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1,5-Benzoheteroazepines through eco-friendly general condensation reactions

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ABSTRACT

Condensation reactions of *o*-phenylenediamine and 2 equiv of acetone produce biaryl-substituted 1,5-benzodiazepines. The synthetic protocol shows general applicability since similar reaction of *o*-phenylenediamines, *o*-aminophenol, and *o*-aminothiophenol with ketones or chalcones leads to formation of functionalized 1,5-benzoheteroazepines in good to excellent yields. The synthetic protocol fulfills many green-chemical requirements using simple MW-assistance to promote the activation of ketones and the eco-compatible Er(III) triflate as activator of chalcones.

The clinical importance and commercial success associated with pharmacologically active benzodiazepines have led to their recognition by the medicinal community as structures of particular significance.[1] 1,5-Benzodiazepines exert a biological activity similar to well known 1,4-derivatives and their ring system has demonstrated considerable utility not only in central nervous system (CNS)-drug design, but also as peptidomimetic scaffolds[2] and key intermediates for the preparation of other fused ring compounds.[3] Consequently, the development of new synthetic approaches to the 1,5-benzodiazepine ring system and their further elaboration have provided access to a broad range of functionalized derivatives that have contributed to advance in understanding the underlying principles of structure and reactivity. The commonly employed methods to construct the ring skeletons involve the cyclocondensation of 1,2-diamines with ketones,[4] enones,[5] β-haloketones,[2] using ytterbium triflate,[6] BF_3-etherate,[2] polyphosphoric acid,[2b] MgO and $POCl_3$,[4] ionic liquids,[7] microwave assistance,[8] $SbCl_3$–Al_2O_3,[9] and zinc montmorillonite heterogeneous catalysts,[10] sulfated zirconia,[11] $Ag_3PW_{12}O_{40}$,[12] CH_3COOH,[13] MCM-41 zeolite,[14] piperidine-AcOH,[15] $Ga(OTf)_3$,[16] PPA/SiO_2,[2b] dodecylsulfonic acid in water,[17] $La(NO_3)_3$,[18] sulfamic acid,[19] etc. Although development of non-hazardous synthetic methodologies for organic reactions is one of the latest challenge to the organic chemists, only few of the known benzodiazepine synthesis methods tried to answer this demand. Nonetheless, the search for a better methodology to synthesize benzodiazepines and analogs continues, whereby general applicability, simplicity, reusability, ecological safety, and economic viability could be achieved.

In the last decade, our research group has been making considerable efforts, designing and carrying out innovative synthetic protocols in organic synthesis adopting a more eco-sustainable approach.[20–22] As a part of this research, we found that lanthanide(III) derivatives such as MW-irradiation can promote reactive pathways in very convenient way from green chemical point of view. Thus, we report herein a new utility of erbium(III) triflate catalyst for MW-assisted condensation reactions of *o*-phenylenediamine **a**, *o*-aminophenol **b** or *o*-aminothiophenol **c** with carbonyl compounds to form functionalized 1,5-benzodiazepines, 1,5-benzoxazepines and 1,5-benzothiazepines.

In an attempt to identify the most optimal experimental conditions, a detailed study was performed on *o*-phenylenediamine **a** and acetone (Scheme 1). Table 1 presents the results obtained using different reaction solvents under the conditions of 5 mol % catalyst and 3–7 h at room temperature. As can be seen from the data, acetonitrile was found to be a good solvent (Table 1, entry 1) giving 1,5-benzodiazepine in 82% yield (Table 1, entry 1). Increasing the amount of $Er(OTf)_3$ to 10 mol % did not significantly improve the yield (Table 1, entry 2). Lower yield of product **1a** was registered when the reaction was performed in some other little polar solvents (Table 1, entries 3–5), whilst only traces of the product were collected carrying out the process in water (Table 1, entries 6). Surprisingly, the reaction of *o*-phenylenediamine **a** and

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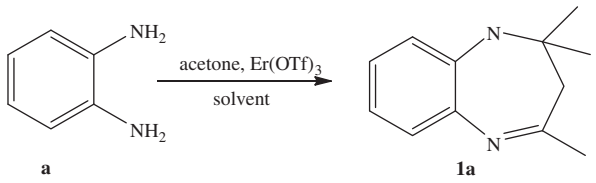


Scheme 1. $Er(OTf)_3$ catalyzed reaction of *o*-phenylendiamine and acetone.

Table 1
$Er(OTf)_3$-catalyzed (5 mol %) reactions of *o*-phenylenediamine and acetone

Entry	Solvent	Time (h)	Yield (%)[a]
1	CH_3CN	3	82
2	CH_3CN[b]	7	84
3	AcOEt	7	56
4	CH_2Cl_2	7	39
5	$CHCl_3$	7	30
6	H_2O	7	Trace
7	Neat	3	98
8	Neat[c]	3	98
9	Neat[d]	12	0

[a] Isolated yield.
[b] 10 mol % of catalyst were used.
[c] 3 mol % of catalyst were used.
[d] No catalyst was used.

acetone catalyzed by $Er(OTf)_3$ (5 mol %) in solvent free conditions gave the corresponding 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine **1a** in almost quantitative yield (Table 1 entry 8), whereas 98% of product was obtained performing the reaction in presence of 3 mol % of catalyst only. Finally, in a control reaction without using the catalyst, no desired product was observed, even after prolonged reaction time (Table 1, entry 9).

Thus, stir a mixture of *o*-phenylenediamine **a** (2 mmol), acetone (4.5 mmol), and $Er(OTf)_3$ (0.1 mmol) at room temperature for 3 h was found to be the best condition for the synthesis of 1,5-benzodiazepine **1a**.[23] This general procedure was used for reactions of *o*-phenylenediamine **a**, *o*-aminophenol **b** and *o*-aminothiophenol **c** with different aryl- and alkylketones (Scheme 2, Table 2). Reactions of *o*-phenylenediamine **a** with acetophenones bearing weak electron-donating and electron-withdrawing substitution groups gave products in good to excellent yields (94–98%) (Table 2, entries 22–4). In contrast, only modest yield of the product was registered when the reaction was performed on the highly electron rich *p*-methoxy acetophenone (Table 2, entries 5).

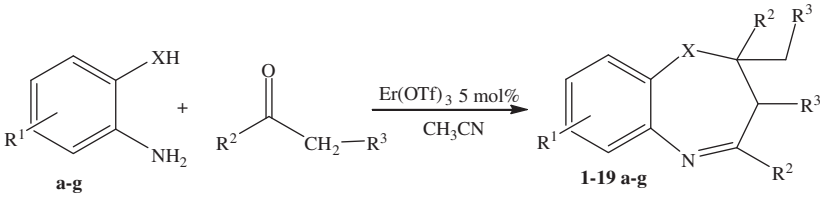
Reactions of alkylketones such as acetone, 2-butanone, 3-pentanone, and 2,4-pentandione, also produced benzodiazapines (Table 2, entries 1, 6–8), however, slightly lower yields were obtained from the more hindered alkylketones (Table 2, entries 6 and 7). Moreover, 4-and 6-methylbenzene-1,2-diamine (**d** and **e**) were used as the substrates to evaluate the substituent effect on *o*-phenylenediamine. Good product yield (99%) and regioselectivity (85:15 in more favorable cases) were obtained from this reaction (Table 2, entry 10). However, only in the case of 4-nitrobenzene-1,2-diamine **f** acceptable yield of 1,5-benzodiazepine derivative was collected (Table 2, entry 11) and no product was detected in the case of 6-nitrobenzene-1,2-diamine **g** (Table 2, entry 12) most likely due to the H-bonding between imine N–H and *o*-nitro group.

In the case of *o*-aminophenol **b**, the increased nucleophilicity of the oxygen atom made the evolution of the imine intermediate toward the 1,5-benzoxazepine derivative more difficult. Nonetheless, *o*-aminophenol **b** reacted with acetone, providing modest yield of products **13b** (Table 2, entry 13), whereas electron-rich or –poor systems did not furnish any cyclic product (Table 2, entry 14). Even more, the highly nucleophilic sulfur atom made unreactive the iminic reaction intermediate, so that no 1,5-benzothiazepine derivatives were collected in any reported examples of reaction between ketones and *o*-aminothiophenol **c** (Table 2, entry 15). These reactions (Table 2, entries 14 and 15), in, fact lead to the formation of the corresponding Schiff bases without further cyclization to form of 1,5-benzoheteroazepine as observed by GC–MS analysis of the crude reaction mixture.

Taking into account the benign effects that the microwave assistance exerts on the synthesis of 1,5-benzodiazepines catalyzed by mesoporous MCM-41,[8] the developed protocol was also performed using MW. In such cases, significant improvements in yield were observed for all reported examples (Table 2).[23] Surprisingly, good results were also obtained when the same MW-assisted reactions were performed in the absence of any catalyst (Table 2).

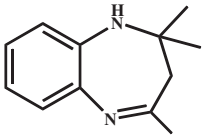
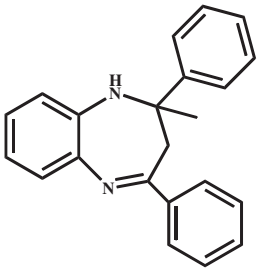
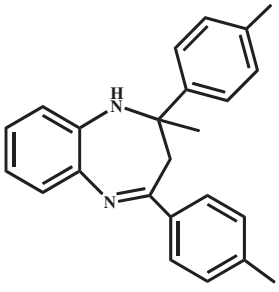
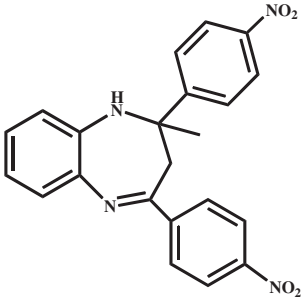
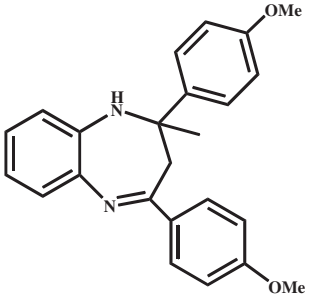
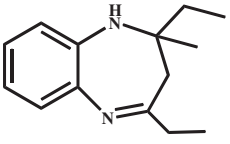
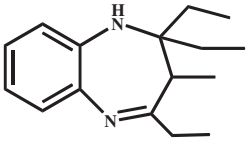
In the attempt to explore the wide applicability of the proposed method, the experiments involving reaction of α,β-unsaturated ketones (chalcones) and *o*-anilino derivatives **a**, **b** and **c** were also carried out (Scheme 3).[24,25] However, only modest yield of condensation product **20h** was detected from the reaction conducted at room temperature with 5 mol % of $Er(OTf)_3$ between *o*-phenylenediamine **a** and (*E*)-chalcone **h**, (Table 3, entry 1), probably due to the low nucleophilicity of the amino group, as described in previous reports.[16] However, the reaction between 2-hydroxylchalcon **i** and *o*-phenylendiamine **a** gave good yield of 1,5-benzodiazepine derivative **21i** (Table 3, entry 2), thus confirming the crucial positive effect of the hydroxyl group at 2-position of chalcone.[16] Even better, almost quantitative yield of product **21j** was collected when the reaction was performed on the more electron-rich (*E*)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one **j** (Table 3, entry 3).

We have also explored the reactions of *o*-aminophenol **b** and *o*-aminothiophenol **c** with chalcone using $Er(OTf)_3$ as a catalyst. Unfortunately, the reaction of *o*-aminophenol **b** with the chalcons **h** did not afford any product and the same unsatisfying result was obtained in the case of more reactive 2′-hydroxychalcone derivatives **i** and **j** (Table 3, entry 4–6). In contrast, the reaction of simple chalcone **h** with *o*-aminothiophenol **c** generated fair yield of product **26h**, whereas, very good results were registered for the more reactive substrates **i** and **j** (Table 3, entries 8 and 9). Confirming the trend reported for the 1,5-benzodiazepine derivatives. All the



Scheme 2. 1,5-benzoheteroazipenes from *o*-phenylendiamines a, d-g, *o*-aminophenol b and *o*-aminothiophenol c.

Table 2
Synthesis of 1,5-benzodiazepines, oxazepines and thiazepine from ketones catalyzed by 5 mol % of Er(III) triflate

Entry	Substrate	Ketone	Product[a]	Yield[b]
1	**a**	Acetone	 **1a**	95 99[c] 99[d]
2	**a**	Acetophenone	 **2a**	98 99[c] 80[d]
3	**a**	*p*-Methyl acetophenone	 **3a**	94 98[c] 82[d]
4	**a**	*p*-Nitro acetophenone	 **4a**	95 99[c] 85[d]
5	**a**	*p*-Methoxy acetophenone	 **5a**	45 80[c] 73[d]
6	**a**	2-Butanone	 **6a**	80 95[c] 70[d]
7	**a**	3-Pentanone	 **7a**	76 83[c] 65[d]

(*continued on next page*)

Table 2 (*continued*)

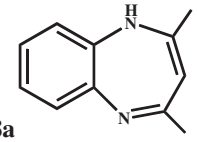
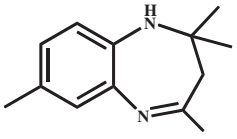
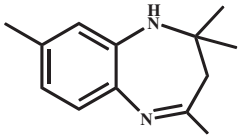
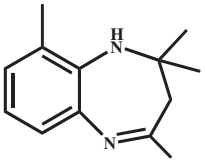
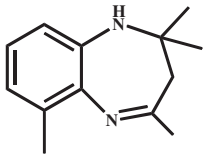
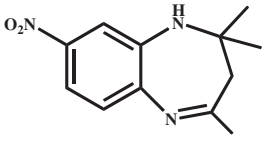
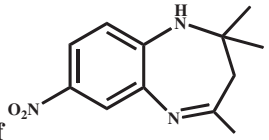
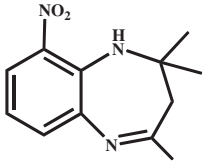
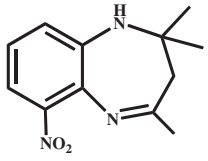
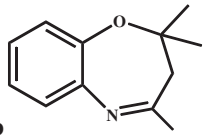
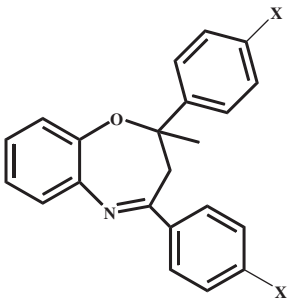
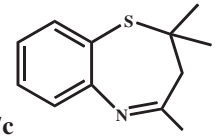
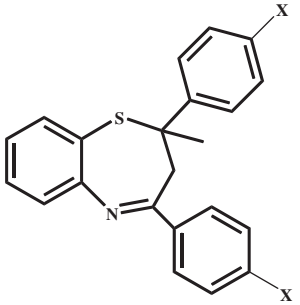
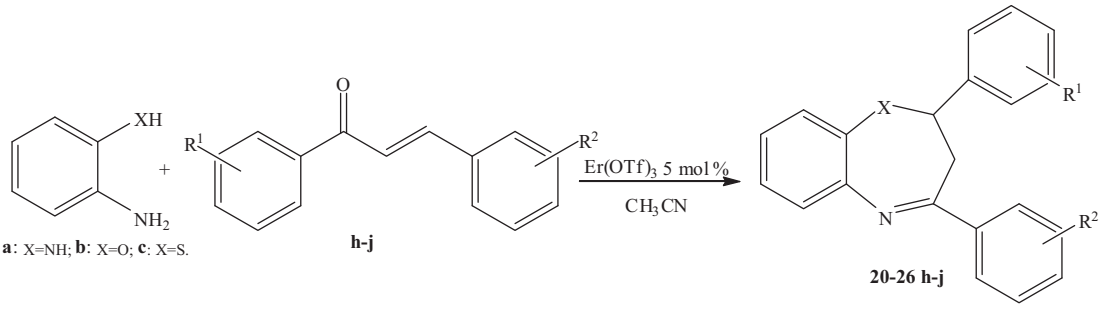
Entry	Substrate	Ketone	Product[a]	Yield[b]
8	**a**	2,4-Pentandione	 **8a**	98 99[c] 99[d]
9	*p*-Methyl phenylenediamine (**d**)	Acetone	 **9d**  **9dd**	99 (5.5/4.5)[e] 99[c] (6.5/3.5)[e,c] 99[c](5.9/4.1)[e]
10	*o*-Methyl phenylenediamine (**e**)	Acetone	 **10e**  **10ee**	99[c] (1.5/8.5)[e,c] 99[c] (2.0/8.0)[e,c] 99[d] (2.5/7.5)[e]
11	*p*-Nitro phenylenediamine (**f**)	Acetone	 **11f**  **11ff**	75[c] (4.0/6.0[c]) 75[c] (3.0/7.0)[e,c] 75[d] (4.2/5.8)[e]
12	*o*-Nitro phenylenediamine(**g**)	Acetone	 **12g**  **12gg**	0[e,c] 0[c,e] 0[d,e]
13	**b**	Acetone	 **13b**	45[c] 55[c] 46[d]

Table 2 (*continued*)

Entry	Substrate	Ketone	Product[a]	Yield[b]
14	**b**	Acetophenone *p*-Nitro acetophenone *p*-Methoxy acetophenone	 **14b**: X=H; **15b**: X=NO_2, **16b**: X=OCH_3;	0[f] 0[c,f] 0[d,f]
15	**c**	Acetone	 **17c**	0[f] 0[c,f] 0[d,f]
16	**c**	Acetophenone *p*-Nitro acetophenone *p*-Methoxy acetophenone	 **18b**: X=H; **19b**: X=NO_2, **20b**: X=OCH_3;	0[f] 0[c,f] 0[d,f]

[a] All products were characterized by ^1H and ^{13}C NMR spectra.[26]
[b] All products were purified by flash column chromatography.
[c] MW-assisted reaction.
[d] MW-assisted reaction without catalyst.
[e] Product ratio was determined by ^1H NMR.
[f] The intermediate Shiff's base was the only product detected by GC–MS and ^1H NMR.



Scheme 3. Synthesis of benzoheterodiazepines from *o*-phenylendiamine **a**, *o*-aminophenol **b** and *o*-aminothiophenol c and chalcones.

attempts to improve the reported results by employing the microwave activation failed and only inextricable mixture of products was collected.

In summary, $Er(OTf)_3$ was found to be an effective catalyst for the synthesis of 2,2,4-trisubstituted-1,5-benzoheteroazepines under very mild reaction conditions promoting the reactions of *o*-phenylenediamine **a** and *o*-aminophenol **b** with several ketones and the reaction of chalcone derivatives with *o*-phenylenediamine **a** and *o*-aminothiophenol **c**. Moreover, a very eco-friendly protocol is proposed to obtain the synthesis of 1,5-benzodiazepines and 1,5-benzoxazepines through a previously unreported solvent-free microwave-assisted condensation process.

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Table 3
Synthesis of 1,5-benzodiazepines, oxazepines and thiazepine from chalcones catalyzed by 5 mol % of Er(III) triflate at room temperature

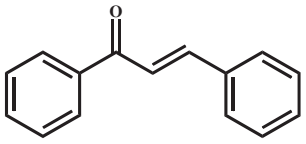
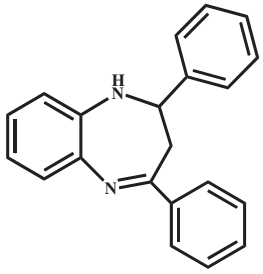
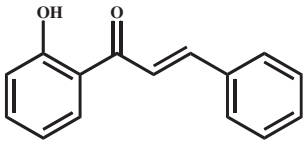
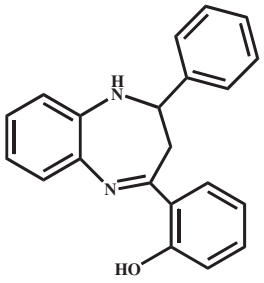
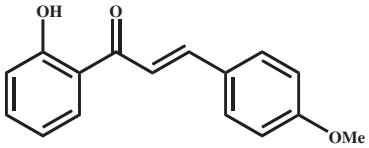
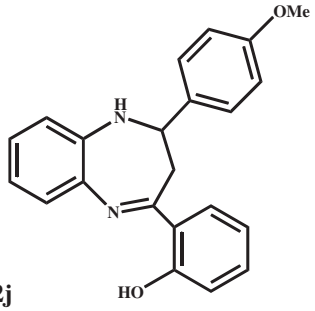
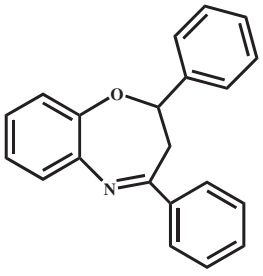
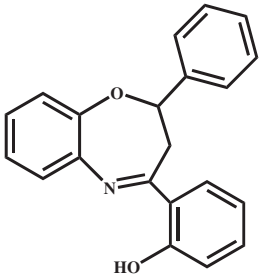
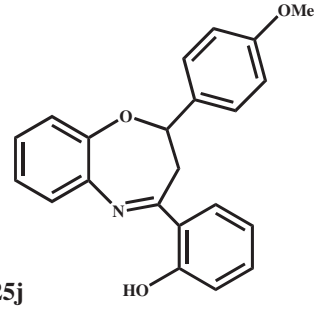
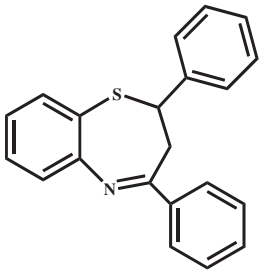
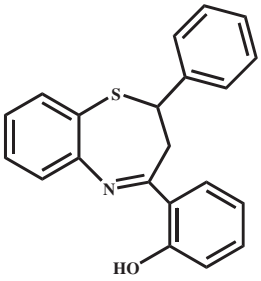
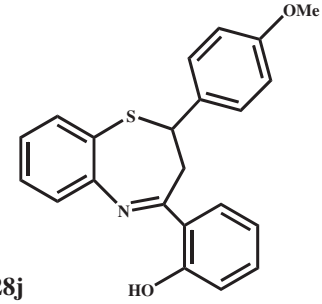
Entry	Substrate	Chalcone	Product[a]	Yield[b]
1	**a**	 **h**	 **20h**	20
2	**a**	 **i**	 **21i**	88
3	**a**	 **j**	 **22j**	98
4	**b**	**h**	 **23h**	0
5	**b**	**i**	 **24h**	0

Table 3 (*continued*)

Entry	Substrate	Chalcone	Product[a]	Yield[b]
6	**b**	**j**	 **25j**	0
7	**c**	**h**	 **26h**	45
8	**c**	**i**	 **27i**	83
9	**c**	**j**	 **28j**	98

[a] All products were characterized by ^{1}H and ^{13}C NMR spectra.
[b] All products were purified by flash column chromatography.

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23. General procedure for synthesis of 1,5-benzodiazepines from ketones by $Er(OTf)_3$: a mixture of o-phenylenediamine (2 mmol) and ketone (4 mmol) was stirred at room temperature in the presence of $Er(OTf)_3$ (0–5 mol %), adding in 5 ml of MeCN in the case of solid reagents only, for 3 h. After completion of the reaction (TLC analysis), the reaction mixture was diluted with water, and extracted with dichloromethane. The combined organic layer was dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by silica gel column chromatography (15% ethyl acetate in hexane) to afford the pure product. All reactions were completed within 3 h. All products were characterized by comparison of their ^1H NMR spectra with those of authentic samples.
24. *General procedure for synthesis of 1,5-benzodiazepines from ketones and from chalcones by microwave*: a mixture of o-phenylenediamine (2 mmol), ketone (2.2 mmol) and 0–5 mol % of $Er(OTf)_3$, suspended in 6.0 ml of MeCN (6.0 ml) in the case of solid reagents only, was put in the teflon reaction vessel of a Synthos 3000 microwave synthesizer and the teflon tube tapped and stirred at 120 °C for 30 min under MW radiation (1000 W). The reaction mixture was diluted with water, and extracted with dichloromethane. The combined organic layer was dried (Na_2SO_4), and concentrated in vacuo.
25. General procedure for synthesis of 2,4-disubstituted-1,5-benzoheteroazepine from calchones: a mixture of *o*-phenylenediamine (2 mmol) and calchone (2.2 mmol) was stirred at room temperature in the presence of $Er(OTf)_3$ (5 mol %) adding 5 ml of MeCN in the case of solid reagents only, for 3 h. After completion of the reaction (TLC analysis), the reaction mixture was diluted with water, and extracted with dichloromethane. The combined organic layer was dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by Silica gel column chromatography (15% ethyl acetate in hexane) to afford the pure product. All reactions were completed within 2 h. All products were characterized by comparison of their ^1H NMR spectra with those of authentic samples.
26. *Spectral data of 1, 5-benzodiazepines and 1, 5-benzothiazepines*. 2,2,4-Trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine **(1a):** yellow solid; ^1H NMR;[4] ^{13}C NMR;[2a] GC/MS: $M^+ = 188$; 2-Methyl-2,4-diphenyl-2,3-dihydro-1*H*-1,5-benzodiazepine **(2a):** orange solid; ^1H NMR;[2b] ^{13}C NMR[6]; 2-Methyl-2,4-di (*p*-tolyl)-2,3-dihydro-1*H*-1,5-benzodiazepine **(3a)**: orange solid[6]; 2-Methyl-2,4-di(4-nitrophenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine **(4a)**: orange oil; ^1H NMR (300 MHz, $CDCl_3$): δ 1.85 (s, 3H, CH_3), 2.98–3.33 (m, 2H, CH_2), 3.63 (brs, 1H, NH), 6.88–8.08 (m, 12H, ArH); ^{13}C NMR[10]; 2-Methyl-2,4-di(4-methoxyphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine **(5a)**: orange oil;[2d]; 2,4-Diethyl-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine **(6a)**: green oil[6]; 3-Methyl-2,2,4-Triethyl-2,3-dihydro-1*H*-1,5-benzodiazepine **(7a)**: green oil[2b]; 2,4-Dimethyl-1*H*-1,5-benzodiazepine **(8a)**: orange oil; ^1H NMR (300 MHz, $CDCl_3$) δ 1.83 (s, 3H, CH_3), δ 2.10 (s, 3H, CH_3), δ 3.82 (s br, 1H, NH), δ 5.23 (s, 1H), δ 6.69–7.36 (m, 4H, ArH); ^{13}C NMR[2c]; GC/MS: $M^+ = 172$; 2,2,4,8-Tetramethyl-2,3-dihydro-1H-1,5-benzo diazepine **(9dd)**; 2,2,4,7-Tetramethyl-2,3-dihydro-1H-1,5-benzodi azepine **(9d)**: brown oil[2d]; 2,2,4,9-Tetramethyl-2,3-dihydro-1H-1,5-benz odiazepine **(10e)**; 2,2,4,6-Tetramethyl-2,3-dihydro-1H-1,5-benzodiazepine **(10ee)**: green oil, ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, 3H, CH_3), 1.31 (s, 6H, $2CH_3$), 1.32 (t, 3H, CH_3), 1.33 (s, 6H, $2CH_3$), 1.81 (d, 1H, CH_2), 1.91 (d, 1H, CH_2), 2.23 (d, 1H, CH_2), 2.29 (d, 1H, CH_2), 2.37 (s, 3H, CH_{3ar}), 2.57 (s, 3H, CH_{3ar}), 6.58–6.51 (m, 3H, CH_{ar}), 6.87–6.91 (m, 3H, CH_{ar}).[10]C NMR[10] GC/MS: $M^+ = 202$; 2,2,4-Trimethyl-8-nitro-2,3-dihydro-1H-1,5-benzodiazepine **(11f)**; 2,2,4-Trimethyl-7-nitro-2,3-dihy dro-1H-1,5-benzodiazepine **(11ff)**: orange oil[2e]; 2,2,4-Trimethyl-2,3-dihydro-1H-1,4-benzooxazepine **(13b)**: yellow solid; ^1H NMR (300 MHz, $CDCl_3$): δ 1.65 (s, 3H, CH_3), 1.88 (d, 1H, CH_2), 2.14 (d, 1H, CH_2), 2.64 (s, 6H, $2CH_3$), 6.08–6.11 (m, 2H, CH_{ar}), 6.72–6.80 (m, 2H, CH_{ar}).[2f] ^{13}C NMR[2f] GC/MS: $M^+ = 189$; 2,4-diphenyl-2,3-dihydro-1H-1,4-benzodiazepine **(20h)**: yellow solid[2n] 2-phenyl-4-(2-hydroxy phenyl)-2,3-dihydro-1H-1,4-benzodiazepine **(21i)**: yellow solid[2e] 4-(2-hydroxy phenyl), 2-(4-methoxy phenyl)-2,3-dihydro-1H-1,4-benzodiazepine **(22j)**: yellow solid[2e] 2,4-Diphenyl-2,3-dihydro-1H-1,4-benzothiazepine **(26h)**: yellow solid.[2e] 2-phenyl-4-(2-hydroxy phenyl)-2,3-dihydro-1H-1,4-benzothiazepine **(27i)**:[2e] 4-(2-hydroxy phenyl), 2-(4-methoxy phenyl)-2,3-dihydro-1H-1,4-benzothiazepine **(28j)**: yellow solid[2e]