Article

Efficient TCT-catalyzed Synthesis of 1,5-Benzodiazepine Derivatives under Mild Conditions

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Abstract: 2,4,6-Trichloro-1,3,5-triazine (TCT) efficiently catalyzed the condensation reactions between 1,2-diamines and various enolizable ketones to afford 1,5-benzodiazepines in good to excellent yields. Simple and mild reaction conditions, the use of a cheap catalyst and easy workup and isolation are notable features of this method.

Keywords: Benzodiazepines, 2,4,6-trichloro-1,3,5-triazine, enolizable ketones, *o*-phenylenediamines.

Introduction

Benzodiazepines and its derivatives constitute an important class of heterocyclic compounds which possess a wide range of therapeutic and pharmacological properties. Derivatives of benzodiazepines are widely used as anticonvulsant, antianxiety, analgesic, sedative, antidepressive, and hypnotic agents [1-2]. In the last decade, the area of biological interest of 1,5-benzodiazepines has been extended to several diseases such as cancer, viral infection and cardiovascular disorders [3-4]. In addition, 1,5-benzodiazepines are key intermediates for the synthesis of various fused ring systems such as triazolo-, oxadiazolo-, oxazino- or furanobenzodiazepines [5-8]. Besides, benzodiazepine derivatives are also of commercial importance as dyes for acrylic fibers in photography [9]. Owing to their

versatile applications various methods for the synthesis of benzodiazepines have been reported in the literature. These include condensation reactions of *o*-phenylenediamines with α,β-unsaturated carbonyl compounds [10], with ketones in the presence of $BF_3 \cdot Et_2O$, $NaBH_4$, polyphosphoric acid or SiO_2, $MgO/POCl_3$, $Yb(OTf)_3$, Al_2O_3/P_2O_5 or AcOH under microwave conditions, Amberlyst-15 in the ionic liquid 1-butyl-3-methylimidazolium bromide ([bmim]Br), $CeCl_3 \cdot 7H_2O/NaI$ supported on silica gel, $InBr_3$, $Sc(OTf)_3$, sulfated zirconia, $InCl_3$, CAN, $ZnCl_2$ under thermal conditions, $AgNO_3$ [11-26]. These reactions also occur with various catalysts under solvent free conditions [27-30]. Nevertheless, many of these methods suffer from shortcomings such as long reaction times, harsh reaction conditions, low product yields, occurrence of several side products and difficulties in recovery of the products. Moreover, some of the reagents employed are very expensive. Consequently, the search continues for better catalysts in terms of operational simplicity and economic viability to synthesize 1,5-benzodiazepines.

In recent years, 2,4.6-trichloro-1,3,5-triazine (TCT) has received considerable attention due to its commercial availability and efficient delivery of anhydrous HCl in reaction media. It is inexpensive, and has been found to be versatile in functional group transformations such as conversions of alcohols to alkyl chlorides, oxidations of sulfides to sulfoxides, oxidative couplings of thiols and selenols, cleavage of thioacetals, etc. [31-36]. TCT reacts with 'incipient' moisture and produces three moles of HCl and cyanuric acid as a by-product (removable by simple washing with water). The HCl generated *in situ* acts as a protic acid, activates the carbonyl oxygen to promote the condensation to give the products [37]. In continuation to our efforts for the development of simple and novel methods for the synthesis of different heterocyclics [38-44], we report herein a simple and efficient method for the synthesis of 1,5-benzodiazepines using TCT as catalyst. While this paper was under peer review, Khodaei *et al.* [45] reported a similar procedure, differing from ours in the preferred solvent – CH_3CN *vs*. MeOH – and the amount of solvent required, 10 mol % *vs*. 4 mol %; the yields were similar although their reported reaction times were shorter, possibly due to the higher catalyst load used.

Results and Discussion

In the first instance, *o*-phenylenediamine (1 equiv.) and acetone (2.5 equiv.) were stirred at ambient temperature in dichloromethane with 4 mol% of TCT (Scheme 1). The reaction was complete within 5.5 h. After screening various solvents like methanol, ethanol, isopropanol, ethyl acetate and acetonitrile, we found that the reaction proceeds well in polar solvents, giving slight variations in reaction time and that methanol was the best choice for this reaction (Table 1).

Scheme 1. Synthesis of 1,5-benzodiazepines.
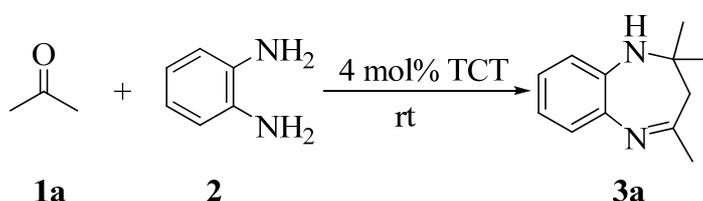
We assume that in the reaction medium TCT generates anhydrous HCl, which would be the active catalyst. When a similar reaction was performed using 10 mol% of aqueous HCl, the reaction took longer time (24 h) for completion, whereas the same conversion was achieved in 1 h with anhydrous 10% HCl in methanol. This further supports the proposed *in-situ* generation of anhydrous HCl in the reaction as the source of the catalytic action.

Table 1. Solvent effects in the reaction.

Entry[a]	Solvent	Time (h)	Yield (%)[b]
1	MeOH	1	99
2	EtOH	2	96
3	IPA	1.5	95
4	CH_2Cl_2	5.5	94
5	THF	6	84
6	EA	4	92
7	CH_3CN	7	93

[a] The reaction was performed with acetone (2.5 mmol) and
diamine (1 mmol) in 1 mL of solvent catalyzed by TCT.
[b] Isolated yield.

Under the optimized conditions, aliphatic ketones such as acetone reacted with 1,2-phenylenediamine in methanol (Scheme 2) to form the corresponding benzodiazepine in excellent yield (Table 2, entry 1). However, the reaction was sluggish with the substrates 2-butanone and 3-pentanone (Table 2, entries 2 and 3), resulting in poor yields. This may be due to the steric hindrance of a methyl group in the proximity of the carbonyl carbon. Alicyclic ketones such as cyclopentanone, cyclohexanone and cycloheptanone (Table 2, entries 4-6) gave excellent yields of products. With the present methodology, aromatic ketones such as acetophenone (Table 2, entry 7) and substituted acetophenones with both electron-donating and withdrawing groups generally produced the corresponding benzodiazepines in good to excellent yields, with the latter performing somewhat better. Thus, for example, an acetophenone bearing a OMe electron-releasing group such as 4-methoxy-acetophenone (Table 2, entry 8) resulted in a poorer yield after a longer period of time, whereas an acetophenone possessing a NO_2 electron-withdrawing group, such as 4-nitroacetophenone (Table 2, entry 11) underwent a smooth reaction to afford a good yield of the corresponding product **3k**.

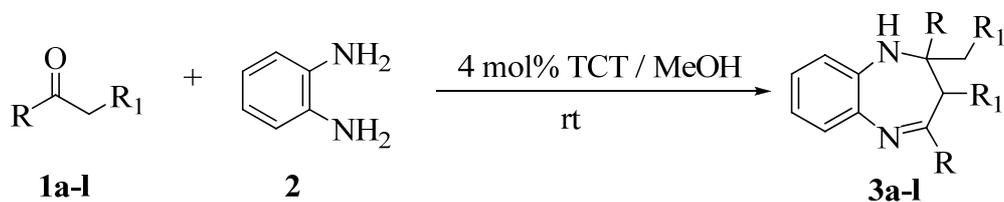**Scheme 2.** Reaction of *o*-phenylenediamines with various ketones in the presence of 4 mol % of TCT.

Table 2. The results of the reaction of *o*-phenylenediamines with various ketones.

Entry	R	R_1	Time (h)	Yield (%)[a]	References
1	CH_3	H	1	**3a** / 99	[21]
2	C_2H_5	H	21	**3b** / 71	[21]
3	C_2H_5	CH_3	21	**3c** / 23	[21]
4	$-(CH_2)_3-$		2	**3d** / 95	[21]
5	$-(CH_2)_4-$		4.5	**3e** / 95	[21]
6	$-(CH_2)_5-$		5.5	**3f** / 99	[21]
7	C_6H_5	H	12	**3g** / 99	[21]
8	$4\text{-OMe-}C_6H_4$	H	72	**3h** / 52	[21]
9	$4\text{-Me-}C_6H_4$	H	20	**3i** / 81	[40]
10	$4\text{-Cl-}C_6H_4$	H	25	**3j** / 75	[40]
11	$4\text{-NO}_2\text{-}C_6H_4$	H	8	**3k** / 87	[25]
12	2-thienyl	H	26	**3l** / 96	[40]

[a] Isolated yields.

Having successfully performed the reactions of 1,2-phenylenediamine with a wide range of ketones, we focused our attention on examining the reactions of various ketones and structurally diverse diamines (Scheme 3). The results revealed that both mono- and disubstituted phenylenediamines reacted with ketones to produce the corresponding benzodiazepines in excellent yields. Diamines bearing substituents with various electronic effects reacted with acetone with equal ease (Table 3,

entries 1, 3, 5 and 8). The reactions of aromatic ketones with monosubstituted diamines furnished the corresponding benzodiazepines in shorter times (Table 3, entries 2 and 4), whereas disubstituted diamines took relatively longer times to afford good yields of products (Table 3, entries 6, 7 and 9). All the monosubstituted diamines gave 1:1 mixtures of regioisomers. The results are summarized in Table 3.

Scheme 3 Reaction of various *o*-phenylenediamines with ketones in the presence of 4 mol % of TCT.
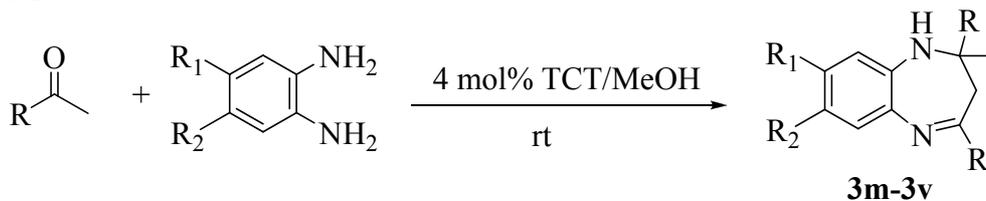

Table 3. The results of the reaction of various *o*-phenylenediamines with ketones.

Entry	R	R_1	R_2	Time(h)	Yield(%)[a]	References
1[b]	CH_3	Cl	H	2	**3m** / 99	[40]
2[b]	C_6H_5	Cl	H	14	**3n** / 71	[40]
3[b]	CH_3	CH_3	H	2	**3o** / 99	[40]
4[b]	C_6H_5	CH_3	H	14	**3p** / 70	[40]
5	CH_3	CH_3	CH_3	2	**3q** / 99	[21]
6	C_6H_5	CH_3	CH_3	23	**3r** / 88	[21]
7	4-Cl-C_6H_4	CH_3	CH_3	5	**3s** / 76	[40]
8	CH_3	Cl	Cl	7.5	**3t** / 72	[40]
9	C_6H_5	Cl	Cl	26	**3u** / 51	[25]
10	CH_3	—$(CH)_4$—		8	**3v** / 65	—

[a] Isolated yields.

[b] 1:1 mixture of two regioisomers.

Finally, the reaction of acetone with a bisdiamine in the presence of 8 mol % TCT gave the corresponding bisbenzodiazepine in moderate yield (Scheme 4). The product **3w** thus obtained proved unstable in solution and readily decomposed in methanol when it was subjected to crystallization.

Scheme 4. Reaction of bisdiamine with acetone in the presence of TCT.
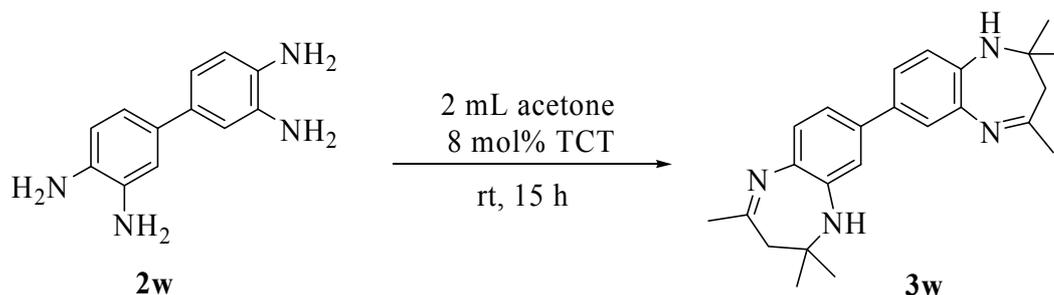
Conclusions

In summary, we have disclosed an efficient and economic method for the synthesis of 1,5-benzodiazepines. We also demonstrated the electronic effects on the reaction of various substitutions on the ketone and the diamine participants. Electron withdrawing groups like the (NO_2) group stimulate the reaction rate, whereas electron releasing groups reduce the reactivity of the ketone. Simple workup and easy isolation under mild reaction conditions are the best features of the present methodology.

Experimental

General

All reagents and chemicals were purchased from Sigma-Aldrich Chemical Company, Acros organics and Merck and were used as received. Analytical thin layer chromatography was performed with E. Merck silica gel 60F glass plates and flash chromatography by the use of E. Merck silica gel 60 (230–400 mesh). ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker Avance EX 400 FT-NMR instrument. Chloroform-*d* was used as the solvent and TMS (δ = 0.00 ppm) as an internal standard. Chemical shift values are reported in ppm relative to TMS in delta (δ) units. Multiplicities are recorded as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), br (broadened), m (multiplet). Coupling constants (*J*) are expressed in Hz. MS and HRMS were measured on JEOL JMS-D300 and JEOL JMS-HX110 spectrometers, respectively.

General procedure for the preparation of 1,5-benzodiazepines

To a stirred solution of *o*-phenylenediamine (1 mmol) in MeOH (1 mL), a ketone (2.5 mmol) and 4 mol% TCT were added. The reaction mixture was stirred at room temperature until the reaction was complete, as judged by TLC analysis. The reaction mixture was then concentrated and washed with water to give the crude product, which was further purified by flash chromatography on silica gel (eluent: hexane-EtOAc= 5:1).

2,2,4-Trimethyl-2,3-dihydro-1H-benzo[b][1,4]diazepine (**3a**): ^{1}H-NMR δ 7.14–7.12 (m, 1H), 7.00–6.96 (m, 2H), 6.74–6.72 (m, 1H), 2.97 (br s, 1H, NH), 2.37 (s, 3H), 2.23 (s, 2H), 1.35 (s, 6H); ^{13}C-NMR δ 172.4, 140.8, 137.9, 126.9, 125.5, 122.1, 121.7, 68.3, 45.2, 30.5, 29.9; MS (EI) *m/z* (relative intensity) 188 (M$^+$, 38), 173 (100), 133 (39), 132 (50); HRMS (EI) *m/z* calcd. for C$_{12}$H$_{16}$N$_2$ (M$^+$) 188.1314, found 188.1314.

2,2-Dimethyl-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine (**3b**): ^{1}H-NMR δ 7.16–7.14 (m, 1H), 6.99–6.95 (m, 2H), 6.73–6.71 (m, 1H) 3.10 (br s, 1H, NH), 2.61–2.57 (m, 2H), 2.22 (d, *J* = 12.9 Hz, 1H), 2.14 (d, *J* = 12.9 Hz, 1H), 1.63 (m, 2H), 1.24 (m, 5H), 0.95 (t, *J* = 7.5 Hz, 1H); ^{13}C-NMR δ 175.9, 140.7, 137.9, 127.1, 125.4, 121.8, 121.7, 70.7, 42.1, 35.7, 26.9, 10.6, 10.6, 8.5; MS (EI) *m/z* (relative intensity) 216 (M$^+$, 19), 201 (20), 187 (100), 145 (18); HRMS (EI) *m/z* calcd. for C$_{14}$H$_{20}$N$_2$ (M$^+$) 216.1627, found 216.1623.

2,2,4-Triethyl-3-methyl-2,3-dihydro-1H-1,5-benzodiazepine (**3c**): ^{1}H-NMR δ 7.35 (dd, 1H, *J* = 7.9, 1.1 Hz), 6.97 (t, *J* = 8.1 Hz, 1H), 6.74 (t, *J* = 7.1 Hz, 1H), 6.62 (dd, *J* = 8.0, 0.5 Hz, 1H), 3.86 (br s, 1H, NH), 2.85 (q, *J* = 7.0 Hz, 1H), 2.60–2.49 (m, 2H), 1.61–1.51 (m, 2H), 1.37 (q, *J* = 7.4 Hz, 2H), 1.24 (t, *J* = 7.4 Hz, 3H), 0.96–0.88 (m, 6H), 0.79 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR δ 173.6, 139.0, 132.8, 132.2, 126.7, 117.9, 117.5, 60.3, 46.1, 35.7, 28.4, 28.0, 12.3, 11.5, 7.8, 7.3; MS (EI) *m/z* (relative intensity) 244 (M$^+$, 14), 216 (12), 215 (100), 147 (23); HRMS (EI) *m/z* calcd. for C$_{16}$H$_{24}$N$_2$ (M$^+$) 244.1940, found 244.1940.

2,3,9,10a-Tetrahydro-1H-spiro[benzo[b]cyclopenta[e][1,4]diazepine-10,1'-cyclopentane] (**3d**): ^{1}H-NMR δ 7.32 (dd, *J* = 1.2, 1.1 Hz, 1H), 6.99–6.76 (m, 2H), 6.57 (dd, *J* = 1.0, 1.0 Hz, 1H), 3.98 (s, 1H), 2.77 (t, *J* = 9.0 Hz, 1H), 2.63–2.59 (m, 2H), 2.15–2.06 (m, 1H), 2.00–1.92 (m, 1H), 1.87–1.56 (m, 9 H), 1.48–1.42 (m, 1H); ^{13}C-NMR δ 178.2, 139.3, 134.1, 132.4, 127.1, 119.5, 118.9, 67.5, 54.4, 39.5, 38.7, 33.6, 29.1, 24.4, 24.2, 23.6; MS (EI) *m/z* (relative intensity) 240 (M$^+$, 39), 211 (87), 183 (42), 145 (41), 132 (100); HRMS (EI) *m/z* calcd. for C$_{16}$H$_{20}$N$_2$ (M$^+$) 240.1626, found 240.1629.

2',3',4',10'-Tetrahydro-1'H-spiro[cyclohexane-1,11'-dibenzo[b,e][1,4]diazepine] (**3e**): ^{1}H-NMR δ 7.29–7.26 (m, 1H), 6.99–6.92 (m, 2H), 6.70 (d, *J* = 1.4 Hz, 1H), 3.78 (br s, 1H, NH), 2.59 (t, *J* = 6.6 Hz, 2H), 2.4–2.36 (m, 1H), 1.86–1.18 (m, 16H); ^{13}C-NMR δ 176.2, 138.6, 138.3, 129.4, 126.0, 121.2, 121.1, 51.9, 41.9, 40.9, 40.6, 34.2, 33.0, 27.2, 26.9, 26.7, 25.3, 24.2, 21.9; MS (EI) *m/z* (relative intensity) 268 (M$^+$, 39), 225 (100), 145 (53), 132 (39); HRMS (EI) *m/z* calcd. for C$_{18}$H$_{24}$N$_2$ (M$^+$) 268.1940, found 268.1945.

7,8,9,10,10a,12-Hexahydro-6H-spiro[benzo[b]cyclohepta[e][1,4]diazepine-11,1'-cycloheptane] (**3f**): ^{1}H-NMR δ 7.21–7.19 (m, 1H), 7.01–6.96 (m, 2H), 6.73–6.71 (m, 1H), 3.59 (br s, 1H, NH), 2.80–2.64 (m, 2H), 2.36–2.32 (m, 1H), 2.05–0.99 (m, 20H); ^{13}C-NMR δ 179.9, 137.1, 127.1, 125.5, 121.8, 121.6, 54.0, 40.6, 38.3, 37.9, 30.2, 29.8, 29.7, 29.0, 28.3, 26.2, 23.2, 22.4; MS (EI) *m/z* (relative intensity) 296 (M$^+$, 39), 239 (100), 145 (29), 132 (35); HRMS (EI) *m/z* calcd. for C$_{20}$H$_{28}$N$_2$ (M$^+$) 296.2253, found 296.2250.

2-Methyl-2,4-diphenyl-2,3-dihydro-1H-benzo[b][1,4]diazepine (**3g**): ^{1}H-NMR δ 7.59–7.57 (m, 4H,), 7.31–7.16 (m, 7H), 7.05–7.03 (m, 2H), 6.83 (d, J = 1.7 Hz, 1H), 3.50 (br s, 1H, NH), 3.12 (d, J = 13.2 Hz, 1H), 2.95 (d, J = 13.2 Hz, 1H), 1.74 (s, 3H); ^{13}C-NMR δ 167.6, 147.6, 140.1, 139.6, 138.0, 129.7, 128.6, 128.3, 128.0, 127.0, 127.0, 126.3, 125.4, 121.6, 121.4, 73.6, 43.0, 29.8; MS (EI) *m/z* (relative intensity) 312 (M$^+$, 24), 297 (25), 235 (23), 194 (100); HRMS (EI) *m/z* calcd. for $C_{22}H_{20}N_2$ (M$^+$) 312.1627, found 312.1632.

2,3-Dihydro-2-methyl-2,4-di(4'-methoxyphenyl)-1H-1,5-benzodiazepine (**3h**): ^{1}H-NMR δ 7.59 (d, J = 8.7 Hz, 2H), 7.51 (d, J = 8.7 Hz, 2H), 7.29 (t, J = 5.2 Hz, 1H), 7.03 (t, J = 4.4 Hz, 2H), 6.81–6.75 (m, 5H), 3.78 (s, 3H), 3.74 (s, 3H), 3.41 (br s, 1H, NH), 3.03 (d, J = 13.2 Hz, 1H), 2.90 (d, J = 13.2 Hz, 1H), 171 (s, 3H); ^{13}C-NMR δ 167.1, 161.0, 158.5, 140.6, 140.1, 138.0, 132.3, 128.8, 128.2, 126.5, 125.8, 121.7, 121.5, 113.5, 113.3, 73.3, 55.3, 55.2, 42.8, 29.7; MS (EI) *m/z* (relative intensity) 372 (M$^+$, 9), 357 (8), 225 (23), 224 (100), 133 (14); HRMS (EI) *m/z* calcd. for $C_{24}H_{24}N_2O_2$ (M$^+$) 372.1838, found 372.1832.

2,3-Dihydro-2-methyl-2,4-di(4'-methoxyphenyl)-1H-1,5-benzodiazepine (**3i**): ^{1}H-NMR δ 7.53 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.31–7.28 (m, 1H), 7.05–6.99 (m, 6H), 6.76–6.74 (m, 1H), 3.44 (br s, 1H, NH), 3.03 (d, J = 13.2 Hz, 1H), 2.92 (d, J = 13.2 Hz, 1H), 2.30 (s, 3H), 2.27 (s, 3H), 1.67 (s, 3H); ^{13}C-NMR δ 167.3, 144.9, 140.2, 139.8, 138.1, 136.9, 136.5, 129.1, 128.9, 128.7, 128.4, 127.1, 126.0, 125.1, 121.5, 121.3, 73.2, 42.7, 29.7, 21.2, 20.8; MS (EI) *m/z* (relative intensity) 340 (M$^+$, 9), 325 (7), 209 (40), 208 (100), 207 (14), 133 (15), 117 (55), 92 (26), 91 (18), 65 (10); HRMS (EI) *m/z* calcd. for $C_{24}H_{24}N_2$ (M$^+$) 340.1940, found 340.1944.

2-Methyl-2,4-di(4-chlorophenyl)-2,3-dihydro-1H-1,5-benzodiazepine (**3j**): ^{1}H-NMR δ 7.52–7.46 (m, 4H), 7.28 (d, J = 2.0 Hz, 1H), 7.21–7.18 (m, 4H), 7.08–7.04 (m, 2H), 6.82 (d, J = 8.8 Hz, 1H), 3.42 (br s, 1H, NH), 3.08–3.04 (d, J = 13.2 Hz, 1H), 2.87 (d, J = 13.2 Hz, 1H), 1.72 (s, 3H); ^{13}C-NMR δ 166.0, 145.8, 139.9, 137.7, 137.6, 136.0, 133.0, 128.6, 128.3, 128.2, 127.0, 126.6, 122.0, 121.5, 73.4, 42.9, 29.7; MS (EI) *m/z* (relative intensity) 380 (M$^+$, 4), 365 (5), 231 (18), 230 (40), 229 (60), 228 (100), 193 (12), 137 (12), 133 (11); HRMS (EI) *m/z* calcd. for $C_{22}H_{18}N_2Cl_2$ (M$^+$) 380.0847, found 380.0849.

2,4-bis(4-Nitrophenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepine (**3k**): yellow solid; m.p. 152—154°C; ^{1}H-NMR δ 8.05 (d, J = 8.5 Hz, 4H), 7.75 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 7.6 Hz, 1H), 7.16 (t, J = 7.5, 7.4 Hz, 1H), 7.09 (t, J = 7.6, 7.3 Hz, 1H), 6.90 (d, J = 7.7 Hz, 1H), 3.67 (br s, 1H), 3.31 (d, J = 13.6 Hz, 1H), 3.00 (d, J = 13.6 Hz, 1H), δ 1.84 (s, 3H); ^{13}C-NMR δ 164.0, 154.2, 148.6, 147.1, 144.9, 139.0, 137.4, 129.8, 127.9, 127.8, 127.0, 123.7, 123.6, 122.3, 121.5, 73.5, 43.1, 30.4; MS (EI) *m/z* (relative intensity) 402 (M$^+$, 18), 387 (17), 280 (18), 239 (100), 193 (20); HRMS (EI) *m/z* calcd for $C_{22}H_{18}N_4O_4$ (M$^+$) 402.1328, found 402.1323.

2-Methyl-2,4-di-thiophen-2-yl-2,3-dihydro-1H-benzo[b][1,4]diazepine (**3l**): ^{1}H-NMR δ 7.39 (d, J = 4.8 Hz, 1H), 7.30–7.28 (m, 1H), 7.12–7.11 (m, 1H), 7.08–7.03 (m, 4H), 6.94–6.91 (m, 2H), 6.83–6.80 (m, 1H), 3.60 (br s, 1H, NH), 3.06 (d, J = 13.2 Hz, 1H), 3.00 (d, J = 13.2 Hz, 1H), 1.84 (s, 3H); ^{13}C-NMR

δ 162.4, 153.2, 137.2, 130.4, 128.6, 127.9, 127.6, 126.8, 126.3, 124.2, 122.8, 122.6, 122.0, 72.6, 44.4, 30.6; MS (EI) *m/z* (relative intensity) 324 (M$^+$, 11), 201 (32), 200 (100), 109 (18); HRMS (EI) *m/z* calcd. for $C_{18}H_{16}N_2S_2$ (M$^+$) 324.0755, found 324.0761.

2,2,4-Trimethyl-2,3-dihydro-8-chloro-1H-1,5-benzodiazepine (**3m**): ^{1}H-NMR δ 7.07 (s, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.89–6.85 (m, 2H), 6.67 (s, 1H), 6.60 (d, *J* = 8.3 Hz, 1H), 3.02 (br s, 2H, NH), 2.30–2.29 (m, 6H), 2.19–2.16 (d, *J* = 12.3 Hz, 4H), 1.27 (s, 12H); ^{13}C-NMR δ 173.8, 172.6, 141.4, 139.1, 138.4, 136.5, 130.0, 128.1, 126.4, 126.3, 125.1, 122.5, 121.3, 120.7, 68.2, 67.6, 45.1, 45.0, 30.4, 30.2, 29.64, 29.62; MS (EI) *m/z* (relative intensity) 222 (M$^+$, 35), 209 (28), 207 (100), 167 (39), 166 (56); HRMS (EI) *m/z* calcd. for $C_{12}H_{15}ClN_2$ (M$^+$) 222.0924, found 222.0924.

2-Methyl-2,4-diphenyl-8-chloro-2,3-dihydro-1H-1,5-benzodiazepine (**3n**): ^{1}H-NMR δ 7.60–7.56 (m, 8H), 7.35–7.18 (m, 14H), 7.05 (dd, *J* = 8.4, 2.4 Hz, 0.7H), 7.01–6.98 (dd, *J* = 8.4, 2.4 Hz, 1.3H), 6.85 (d, *J* = 2.4 Hz, 1.3H), 6.78 (d, *J* = 8.4 Hz, 0.7H), 3.62 (br s, 1.3H, NH), 3.52 (br s, 0.7H, NH), 3.17 (t, *J* = 13.4 Hz, 2H), 3.00–2.96 (m, 2H), 1.78 (s, 3H), 1.77 (s, 3H); ^{13}C-NMR δ 168.7, 167.6, 147.1, 139.4, 139.1, 138.1, 131.0, 130.1, 130.1, 129.9, 128.4, 128.4, 128.1, 128.0, 127.2, 127.1, 127.0, 126.0, 125.3, 122.4, 121.3, 120.5, 73.7, 72.9, 43.2, 43.0, 30.0, 29.8; MS (EI) *m/z* (relative intensity) 346 (M$^+$, 12), 230 (35), 229 (32), 228 (100), 167 (19), 103 (53); HRMS (EI) *m/z* calcd. for $C_{22}H_{19}ClN_2$ (M$^+$) 346.1237, found 346.1229.

2,2,4,8-Tetramethyl-2,3-dihydro-1H-1,5-benzodiazepine (**3o**): ^{1}H-NMR δ 7.00 (d, *J* = 7.8 Hz, 1H), 6.93 (s, 1H), 6.77–6.75 (m, 2H), 6.62 (d, *J* = 7.8 Hz, 1H), 6.50 (s, 1H), 2.87 (br s, 1H, NH), 2.33 (s, 3H), 2.32 (s, 3H), 2.26 (s, 3H), 2.25 (s, 3H), 2.19 (s, 2H), 2.16 (s, 2H), 1.30 (s, 6H), 1.29 (s, 6H); ^{13}C-NMR δ 172.4, 171.3, 140.9, 137.8, 137.7, 135.2, 135.1, 131.6, 126.9, 126.8, 126.0, 122.6, 121.9, 121.7, 68.3, 67.5, 45.1, 45.0, 30.4, 30.1, 29.7, 20.8, 20.5; MS (EI) *m/z* (relative intensity) 202 (M$^+$, 30), 187 (100), 147 (23), 146 (38); HRMS (EI) *m/z* calcd. for $C_{13}H_{18}N_2$ (M$^+$) 202.1470, found 202.1469.

2-Methyl-2,4-diphenyl-2,3-dihydro-8-methyl-1H-1,5-benzodiazepine (**3p**): ^{1}H-NMR δ 7.65–7.59 (m, 8H), 7.32–7.18 (m, 14H), 6.93 (d, *J* = 7.8 Hz , 0.8H), 6.88 (d, *J* = 7.8 Hz, 1.2H), 6.78 (d, *J* = 7.8 Hz, 0.8 H), 6.67 (s, 1.2H), 3.51 (br s, 2H, NH), 3.15 (t, *J* = 13.2 Hz, 2H), 2.98 (q, *J* = 7.2 Hz, 2H), 2.37 (d, *J* = 3.6 Hz, 6H), 1.77 (d, *J* = 4.2 Hz, 6H); ^{13}C-NMR δ 167.8, 166.6, 147.7, 140.4, 139.8, 139.5, 137.9, 137.2, 136.2, 135.4, 131.2, 129.7, 129.5, 128.9, 128.6, 128.2, 128.0, 127.9, 127.0, 126.9, 125.4, 125.4, 125.3, 122.3, 121.4, 121.5, 73.8, 72.8, 43.3, 42.9, 29.9, 29.6, 21.0, 20.5; MS (EI) *m/z* (relative intensity) 326 (M$^+$, 16), 311 (19), 209 (40), 208 (100), 207 (27), 200 (21), 103 (17), 77 (23); HRMS (EI) *m/z* calcd. for $C_{23}H_{22}N_2$ (M$^+$) 326.1783, found 326.1780.

2,2,4,7,8-Pentamethyl-2,3-dihydro-1H-banzo[b][1,4]diazepine (**3q**): ^{1}H-NMR δ 6.92 (s, 1H), 6.52 (s, 1H), 2.34 (s, 3H), 2.20 (s, 3H), 2.19 (s, 3H), 2.18 (s, 3H), 1.32 (s, 6H); ^{13}C-NMR δ 171.6, 138.5, 135.5, 133.7, 130.1, 127.9, 122.8, 67.9, 45.3, 30.4, 29.8, 19.2, 18.9; MS (EI) *m/z* (relative intensity) 216 (M$^+$, 26), 201 (100), 161 (29), 160 (39), 145 (20); HRMS (EI) *m/z* calcd. for $C_{14}H_{20}N_2$ (M$^+$) 216.1626, found 216.1621.

2,7,8-Trimethyl-2,4-diphenyl-2,3-dihydro-1H-benzo[b][1,4]diazepine (**3r**): ^{1}H-NMR δ 7.57 (t, J = 8.6 Hz, 4H), 7.23–7.12 (m, 7H), 6.62 (s, 1H), 3.40 (br s, 1H, NH), 3.09 (d, J = 8.7 Hz, 1H), 2.96 (d, J = 8.7 Hz, 1H), 2.24 (s, 6H), 1.73 (s, 3H); ^{13}C-NMR δ 166.8, 147.8, 139.8, 137.7, 135.8, 134.8, 129.7, 129.6, 129.4, 128.2, 127.9, 126.9, 125.4, 122.3, 73.1, 43.3, 29.8, 18.4, 18.8; MS (EI) m/z (relative intensity) 340 (M$^+$, 19), 325 (27), 223 (47), 222 (100); HRMS (EI) m/z calcd. for $C_{24}H_{24}N_2$ (M$^+$) 340.1939, found 340.1934.

2,4-bis(4-Chlorophenyl)-2,7,8-trimethyl-2,3-dihydro-1H-benzo[b][1,4]diazepine (**3s**): ^{1}H-NMR δ 7.52–7.19 (m, 8H), 7.9 (s, 1H), 6.62 (s, 1H), 3.32 (br s, 1H, NH), 3.05 (d, J = 13.2 Hz, 1H), 2.87 (d, J = 13.2 Hz, 1H), 2.24 (s, 6H), 1.71 (s, 3H); ^{13}C-NMR δ 165.2, 146.1, 138.1, 137.1, 135.8, 135.4, 135.3, 132.9, 130.0, 129.7, 128.4, 128.3, 128.2, 127.1, 122.4, 73.0, 43.1, 29.8, 19.4, 18.8; MS (EI) m/z (relative intensity) 408 (M$^+$, 3), 305 (12), 304 (70), 289 (100), 131 (18); HRMS (EI) m/z calcd. for $C_{24}H_{22}N_2Cl_2$ (M$^+$) 408.1160, found 408.1155.

7,8-Dichloro-2,2,4-trimethyl-2,3-dihydro-1H-benzo[b][1,4]diazepine (**3t**): ^{1}H-NMR δ 7.20 (s, 1H), 6.81 (s, 1H), 3.07 (br s, 1H, NH), 2.34 (s, 3H), 2.25 (s, 2H), 1.33 (s, 6H); ^{13}C-NMR δ 173.9, 139.7, 137.7, 128.3, 128.1, 124.4, 122.2, 67.7, 45.3, 30.5, 29.9; MS (EI) m/z (relative intensity) 256 (M$^+$, 28), 258 (18), 243 (58), 241 (100), 203 (25), 202 (37), 201 (46), 200 (58); HRMS (EI) m/z calcd. for $C_{12}H_{14}N_2Cl_2$ (M$^+$) 256.0534, found 256.0529.

(E)-7,8-Dichloro-2-methyl-2,4-diphenyl-2,3-dihydro-1H-benzo[b][1.4]diazepine (**3u**): ^{1}H-NMR δ 7.54 (t, J = 6.8, 6.6 Hz, 4H), 7.40 (s, 1H), 7.33-7.17 (m, 6H), 6.92 (s, 1H), 3.59 (br s, 1H, NH), 3.17 (d, J = 13.4 Hz, 1H), 2.97 (d, J = 13.4 Hz, 1H), 1.75 (s, 3H), 1.57 (s, 1H); ^{13}C-NMR δ 168.8, 146.8, 139.2, 138.9, 137.7, 130.2, 129.9, 128.8, 128.1, 127.1, 125.3, 124.1, 121.8, 72.9, 43.2, 29.9; MS (EI) m/z (relative intensity) 380 (M$^+$, 8), 260 (10), 265 (19), 264 (61), 262 (100), 103 (23), 77 (12); HRMS (EI) m/z calcd. for $C_{22}H_{18}N_2Cl_2$ (M$^+$) 380.0874, found 380.0842.

2,2,4-Trimethyl-2,3-dihydro-1H-naphtho[2,3-b][1,4]diazepine (**3v**): ^{1}H-NMR δ 7.72 (d, J = 7.8 Hz, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.55 (s, 1H), 7.33-7.29 (m, 2H), 7.08 (s, 1H), 2.38 (s, 3H), 2.17 (s, 2H), 1.33 (br s, 1H, NH); ^{13}C-NMR δ 173.1, 141.9, 137.6, 131.9, 130.3, 127.4, 125.8, 125.2, 124.0, 123.6, 117.6, 65.9, 44.6, 29.9, 29.6; MS (EI) m/z (relative intensity) 238 (M$^+$, 25), 224 (18), 223 (100), 183 (42), 182 (37), 115 (17); HRMS (EI) m/z calcd. for $C_{16}H_{18}N_2$ (M$^+$) 238.1470, found 238.1465.

2,2',4,4,4',4'-Hexamethyl-4,4',5,5'-tetrahydro-3H,3'H-7,7'-dibenzo[b][1,4]diazepine (**3w**): mixture of two isomers; ^{1}H-NMR δ 7.39 (s, 1H), 7.20 (m, 3H), 6.92 (d, 1H, J = 9.7 Hz), 6.74 (d, 1H, J = 5.0 Hz) 1H), 3.01 (br s, 2H), 2.36 (s, 6H), 2.56 (s, 4H), 1.32 (s, 12H); ^{13}C-NMR δ 172.8, 172.7, 172.5, 172.4, 138.4, 138.3, 138.1, 138.0, 137.5, 136.9, 134.4, 127.5, 127.4, 125.3, 124.8, 123.9, 123.7, 122.1, 122.0, 120.5, 120.2, 119.8, 119.6, 68.1, 67.9, 45.4, 45.3, 30.7, 30.6, 29.9, 29.8. MS (EI) m/z (relative intensity) 374 (M$^+$, 40), 359 (100), 319 (23), 263 (7).

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