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An efficient synthesis of benzodiazepine derivatives under environmentally benign conditions

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Abstract:

An efficient and clean synthesis of benzodiazepines is described by the reaction of o-phenylenediamine with various types of Chalcones in the presence of catalytic amounts of Lanthanum Nitrate under mild conditions at room temperature in excellentyields, the products were tested for purity by TLC and characterized by M.P, IR and ^{1}H NMR spectral studies.

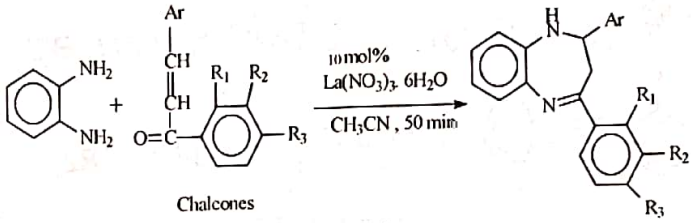
Keywords : La $(NO_3)_3$. $6H_2O$,o-Phenylenediamine, Chalcones, mild conditions.

INTRODUCTIONS:

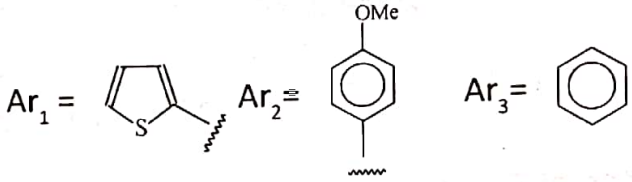
The organic transformation using reusable and water tolerant catalyst in recent years received much attention. Use of water tolerant catalystis an ideal methodologysince they can conveniently be handled and make the experimental procedure simple and ecofriendly [1]. The synthesis of benzodiazepine derivatives

have received a great deal of interest as they are widely used class of bioactive compounds due to their remarkable biological and pharmacological properties. [2,3]such as antianxiety, hypnotic, tranquilizing, anti-inflammatory, anticonvulsant, antifeedant, antibacterial, analgesic, sedative and anti-depressive properties. [2]. The benzodiazepine derivatives also used as valuable precursors in the synthesis of various fused heterocyclic systems [4] such as triazolo-, oxazino-, oxadiazolo- and furano-benzodiazepines. In addition to this some benzodiazepines are used in fine chemical industries such as photographical dyes for acrylic fibers [5]. In view of their biological and pharmacological importance in the literature few methods for their preparation have been reported.These include condensation of *o*-phenylenedi-aminewith á-â unsaturated compounds[6], â-haloketones or ketones in the presence of catalyst such as Yb $(OTf)_3$ [7], $InBr_3$ [8], BF_3-etherate [9], Amberlyst-15, [10] ionic liquid,[11] SbCl3-Al2O3, [12] and Zn[L-Proline]$_2$,[13], TBAB[14],SiO_2 [15], Citric Acid[16], Acetic Acid –under MWI, [17] I_2 [18], Zirconium Oxychloride [19] ,Ag3PW12O40, [20] $AgNO_3$ [21], Cu-bronze [22], Zirconia solid acid,[23],Chloroacetic acid [24],Silica gel using ultrasound [25] but unfortunately, fewof the reported processes suffer from major or minor limitations,In view of current interest in catalytic processes, there is a advantage in developing synthesis of benzodiazepines using inexpensive, mild and non-polluting reagent.To contribute our efforts, we investigated the synthesis of 2, 3-dihyro-1, 5-benzodiazepines catalyzed by La $(NO_3)_3 \cdot 6H_2O$ though it is reported[26] in the literature for the synthesis of 1, 5-benzodiazepines, but it is for their synthesis from ketones. The present work involves novel chalcones as starting material for the synthesis of new 1, 5-benzodiazepine derivatives using La $(NO_3)_3 \cdot 6H_2O$ as a catalyst. In conclusion the present procedure for the synthesis of benzodiazepines in presence of catalytic amount of La $(NO_3)_3 \cdot 6H_2O$ has the advantage of mild reaction conditions, inexpensive catalyst with high yields of products and simple experimental work-up which makes it is a useful and important addition to the present existing methods.

Scheme-I

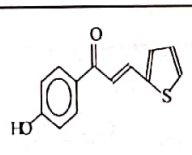
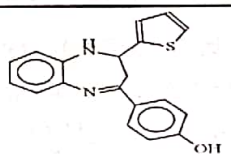
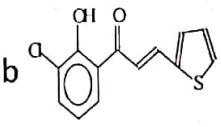
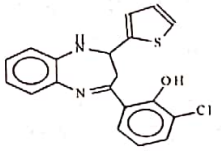
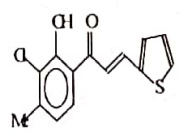
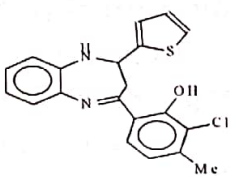


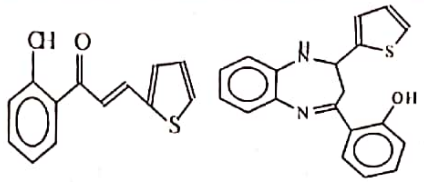
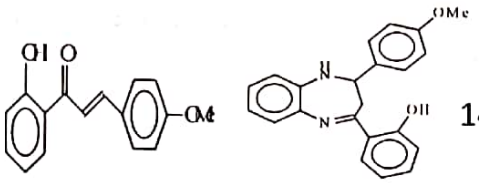
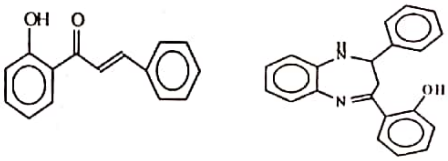
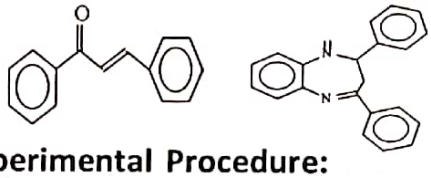
Chalcones



Entry	R_1	R_2	R_3	Ar
3a	H	H	OH	Ar_1
3b	OH	Cl	H	Ar_1
3c	OH	Cl	Me	Ar_1
3d	OH	H	H	Ar_1
3e	OH	H	H	Ar_2
3f	OH	H	H	Ar_3
3g	H	H	H	Ar_3

Table-I: Synthesis of benzodiazepines(3a-g) using lanthanum Nitrate
as an efficient and mild Catalyst.

Entry	Chalcones	Products	M.P (°C)	Yield (%)
3a			138	80
3b			190	85
3c			155	84

3d		110	85
3e		145	80
3f		119	82
3g		127	85

Experimental Procedure:

A mixture of o-Phenylenediamine (1 mmol), Chalcones (1 mmol), and $La(NO_3)_3.6H_2O$ (10 mol %) in 10 mL of MeCN was stirred at 50°C for 50min. After completion of the reaction as monitored by TLC [eluent: ethyl acetate: pet. ether (3:7)], the crude product washed with water and extracted into ethyl acetate and purified by column chromatography to afford pure 2, 4-disubstituted-1, 5-benzodiazepines (3a-g) in 80-85% yield [Scheme-I].The formation of 1,5-benzodiazepine derivatives was ascertained by their M.P and spectral analysis (IR,^{1}H-NMR and Mass).Their M.P and Yields are Shown in Table-I.

The catalyst wasrecovered from the aqueous layer by evaporation underreduced pressure and can be reuse. From the results (Table -I) it is clear that $La(NO_3)_3.6H_2O$ is an efficient catalystfor the synthesis of 1, 5-benzodiazepines under environmentally benign conditions.

Characterizations

All ^{1}H NMR spectra were recorded in $CDCl_3$ / DMSO-d6 on a Brucker AC 200 and Brucker MSL 300 spectrometers and chemical shift were reported in ppm downfield from tetra methyl silane. Infrared spectra were recorded on a PerkinElmer infra-red spectrophotometer using KBr discs, TLC was performed on silica gel coated aluminum plates using ethyl acetate and pet ether (3:7 v/v) as eluent, melting points were determined on an electronic melting point apparatus and were uncorrected.

Compound 3a :

^{1}H NMR ($CDCl_3$) : δ = 3.70(t, 1H, J=12.2Hz,), 3.4 (dd, 1H, J=12.2Hz, 4.4Hz), 4.46(s, 1H), 5.0(dd, 1H, J=12.2Hz, 4.4Hz), 6.2-7.2 (m, 11H). MS [m/z], :321 (M^+)

Compound 3b:

^{1}HNMR (DMSO-d6) : δ = 3.4(s, 1H, NH), 3.75(t, 1H, J=12.2Hz,), 4.35 (dd, 1H, J=12.2Hz, 4.4Hz),5.1(dd, 1H, J=12.2Hz, 4.4Hz), 6.2-7.2 (m, 10H).

Compound 3c :

^{1}HNMR(DMSO-d6) : δ = 3.44(s, 1H, NH),4.20(t, 1H, J=12.2Hz), 4.6 (dd, 1H, J=12.2Hz, 4.4Hz), 4.8 (dd, 1H, J=12.2Hz, 4.4Hz), 6.4-7.4 (m, 9H).

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