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ONE-POT SYNTHESIS OF 1,5-BENZODIAZEPINE DERIVATIVES CATALYZED LEAD ACETATE UNDER SOLVENT FREE CONDITION

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ABSTRACT

A simple and efficeint method has been developed for synthesis of 1,5-benzdiazepines from o- phenylenediamine and substituted ketones in presence of a catalytic amount of Lead acetate at room temperature under solvent free condition.The remarkable selectivity under mild, neutral and, inexpensive catalystare attractive features.

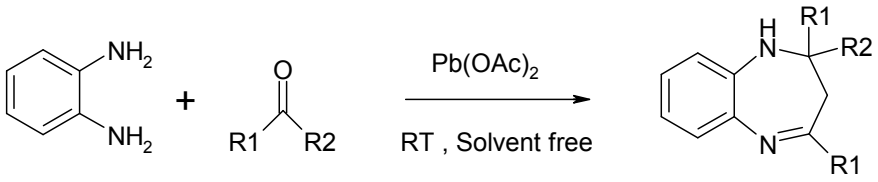
KEY WORDS: Lead acetate, o-phenylenediamine, ketones, 1,5-benzodiazepines, solvent free.

INTRODUCTION

The development of simple, efficient and economically viable chemical process or methodologies for widely used organic compounds are in great demand[1].Benzodiazepine is significant class of biologically active compounds and gaining great consideration in the field of medicinal and pharmaceutical chemistry due to their application as anticonvulsant, anti-inflammatory, analgesics, sedative agents and hypnotic activity[2-6]. The 1,5-benzodiazepine derivatives are also employed as dyes for acrylic fibres in photography[7]. Moreover ben-zodiazepines are effective precursors for the synthesis of other fused ring compounds such as triazolo, oxadiazolo, oxazino or furano-benzodiazepines[8-11]. In general, cyclo-condensation of *o*-phenylenediamines with carbonyl compounds is one of the conventional synthetic methods for the synthesis of 1,5-benzodiazepine derivatives[12].

A variety of catalysts, such as $CeCl_3$-NaI/SiO_2,[13] SmI_2,[14] $YbCl_3$,[15]MgO/$POCl_3$,[16]zeolites,[17]$Ga(OTf)_3$,[18] Amberlyst-21-$Yb(OPf)_3$,[19] $Ag_3PW_{12}O_{40}$,[20] boric acid,[21]fluorous aqueous emulsion[22]FeAlP–550,[23] iodine,[24] Ytterbium perfluoro-octanesulphonate [$Yb(OPf)_3$],[25] 2,4,6-Trichloro-1,3,5-triazine[26] and multicite solid catalyst[27,] $PhB(OH)_2$[28] have been utilized for this synthesis. However, these protocols are related with some disadvantages like hazardous reaction condition, extended reaction time and also use of harmful catalyst and organic solvent. Since, 1,5-benzodiazepines having great significance in pharmaceutical and medicinal fields. Thus, there is still necessity to develop an efficient protocol for thesynthesis of 1,5-benzodiazepines. Recently Lead acetate have been employed

as an efficient organometallic catalyst in synthetic organic chemistry.[29-36]
(Synthesis of 1,5-benzodiazepines via condensation of o-phenylenediamine with ketone)



R1=R2 = alkyl, aryl
Scheme-I

EXPERIMENTAL

General Experimental Procedure for 1,5-benzodiazepines:

A mixture of o-phenylenediamine (1mmol), ketones (2 mmol), and anhydrous $Pb(OAc)_2$ (0.1 mmol, 30 mg) was stirred magnetically at room temperature. After completion of reaction and the progress of the reaction was monitored by thin-layer chromatography. The product was dried over anhydrous Na_2SO_4 and further purification by column chromatography.

RESULTS AND DISCUSSION

The Catalytic activity of $Pb(OAc)_2$ was investigated with respect to loadings. It was observed that when less than 0.1 mmole % $Pb(OAc)_2$ was used, more time was required to get corresponding products with considerable yields (Table 3, entries 1 and 2). On the other hand a catalyst more than 0.1mmol% gives excellent yields and require less time(Table 3,entries 3 and4)

Table- 1.Catalytic effect of $Pb(OAc)_2$ with o-phenyldiamine and Ketone at room temperature

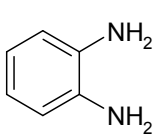
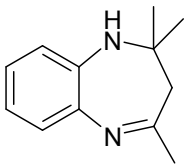
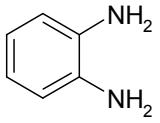
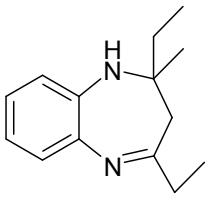
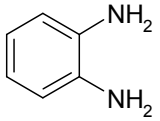
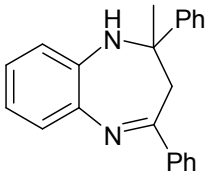
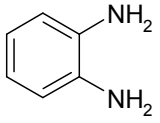
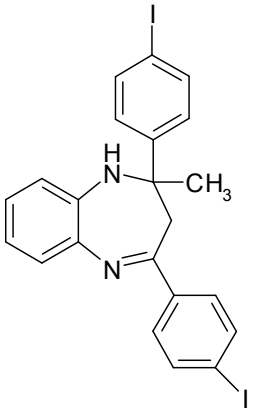
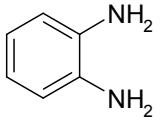
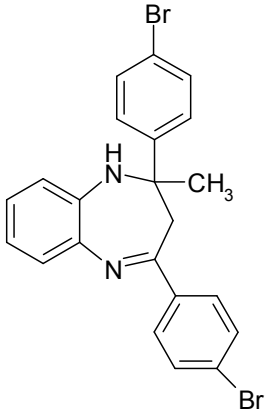
Entry	$Pb(OAc)_2$ (mmol%)	Time(min)	Yield[a](%)
1	0.01	60	55
2	0.05	60	65
3	0.10	25	96
4	0.15	25	96
5	0.20	25	96

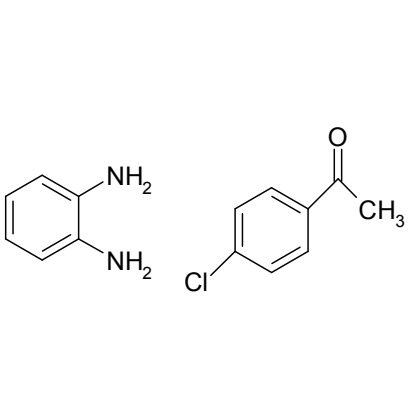
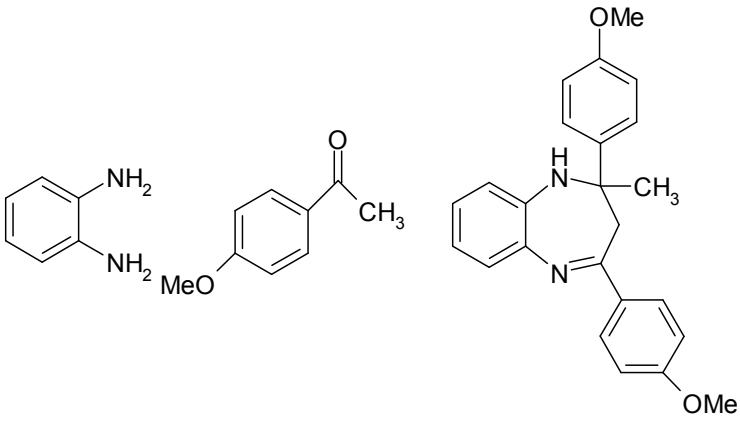
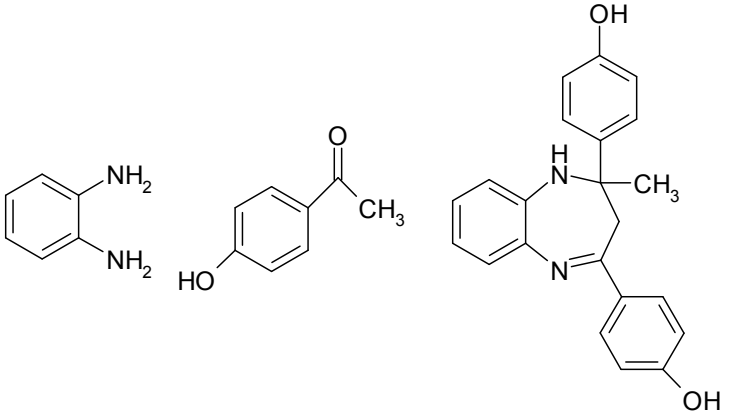
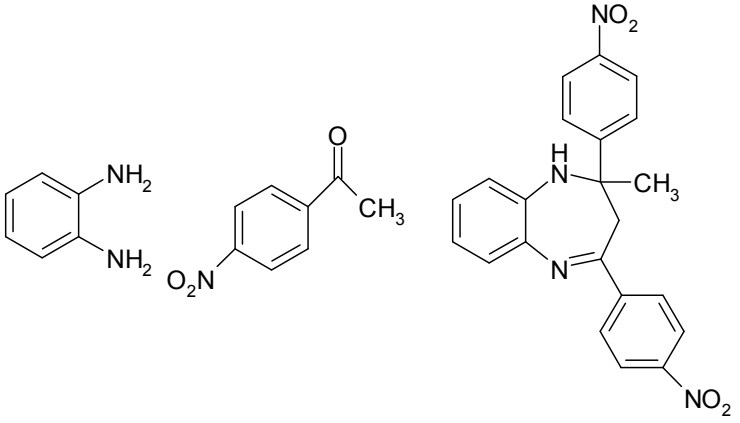
[a] Isolated yield of corresponding product

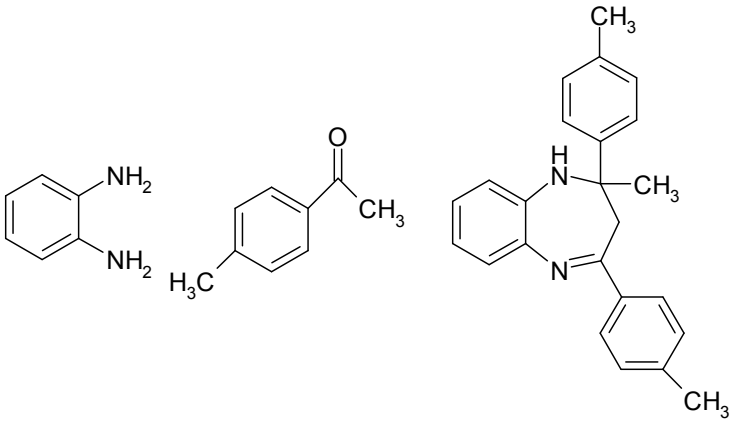
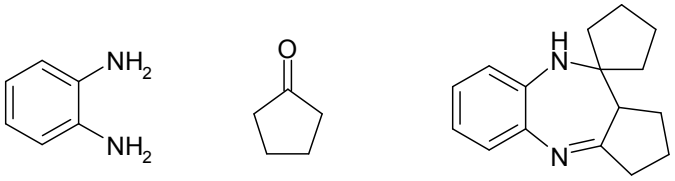
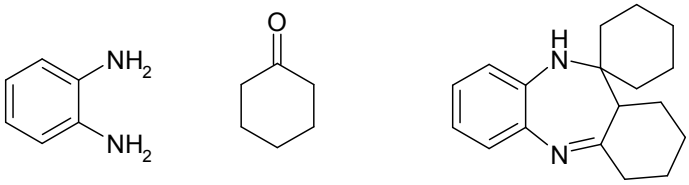
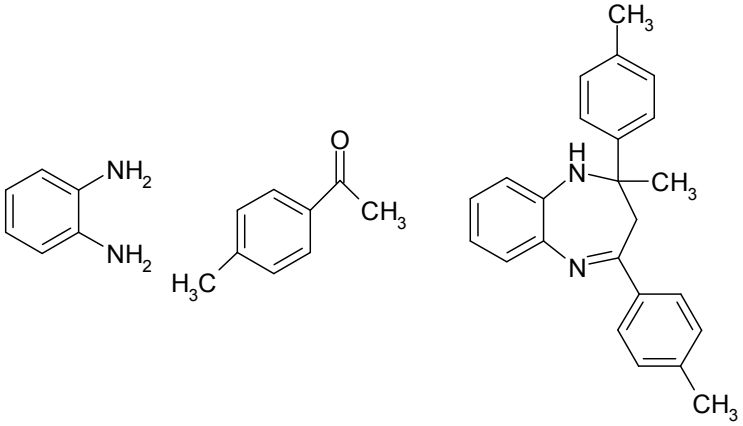
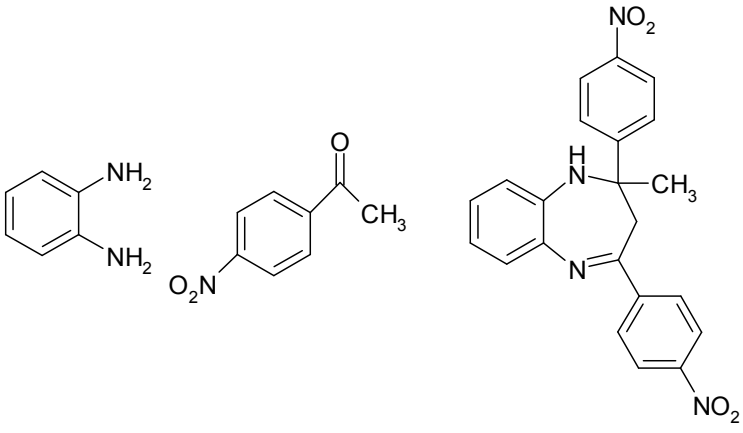
In this communication, we describe the use of Lead acetate catalyst for the synthesis of 1,5-benzodiazepine derivatives. This transformation was performed by condensation reaction of *o*-phenylenediamine and ketones in the presence of catalytic amount of lead acetate under room temperature, solvent free condition.

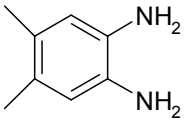
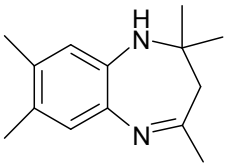
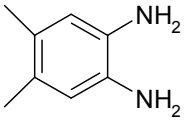
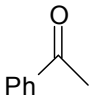
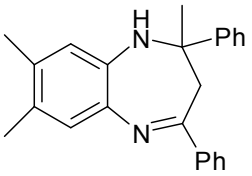
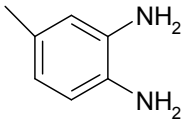
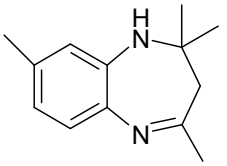
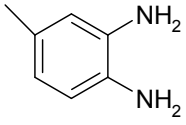
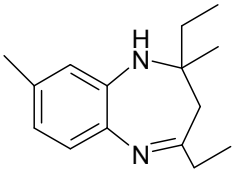
In order to understand the wide utility of Leadacetate, the optimized system was used for the synthesis of a variety of 1,5-benzodiazepines (table 2).Having established reaction conditions, various ketones reacted smoothly with o-phenylenediamine or with substituted o-phenylenediamine under similar reaction conditions to afford the corresponding 1,5-benzodiazepine derivative in good to excellent yields in relatively short reaction times(entries 1-18 Table 2). It should be noted that this method is suitable for the preparation of 1,5-benzodiazepines derivatives with both electron rich as well as electron deficient ketones and o-phenylenediamine derivatives with fine results.

Table- 2. Synthesis of 1,5-benzodiazepines catalysed by Leadacetate[a]

Entry	Substrateketones (a)	Product (b)	Time (min)	Yield[c] (%)
1.			25	96
2.			25	96
3.			30	96
4.			40	84
5.			30	86

6.		40	83
7.		30	97
8.		30	95
9.		35	92

10.			25	94
11.			25	95
12.			25	94
13.			25	90
14.			25	92

15.				25	84
16.				30	84
17.				25	87
18.				30	86

[a]o-phenyldiamine (1mmol), acetophenone (2mmol) by using 0.1 mmol of $Pb(OAc)_2$ at room temperature under solvent free conditions.
[b] All products were identified by their IR and ^1H NMR spectra
[c]Isolated yields.

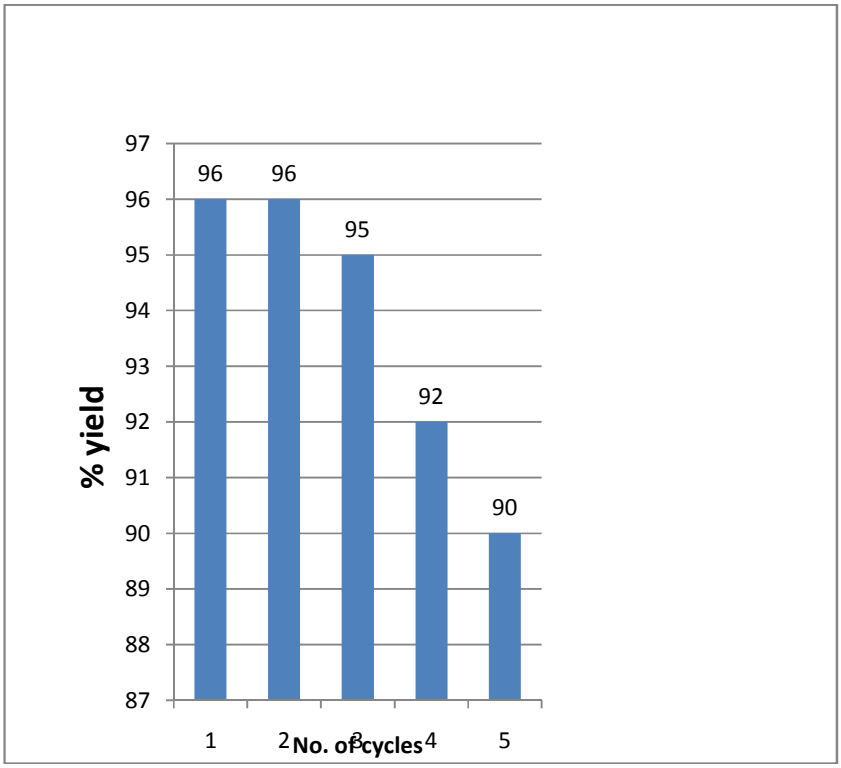
The reusability of the catalyst was investigated.For this purpose, the same model reaction was again studied under optimized conditions. After completion of the reaction, by addition of hot ethanol, insoluble catalyst was filtered off. Then catalyst was washed with acetone and dried. It was reused in subsequent reaction without reduction in activity as shown in (Table 3). Results showed that Lead acetate could be used for five successive runs without significant decrease in catalytic activity

Table- 3. Reuse of catalyst in synthesis of 1,5-benzodiazepines

Entry	1	2	3	4	5
Yield[a](%)	96	96	95	92	90

[a] Isolated yield of corresponding product

Fig 1: Recycling of Catalyst



Compound characterization

*2,3-Dihydro-2,2,4-trimethyl-1H-benzo-[1,4]diazepine(Table 2 Entry**1**)*: Yellow solid;M.P-140 (Lit.139-141)^{1}H NMR (300 MHz, $CDCl_3$*)*:*δ*1.62 (s, 6H), 2.42 (s, 2H), 2.68 (s, 3H), 3.10 (br s, 1H, NH), 6.72-7.10 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$*)*: *δ* 30.8, 33.5, 43.6, 66.4, 118.4, 122.6, 127.2, 128.8,135.7, 142.1, 170.3; GC-MS, *m*/*z*: 188 (M+).; Elemental Analysis: Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88; Found C, 76.52; H, 8.59; N, 14.84.

*2,3-dihydro-2-methyl-2,4-diphenyl-1H-benzo-[1,4]diazepine(Table 2,Entry**3**)*: Yellow solid;M.P-141(Lit.152-153)^{1}H NMR (300 MHz,$CDCl_3$*)*: *δ* 1.82 (s, 3H), 3.14 (s, 2H), 3.60 (br s, 1H, NH), 6.72-7.14 (m, 2H), 7.30–7.49 (m, 10H), 7.64– 7.74 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$*)*: *δ* 32.3, 44.2, 72.5, 122.5, 123.8, 125.9, 127.8, 128.2, 128.9, 130.0, 130.6, 131.2, 132.5, 137.5, 139.8, 142.1, 147.2, 168.3; GC-MS, *m*/*z*: 312 (M+); Elemental Analysis: Anal. Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97; Found C, 84.55; H, 6.47; N, 8.94.

CONCLUSIONS:

In conclusion, this manuscript describes a method in which $Pb(OAc)_2$ is a highly efficient catalyst for the synthesis of 1,5-Benzodiazepine derivatives by o-phenylenediamine and ketones at room temperature with solvent free conditions. This transformation was successfully studied for different range of ketones. The advantages include low cost, ease of catalyst handling, mild reaction conditions and reactions carried out at room temperature with excellent yields.

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