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$LaCl_3 \cdot 7H_2O$ catalysed cyclocondensation of *o*-phenylenediamine and ketones under solvent-free conditions

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Abstract. 2,3-Dihydro-1*H*-1,5-benzodiazepine derivatives are synthesized by the condensation of *o*-phenylenediamine and various ketones in the presence of catalytic amount of $LaCl_3$ under solvent-free condition.

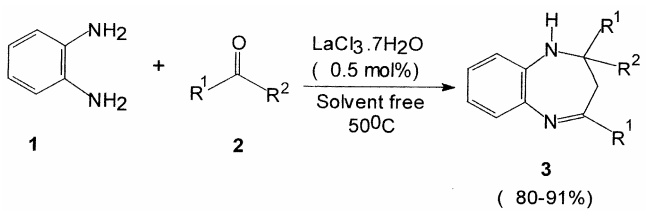
Keywords. Ketones; *o*-phenylenediamine; benzodiazepines; lanthanum chloride.

1. Introduction

Benzodiazepines and their polycyclic derivatives are important classes of bio-active compounds. They find numerous applications as anti-convulsant, anti-anxiety and hypnotic agent.[1,2] More recently the biological interest of 1,5-benzodiazepines has been extended to various diseases like cancer, viral infection and cardiovascular disorders.[3] Some benzodiazepine derivatives are used as dyes for acrylic fibers[4] in photography and also as anti-inflammatory agents.[5] Particularly, 1,5-benzodiazepines are useful precursors for synthesis of some fused ring benzodiazepine derivatives[6] such as triazolo-, oxadiazolo-, oxazino- or furano-benzodiazepines. Despite their wide range of pharmacological activity, industrial and synthetic applications the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines have received little attention. The following methods, not generally applicable, have been reported in the literature include condensation of *o*-phenylenediamine with α,β-unsaturated compounds,[7] β-haloketone.[8] Recently reported condensation of methyl ketones in the presence of PPA or SiO_2 at high temperature,[9] includes BF_3-etherate,[10] $NaBH_4$,[11] $MgO–POCl_3$,[12] $Yb(oTf)_3$,[13] Al_2O_3/P_2O_5 or CH_3COOH under microwave conditions.[14] $CeCl_3 \cdot 7H_2O$/NaI supported on silica gel,[15] 1-butyl-3-methylimidazolium bromide (ionic liquid),[16] Amberlist-15 in ionic liquids,[17] CAN,[18] $Sc(oTf)_3$,[19] $ZnCl_2$ under thermal conditions,[20] $AgNO_3$,[21] and sulphated zirconia[22] as a catalyst. However, many of these methods have some drawbacks such as low yields, high temperature, long reaction time, occurrence of side products and relatively expensive catalysts. Therefore, the search continues for better catalysts for the synthesis of 1,5-benzodiazepines derivatives in terms of operation simplicity and economic viability. In the present work we report the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines by the condensation of *o*-phenylenediamine with ketones in the presence of catalytic amount of lanthanum chloride under solvent-free conditions, whereupon benzodiazepine derivatives are obtained in high yields (scheme 1).

2. Experimental

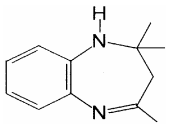
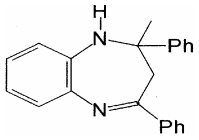
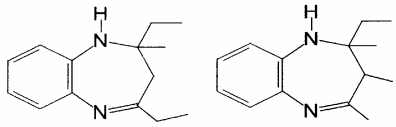
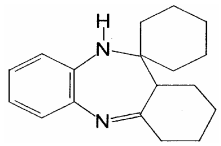
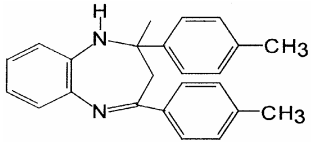
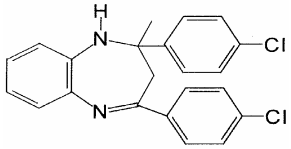
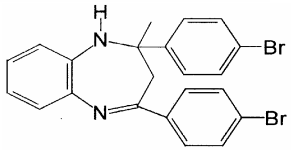
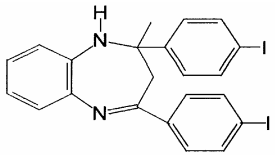
All chemicals were used as AR grade. The reactions were carried out in borosil beaker of 50 ml capacity and monitored by TLC using silica gel 60–120 mesh. Melting points were recorded by open capillary method and uncorrected. IR spectra were recorded on Perkin–Elmer FTIR-240C spectrophotometer on KBr disc. ^{1}H NMR spectra were recorded on 300 MHz



Scheme 1.

*For correspondence
Dedicated to Loknete Balasaheb Vikhe Patil on the occasion of his 75th birthday

Table 1. $LaCl_3 \cdot 7H_2O$ catalysed synthesis of 1,5-benzodiazepines.

Entry	Ketone (2)	Products (3)	Yields (%)	mp (°C)
a	Acetone		86	120–122
b	Acetophenone		82	148–150
c	2-Butanone		89	–
d	Cyclohexanone		80	136–138
e	4-Methyl-acetophenone		91	89–98
f	4-Chloro-acetophenone		84	140–142
g	4-Bromo-acetophenone		82	145–146
h	4-Iodo-acetophenone		80	142–142

[a]Isolated yields
[b]All products are known, characterized by IR, ^{1}H-NMR and compared with authentic samples

spectrometer in $CDCl_3$ using TMS as an internal standard.

2.1 *Typical procedure*

The mixture of *o*-phenylenediamine (2 mmol, 216 mg) and *p*-chloro-acetophenone (4 mmol, 612 mg) ground for 10 min. After grinding lanthanum chloride (0·5 mol.%) was added. The whole mixture was heated for 30 min at 50°C. The completion of the reaction was monitored by TLC (hexane: Ethyl acetate, 8·5 : 1·5). After completion of the reaction dichloromethane (20 ml) was added and the catalyst was recovered by filtration. The organic layer was concentrated and the product purified by silica gel chromatography using *n*-hexane and ethyl acetate (8·5 : 1·5) to afford 2,4-*bis*(4-chlorophenyl)-2-methyl-2,3-dihydro-1*H*-1,5-benzodiazepines (**3f**, 84% in yields). The catalyst was re-used and no appreciable change in the activity was noticed.

Spectroscopic data: Yellow solid, mp 140–142°C, IR (KBr), 3260, 1640, 1593, 810, 760 cm^{-1}, ^{1}H-

NMR (300 MHz, $CDCl_3$): δ, 1·7 (*s*, 3H), 2·7 (*d*, $J = 12$ Hz, 1H), 2·8 (*d*, $J = 12$ Hz, 1H), 3·2 (*s*, 1H), 6·5–6·7 (*m*, 1H), 6·9–7·1 (*m*, 1H), 7·2–7·5*m*, 10H). Yellow solid, mp 145–146°C, IR (KBr) 3220, 1640, 1595, 1120, 812 cm^{-1}, ^{1}H-NMR (300 MHz, $CDCl_3$): δ, 1·7 (*s*, 3H), 2·6 (*s*, 1H), 2·8 (*d*, $J = 12$ Hz, 1H), 3·1 (*d*, $J = 12$ Hz, 1H), 6·8–6·9 (*m*, 1H), 6·8–7·1) (*m*, 1H), 7·2–7·4*m*, 10H).

3. Results and discussion

The results summarized in table 1 show that the condensation reaction between *o*-phenylenediamine and aliphatic, aromatic and cyclic ketones gives rise to excellent isolated yields of the 1,5-benzodiazepines derivatives in relatively short reaction time (30 min). The 2,3-dihydro-2,2,4-trimethyl-1*H*-1,5-benzodiazepine (86%, **3a)** was obtained in the condensation reaction between acetone and *o*-phenylenediamine, the acetophenone and substituted acetophenones **(3b**, **3e**, **3f**, **3g**, **3h)** condensation with *o*-phenylenediamine in the presence of $LaCl_3 \cdot 7H_2O$ affords the 1,5-benzodiazepine derivatives in good to excellent yields. The cyclic ketones as cyclohexanone (entry, **3d)** condense with *o*-phenylenediamine in the presence of $LaCl_3 \cdot 7H_2O$ to afford the cyclic/fused ring 1,5-benzodiazipine derivatives in good yield. The condensation of 2-butanone (entry, **3c)** with *o*-phenylene diamine in the presence of $LaCl_3 \cdot 7H_2O$ gives two distereoisomers, (detected by TLC) which were not separated. No reaction was observed when *o*-phenylenediamine reacted with ketones in the absence of catalyst under the same reaction conditions.

In conclusion, a simple workup procedure, mild reaction condition, selectivity and good to excellent yield make this methodology a valid alternative to other methods found in the literature in the field of 1,5-benzodiazipine derivatives. The synthesis of 2,3-dihydro-1*H*-1,5-benzodiazipines by the condensation of *o*-phenylenediamine with ketone in the presence of catalytic amount of lanthanum chloride under solvent-free conditions are achieved.

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