica gel under solvent-free conditions (Scheme 1). The reaction of *o*-phenylenediamine (1 mmol) with acetone (2.2 mmol) was carried out in the presence of 30 mol % of $CeCl_3 \cdot 7\,H_2O$ and 30 mol % of NaI supported on silica gel (0.5 g/mmol of diamine)[16] under solvent-free conditions at room temperature. The reaction proceeded smoothly to give the corresponding 1,5-benzodiazepine in 95% yield within 45 minutes. Diethyl ether was added to the reaction mixture and the product was isolated simply by filtering the mixture and evaporating the solvent from the filtrate and it was further purified by silica gel column chromatography. In a similar fashion, *o*-phenylenediamine and substituted *o*-phenylenediamines reacted well with ketones and gave the corresponding 1,5-benzodiazepines in good to excellent yields. Cyclic ketones such as cyclopentanone and cyclohexanone (entries f and g) also reacted efficiently to afford the fused ring benzodiazepines. In all cases the reaction works well and complete conversion was obtained within 40–90 minutes leading to the correspond-




1 2 3

**Scheme 1.**

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ing 1,5-benzodiazepines in high yields. The scope and efficiency of our method are summarized in Table 1. The products were characterized by spectroscopic methods such as IR, $^1$H NMR, $^{13}$C NMR and mass spectroscopy and have also been identified by comparison of spectral data and mp with those reported. Although these reactions can be accomplished using cerium(III) chloride/NaI without silica gel support, long reaction times, low yields of products were observed when compared to those with the cerium(III) chloride/NaI supported catalyst and moreover, the work-up procedures were not clean. Other remarkable features of the procedure are its simplicity, together with the easy and inexpensive preparation, air stability of the catalyst, and the use of cerium(III) compounds as environmentally friendly reagents.[18] The catalyst can be easily recovered by filtration and reused for 4–5 cycles with little decrease in activity.

In conclusion, we have developed a novel and environmentally friendly method for the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines at room temperature using a cerium(III) chloride/NaI combination adsorbed on silica gel under solvent free conditions. The advantages of the present protocol are mild, heterogeneous conditions, shorter reaction times, easy work-up, and low toxicity, inexpensive, ready availability, recoverability, recyclability of the catalyst that make the procedure an attractive alternative to the existing methods for the synthesis of 1,5-benzodiazepines.

## Experimental Section

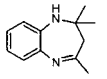
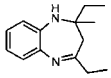
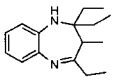
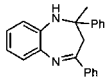
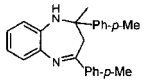
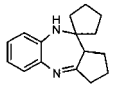
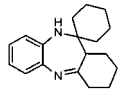
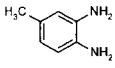
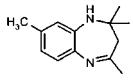
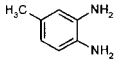
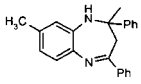
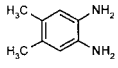
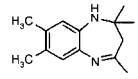
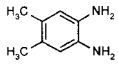
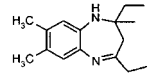
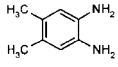
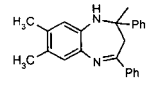
### Preparation of Solid Supported Catalyst

Silica gel (Merck 60–120 mesh, 0.5 g) was added to a mixture of cerium(III) chloride (0.113 g, 0.3 equivs.), NaI (0.046 g, 0.3 equivs.) in acetonitrile (8 mL), and the mixture was stirred overnight at room temperature. The acetonitrile was removed by rotary evaporation to leave a solid catalyst.

### Typical Procedure

*o*-Phenylenediamine **1e** (1 mmol), *p*-methylacetophenone (**2e**, 2.2 mmol) and the above solid support catalyst were mixed and the heterogeneous mixture was stirred rapidly at room temperature for the specified time (see Table 1). After the TLC indicated the disappearance of starting material, diethyl ether was added and the reaction mixture was filtered to separate the catalyst. The filtrate was concentrated under vacuum and the product was purified on a small silica gel column eluting with EtOAc:*n*-hexane (2:8) to afford a pure product **3e** in 84% yield (isolated yields after each cycle 76%, 63%, 58%). The catalyst could be recovered and reused for further reactions. Viscous liquid; IR (KBr): $\nu = 3325$, 1636, 1594 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta = 1.72$ (s, 3H), 2.26 (s, 3H), 2.32 (s, 3H), 2.98 (d, 1H, $J = 12.8$ Hz), 3.05 (d, 1H, $J = 12.8$ Hz), 3.38 (brs, NH), 6.98 (m, 1H), 7.00 (m, 6H), 7.22 (m, 1H), 7.47 (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 20.78$, 21.18, 29.80, 42.74, 73.09, 121.30, 121.45, 125.13, 125.99, 127.08, 128.49, 128.69, 128.87, 129.13, 136.47, 136.98, 138.16, 139.76, 140.23, 144.95, 167.21; MS: $m/z = 340$ ($M^+$).

**Table 1.** $CeCl_3 \cdot 7\,H_2O$/NaI supported on silica gel catalyzed synthesis of 1,5-benzodiazepines.

| Entry | Diamine **1** | Ketone **2** | Product[a] **3** | Time [min] | Yield[b] [%] |
|---|---|---|---|---|---|
| a |  | $CH_3COCH_3$ |  | 45 | 95[12a] |
| b |  | $CH_3COCH_2CH_3$ |  | 50 | 92[9] |
| c |  | $CH_3CH_2COCH_2CH_3$ |  | 45 | 94[12a] |
| d |  | $PhCOCH_3$ |  | 80 | 86[12a] |
| e |  | *P* Me-$C_6H_4COCH_3$ |  | 90 | 84 |
| f |  |  |  | 80 | 82[9] |
| g |  |  |  | 85 | 80[9] |
| h |  | $CH_3COCH_3$ |  | 40 | 96[12b] |
| i |  | $PhCOCH_3$ |  | 80 | 85[12b] |
| j |  | $CH_3COCH_3$ |  | 45 | 95[11b] |
| k |  | $CH_3CH_2COCH_3$ |  | 50 | 92[11b] |
| l |  | $PhCOCH_3$ |  | 75 | 86[11b] |

[a] All products were characterized by $^1$H NMR, IR, mass spectral data and mps compared with the literature values.
[b] Yield of isolated products.

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