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Organo Catalysed Microwave Assisted Three Component Reaction to Produce 1, 5-Benzodiazepine Derivatives

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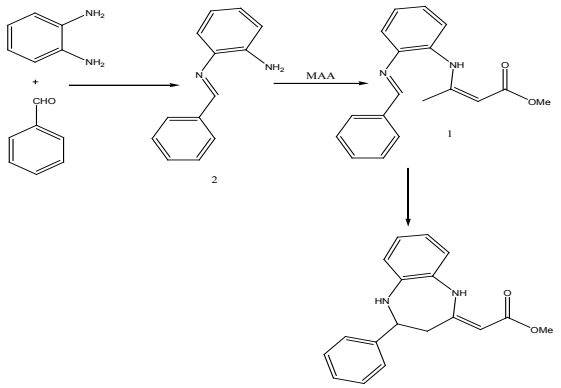
Abstract: *A microwave assisted solventless one pot three component reaction of 1, 2 phenylenediamine, aromatic aldehydes and ß-keto esters in presence of catalytic amount of tirchloroacetic acid to produce 1, 5-benzodiazepines is reported. A series of 1, 5-benzodiazepine derivatives were synthesized in good yields and short reaction times (1-2minutes). This reaction involves the γ- selective C-C bond formation of ß-keto esters to produce 1, 5 benzodiazepine derivatives. This method is very easy, rapid and high yielding for the synthesis of 1, 5-benzodiazepine derivatives.*

1. Introduction

Benzodiazepines are important compounds because of their pharmacological properties [1, 2]. 1, 5-Benzodiazepines have been extensively used as anticonvulsant, antianxiety, analgesic, sedative, antidepressive, hypnotic and antiinflamatory agents [2-5]. Benzodiazepine derivatives are also commercially used such as dyes for acrylic fibers (3). In the last decade, the area of biological interest of 1, 5-benzodiazepines has been extended to several diseases such as cancer [7] viral infection [8] and cardiovascular disorders [9]. In particular, 1, 5-benzodiazepines are useful precursors for the synthesis of fused ring benzodiazepine derivatives such as triazolo, oxadiazolo, oxazino, and furano benzodiazepines [10, 11]. Due to their wide range of applications, these compounds have received a great deal of attention in connection with their synthesis [12]. Their utilities were fully realized in the process of drug discovery [13] and the total synthesis of complex natural products [14]. Although a great number of such useful reactions have been reported, the development of a novel multi-component reaction is still important in the fields of medicinal and organic syntheses. Despite their importance from a pharmacological, industrial and synthetic point of view, comparatively few methods for their preparation are reported in the literature. These include condensation reactions of 1, 2 phenylenediamines with α, ß-unsaturated carbonyl compounds [15] ß-haloketones [16] or ketones in the presence of In-Br_3 [17], $NaBH_4$ [18], solid super acid sulfated zirconia [19] Zirconia solid acid [20] SiO_2 [21] MgO-$POCl_3$, [22] $Yb(OTf)_3$ [23], Al_2O_3/P_2O_5 under microwave [24], molecular iodine (25), and under microwave irradiation using acetic acid (26).Unfortunately, many of these processes suffer major or minor limitations, such as drastic reaction conditions, expensive reagents, low yields, tedious work-up procedures and the occurrence of several side reactions. The application of microwave energy for conducting organic reactions at highly accelerated rates is an emerging technique. Moreover often when carrying out a reaction in a microwave oven, the use of a solvent can be avoided, which is important in order to make the synthesis more environmentally friendly (green chemistry). These observations led us to investigate the possibility of improving the methods used for the synthesis of the 1, 5-benzodiazepine scaffold [27-28]. We hereby report first time the use of trichloroacetic acid as a catalyst to carry out synthesis of 1, 5 benzodiazepine derivatives under microwave irridation.

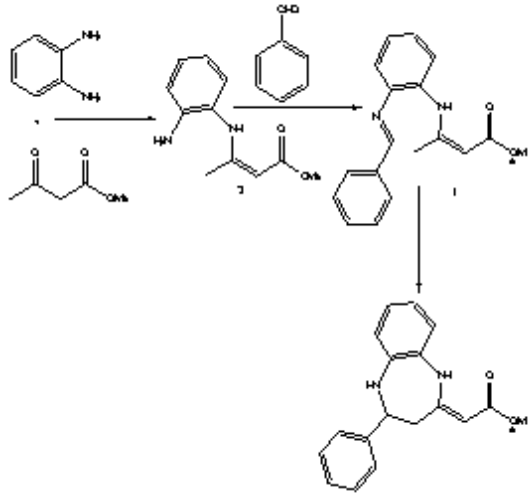
2. Results and discussion

The reaction was examined in details for the formation of intermediate (1) [29]. In case phenylenediamine and aldehydes are mixed first in presence of acid catalysts, intermediate (2) is formed which gives intermediate (1) on addition of methyl acetoacetate. The step involving the formation of (1) from (2) is slow (scheme1).



Scheme1: 1, 2 Phenylenediamine reacts with aldehyde and then with methyl acetoacetate

In case 1, 2 phenylenediamine and methyl acetoacetate are reacted first in presence of acid catalysts, intermediate (3) is formed which gives intermediate (1) on addition of aldehydes. This step is fast. It is obvious that mixing all there component 1, 2 phenylene diamine, aldehydes and methyl acetoacetate will lead to the formation of final product following scheme 2.



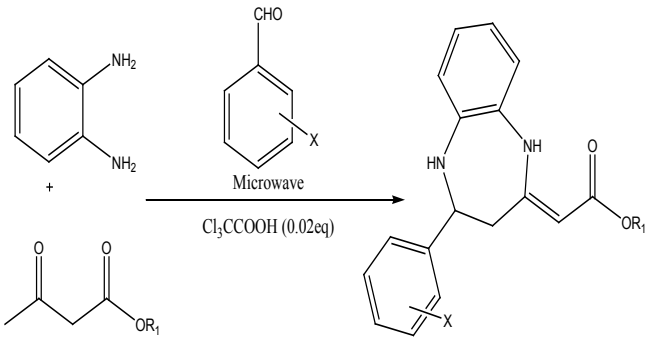
Scheme2: 1, 2 phenylenediamine reacts with methyl acetoacetate then with aldehyde

We tried this reaction without catalyst and found that the reaction did not take place in case aldehydes were solid while proceeded very slowly in case aldehydes were liquids at room temperature.

Reaction was optimized for the amount of catalyst and it was formed that reaction could be carried well taking 0.02 equivalent of catalyst. Minimum amount of catalyst used by conventional methods was 0.1 equivalent [25]. We got success in reducing the amount of catalyst siginificantly.

3. Experimental section

(a). One-pot three-component reaction Typical procedure: Trichloroacetic acid was added to the mixture of 1, 2 phenylenediamine (1.0mm), ß – ketoesters (1.3mm) and aldehydes (1.0mm). (Scheme 3).The mixture was placed in microwave under irradiation for a period of 1-2 minutes. After the completion of the reaction (monitored over silica gel TLC) the reaction mixture was cooled to room tempeture and was extracted with ethyl acetate. The solvent was evaporated in vacuo.

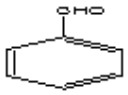
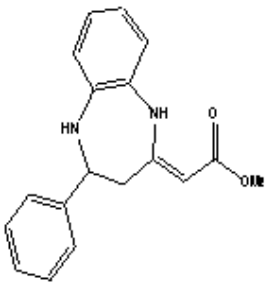
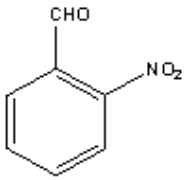
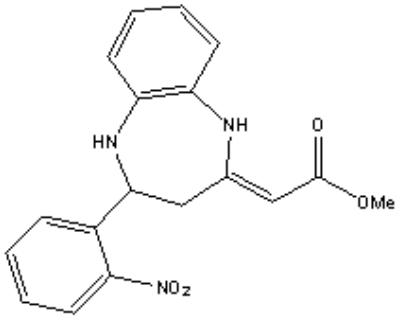
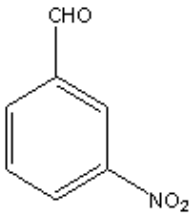
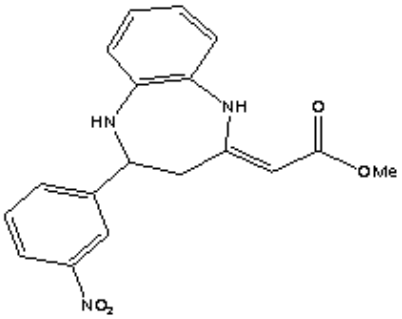
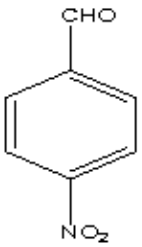
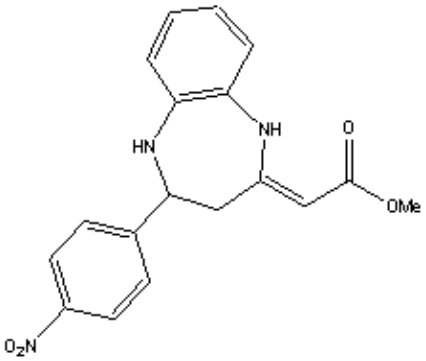


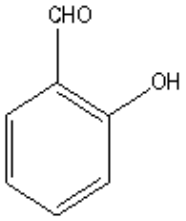
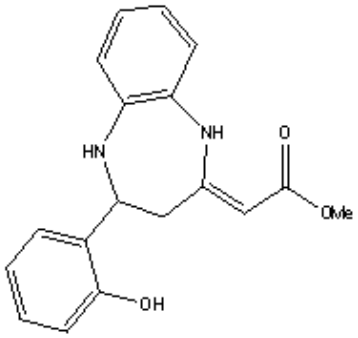
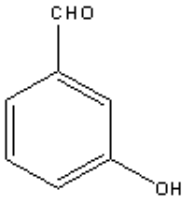
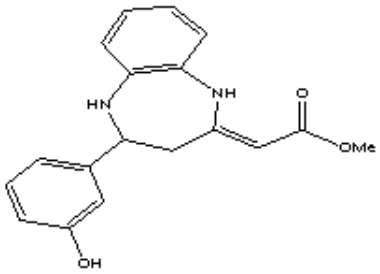
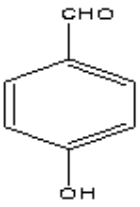
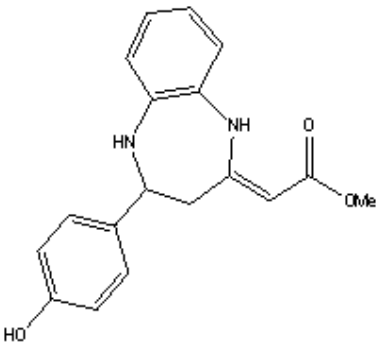
R_1= OMe, $CH_2C_6H_5$

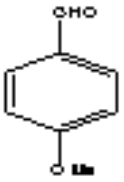
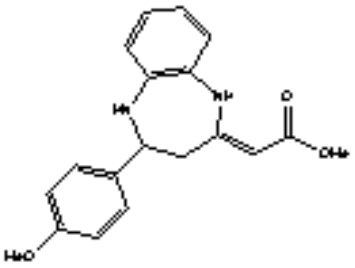
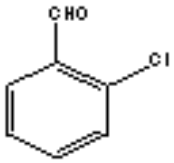
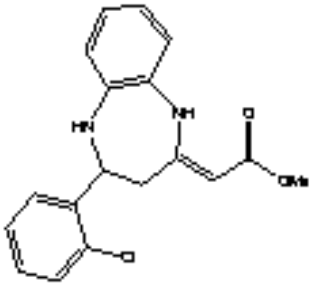
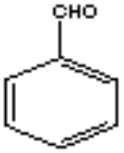
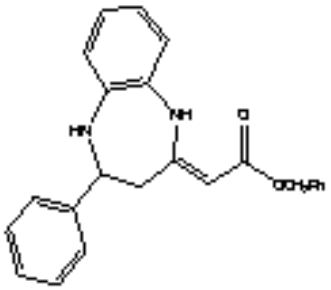
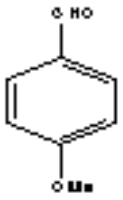
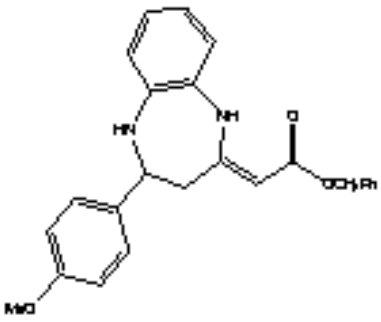
X= 2-NO_2, 3-NO_2, 4-NO_2, 2-OH, 3-OH, 4-OH, OMe, Cl

Scheme3: Reaction of 1, 2 phenylenediamine, ß-keto esters and aldehydes

Table1: Synthesis of various 1, 5- benzodiazepine derivatives

	Ester	Aldehyde	Product	Yield
1	MAA		 **1a**	92%
2	MAA		 **2a**	80%
3	MAA		 **3a**	81%
4	MAA		 **4a**	82%

5	MAA			**5a**	88 %
6	MAA			**6a**	80%
7	MAA			**7a**	80%

8	MAA			**8a**	93%
9	MAA			**9a**	92%
10	BAA			**10a**	95%
11	BAA			**11a**	86%

MAA=Methyl acetoacetate
BAA=Benzyl acetoacetate

Compound 1a

Reaction was carried out according to the typical procedure with 1, 2-phenylenediamine (0.108g, 1.0mm), methyl acetoacetate (0.139ml, 1.3mm), benzaldehyde (0.101ml, 1.0mm), and CCl_3COOH (0.003g, 0.02mm) to give **1a** (92%) , a pale yellow oil. IR (KBr) 3060, 1662, 1623, 1593, 1494, 1252, 1111.52 cm^{-1}. ^{1}HNMR ($CDCl_3$, 300MHz) δ 2.39 (m, 2H, CH_2): 3.47 (s, 3H, CH_3): 3.83 (s, 1H, CH): 3.86 (d, 1H, NH): 3.87 (dd, 1H, J= 8.1, 4.44 Hz NH): 7.52-9.33 (m, 5H, Ph): 7.85-7.81 (m, 4H, Ph)

Compound 2a

Reaction was carried out according to the typical procedure with 1, 2-phenylenediamine (0.108g, 1.0mm), methyl acetoacetate (0.139ml, 1.3mm), 2-nitro benzaldehyde (0.151g, 1.0mm), and CCl_3COOH (0.003g, 0.02mm) to give **2a** (80%),a pale yellow amorphous.

Compound 3a
Reaction was carried out according to the typical procedure with 1, 2-phenylenediamine (0.108g, 1.0mm), methyl acetoacetate (0.139ml, 1.3mm), 3-nitro benzaldehyde (0.151g, 1.0mm), and CCl_3COOH (0.003g, 0.02mm) to give **3a** (81%), a pale yellow amorphous.

Compound 4a
Reaction was carried out according to the typical procedure with 1, 2-phenylenediamine (0.108g, 1.0mm), methyl acetoacetate (0.139ml, 1.3mm), 4-nitro benzaldehyde (0.151g, 1.0mm), and CCl_3COOH (0.003g, 0.02mm) to give **4a** (82%), a pale yellow amorphous.

Compound 5a
Reaction was carried out according to the typical procedure with 1, 2-phenylenediamine (0.108g, 1.0mm), methyl acetoacetate (0.139ml, 1.3mm), 2-hydroxy benzaldehyde (0.104ml, 1.0mm), and CCl_3COOH (0.003g, 0.02mm) in to give **5a** (88%), a pale yellow amorphous.

Compound 6a
Reaction is carried out according to the typical procedure with 1, 2-phenylenediamine (0.108g, 1.0mm), methyl acetoacetate (0.139ml, 1.3mm), 3-hydroxy benzaldehyde (0.122g, 1.0mm), and CCl_3COOH (0.003g, 0.02mm) to give **6a** (80%), a pale yellow amorphous.

Compound 7a
Reaction was carried out according to the typical procedure with 1, 2-phenylenediamine (0.108g, 1.0mm), methyl acetoacetate (0.139ml, 1.3mm), 4-hydroxy benzaldehyde (0.122g, 1.0mm), and CCl_3COOH (0.003g, 0.02mm) to give **7a** (80%), a pale yellow amorphous.

Compound 8a
Reaction was carried out according to the typical procedure with 1, 2-phenylenediamine (0.108g,1.0mm) methyl acetoacetate (0.139ml, 1.3mm), 4-methoxybenzaldehyde (0.121ml, 1.0mm), and CCl_3COOH (0.003mg, 0.02mm) in to give **8a** (93%), a pale yellow amorphous. IR (KBr) 3360, 2953, 2840, 1600, 1512, 1436, 1258, 1174 cm^{-1}. ^{1}HNMR ($CDCl_3$, 300MHz) δ 2.4-2.27 (m, 2H, CH_2): 3.74 (s, 3H, OCH_3): 3.85 (s, 2H, CH): 3.86 (s, 3H, OCH_3): 3.84 (s, 1H, NH): 3.89 (dd, 1H, NH): 7.62 (dd, 4H, Ph): 7.85-7.51 (m, 4H, Ph)

Compound 9a
Reaction was carried out according to the typical procedure with 1, 2-phenylenediamine (0.108g, 1.0mm), methyl acetoacetate (0.139ml, 1.3mm), 2-chlor benzaldehyde (0.1121ml, 1.0mm), and CCl_3COOH (0.003g, 0.02mm) to give **9a** (92%), a pale yellow amorphous.

Compound 10a
Reaction was carried out according to the typical procedure with 1, 2-phenylenediamine (0.108g, 1.0mm), benzyl acetoacetate (0.224ml, 1.3mm), benzaldehyde (0.101ml, 1.0mm), and CCl_3COOH (0.003g, 0.02mm) in to give **10a** (95%), a pale yellow oil. ^{1}HNMR ($CDCl_3$, 300MHz) δ 2.39 (s, 2H, CH_2): 2.23 (m, 2H, CH_2): 3.49 (s, 1H, CH): 3.49 (s, 1H, NH): 4.69 (dd, J= 9.1, 4.1 Hz, NH): 7.43-7.24 (m, 5H, Ph): 7.56-7.45 (m, 5H, Ph): 8.12-7.59 (m, 4H, Ph).

Compound 11a
Reaction was carried out according to the typical procedure with 1, 2-phenylenediamine (0.108mg,1.0mm) benzyl acetoacetate (0.224ml, 1.3mm), 4-methoxybenzaldehyde (0.121ml, 1.0mm), and CCl_3COOH (0.003mg, 0.02mm) in to give **11a** (86%), a pale yellow oil.

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