

A Facile synthesis of 3-Methylene-4-aryl-1,3,4,5-tetrahydro-benzo[*b*][1,4] diazepin-2-ones and 3-arylmethylene-4,5-dihydro-3*H*-benzo[*b*][1,4]diazepin-2-ylamines¹

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Abstract: A simple and convenient synthesis of 3-methylene-4-aryl-1,3,4,5-tetrahydro-benzo[*b*][1,4] diazepin-2-ones was accomplished by the S_N2 nucleophilic substitution of the acetates of Baylis-Hillman adducts of acrylate with 1,2-phenylenediamines followed by base-mediated intramolecular cyclization. On the other hand similar substrates derived from the Baylis-Hillman adducts of acrylonitrile via Pinner's reaction leads to 3-arylmethylene-4,5-dihydro-3*H*-benzo[*b*][1,4]diazepin-2-ylamines in good yields.

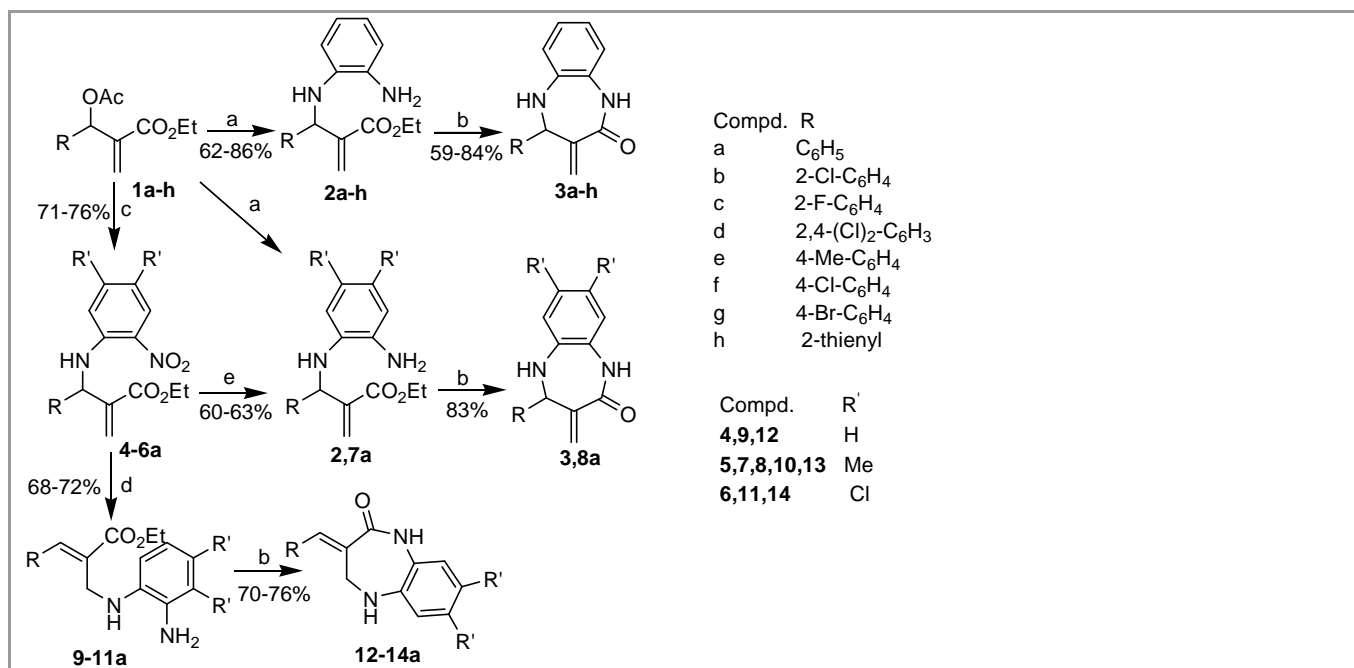
Key words: Baylis-Hillman, 1,2-phenylenediamine, 3-Methylene-4-aryl-1,3,4,5-tetrahydro-benzo[*b*][1,4] diazepin-2-ones, 3-arylmethylene-4,5-dihydro-3*H*-benzo[*b*][1,4]diazepin-2-ylamines.

A large number of pharmaceutical and biologically active agents incorporate heterocycles as a substructural unit. This has maintained researchers motivated to develop new synthetic strategies to achieve the synthesis of heterocyclic architectures in simple and convenient fashion. In recent times, the derivatives afforded via the Baylis-Hillman reaction have proved to be fascinating precursors for the construction of biologically relevant heterocyclic systems in convenient ways.² This is attributed to the propensity of this robust C-C bond forming reaction to deliver products consisting of highly reactive functional groups. We have been interested in the synthesis of heterocycles containing exocyclic methylene group utilizing derivatives of the Baylis-Hillman adduct. In this context, recently we have described the synthesis of α -methylene- δ -valerolactones, 3-methylene-piperidin-2,6-diones and 3-methylene-2-pyrrolidinones in excellent yields.³ In our continued efforts in this direction, we have now achieved a facile and diversity oriented synthesis of 3-methylene-4-aryl-1,3,4,5-tetrahydro-benzo[*b*][1,4] diazepin-2-ones and 3-arylmethylene-4,5-dihydro-3*H*-benzo[*b*][1,4]diazepin-2-ylamines.

The benzo[*b*][1,4] diazepin-2-ones are considered to be privileged structures exhibiting a spectrum of biological activities such as interleukin 1 β enzyme inhibitor, potassium current blocker and others.⁴ A careful literature survey indicated that several methods have been reported,⁵ both in solution and on solid phase, wherein 1,2-phenylenediamine or its precursor the 2-nitroaniline, have been successfully employed for the synthesis of this structural motif. In principle, the S_N2 reaction of 1,2-phenylenediamine with the acetyl derivative of the Baylis-Hillman adduct should result in a diamino ester derivative, which can be intramolecularly cyclized to yield the methylene benzo[*b*][1,4] diazepin-2-one. Earlier Chuang and Sharpless have described the nucleophilic

ring opening of the aziridinium ion with 1,2-phenylenediamine followed by base-mediated ring-closure to afford the benzo[*b*][1,4] diazepin-2-one.^{5a} On the other hand Kim et al. have carried out the S_N2' reaction of 1,2-phenylenediamine with the acetyl derivatives of the Baylis-Hillman adduct to afford the diamino ester, which were cyclized in the presence of acetic acid to yield arylmethylene-benzo[*b*][1,4] diazepin-2-ones in low yields with other side products.^{5b} Intrigued by these reports, we initiated the studies for the synthesis of diverse benzo[*b*][1,4] diazepin-2-ones possessing exocyclic methylene moiety from the Baylis-Hillman adducts, the results of which are described in this communication.

The starting substrates for the study, the acetyl derivatives **1a-h** of the Baylis-Hillman adduct, were synthesized following the literature procedure.⁶ The S_N2 nucleophilic substitution reaction of 1,2-phenylenediamine with the acetates **1a-h** was easily accomplished in the presence of DABCO in a THF: water system leading to the formation of diamino esters **2a-h** in excellent yields (scheme 1). Treatment of diamino esters **2a-h** with NaH in the toluene at 80°C temperature in 2h furnished the desired diazepinones **3a-h** in good to excellent yields. In order to make the strategy diversity-oriented, it was envisaged that the substituted 2-nitroanilines can be introduced instead of the 1,2-phenylenediamine during the S_N2 nucleophilic substitution. Subsequently the nitro group can be reduced chemoselectively to furnish the amine which can be cyclized in the usual fashion. Accordingly, the 2-nitroaniline was treated with the acetyl derivative of the Baylis-Hillman adduct in the presence of DABCO in a THF: H₂O system. Unfortunately, this reaction failed to occur even after prolonged reaction time. We reasoned that probably the nucleophilicity of the aniline is reduced due to the deactivating effect of the nitro group present in the molecule leading to the failure of reaction. Thus in an altered strategy for the synthesis of desired substrates, the 2-nitroaniline anion was generated by the treatment of 2-nitroaniline with NaH in anhydrous THF. On the other hand, the acetate **1a** was treated with 4.5 equivalents of DABCO in anhydrous THF for 10 min. It is worth mentioning that we arrived at the conclusion to use 4.5 equiv. of DABCO after lot of optimization. Thereafter this mixture was added dropwise to the vessel containing the aniline anion. Gratifyingly, this reaction was complete in 1.5h to furnish the desired product **4a**. Similarly, the reaction of acetate **1a** with 4,5-dimethyl- and 4,5-dichloro-2-nitroanilines



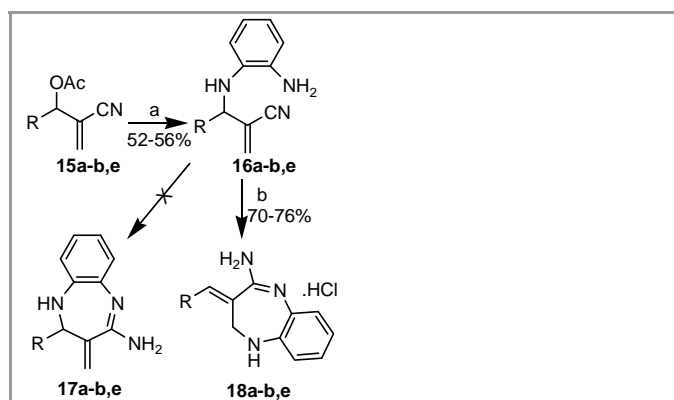
Scheme 1. Reagents and conditions: a) DABCO, 1,2 Phenylenediamine or substituted 1,2-Phenylenediamine, THF:H₂O (1:1), rt, 4-5h. b) NaH, THF, 80°C, 2h. c) i. Acetate, DABCO, THF, 15 min, ii. (Substituted) 2-nitroaniline, NaH, THF, 15 min, iii. Add i to ii, rt, 1.5h. d) SnCl₂·2H₂O, MeOH, reflux, 12h. e) Zn, HCO₂NH₄, MeOH, rt, 3h.

afforded the compounds **5-6a**, respectively.

In the next step, the reduction of the nitro group in compounds **4-6a** was attempted with SnCl₂·2H₂O. Surprisingly, though the nitro group was reduced to furnish the amino group, a rearrangement occurred simultaneously resulting in products **9-11a** as *E*-isomer only.¹⁰ It was presumed that the acidic medium of the reaction mixture may have initiated this unusual rearrangement. In order to validate this assumption, compound **2a** was treated with HCl and phosphoric acid separately. Expectedly, in both cases the rearrangement occurred to yield diaminoester **9a**. Additional chemical evidence for the rearrangement was obtained by treating the compounds **9-11a** with NaH to furnish the 3-arylmethylene-1,3,4,5-tetrahydro-benzo[*b*][1,4]diazepin-2-one (**12-14a**) in good yields. In view of these results, we decided to examine reduction of the nitro group via Zn in the presence of ammonium formate.⁷ We were pleased to observe that the treatment of compounds **4-5a** with Zn in the presence of ammonium formate in methanol at room temperature afforded the desired products **2,7a** in good yields. These diamino esters were treated with NaH to afford products **3,8a**, respectively. In order to achieve better yields, we also evaluated an alternate strategy wherein the substituted 2-nitroaniline was first converted to substituted 1,2-phenylenediamine via catalytic reduction and then subject them to the S_N2 reaction. Hence, the 4,5-dimethyl-2-nitroaniline was hydrogenated in the presence of Palladium-on-carbon to furnish the 4,5-dimethyl-1,2-phenylenediamines in excellent yield. Further, this amine was subjected to similar synthetic protocol to furnish the diaminoester **7a** in 74% yield. Since the difference between the yields was not significant, it was

concluded that either strategy could be adopted for the generation of this class of compounds.

Once the objective of obtaining the benzodiazepine-2-ones from the acetyl derivatives of the Baylis-Hillman adduct of acrylate was accomplished, we turned our attention to similar derivatives of acrylonitrile. It was envisaged that the acetyl derivative **15** on treatment with 1,2-phenylenediamine will lead to diamino nitrile derivative **16**, wherein the free amino group on the phenyl ring may attack the cyano moiety resulting in an intramolecular cyclization to afford product **17**. Therefore, compounds **16a-b,e** were synthesized via S_N2 reaction of 1,2-phenylenediamine on the acetyl derivatives **15a-b,e** (scheme 2). However, the desired cyclization failed in our hands under several conditions which were attempted. Therefore, in our objective to achieve the desired cyclization, we decided to examine the



Scheme 2. Reagents and Conditions: a. DABCO, 1,2 Phenylenediamine, THF:H₂O(1:1), rt, 4-5h. b) EtOH, CH₂Cl₂, Dry HCl gas, 0°C, 8h.

transformation of the cyano group into the imidates. In principle, the nucleophilic attack of the amino group on this imidate in situ would result in the desired benzodiazepinamine **17**. Thus, reaction of substrates **16a-b,e** with dry HCl in ethanol was carried out, which led to isolation of the solid products in good yields. The spectral analysis of these compounds led to assign the structure of these products as **18a-b,e**, instead of the expected compounds **17a-b,e**. As indicated, here too the acidic medium of the reaction would have resulted in the rearrangement of the aniline moiety leading to the isolation of products **18a-b,e**.

In summary we have demonstrated a straightforward convenient and practical synthesis of 3-methylene-4-aryl-1,3,4,5-tetrahydro-benzo[*b*][1,4] diazepin-2-ones with at least two point diversity utilizing the derivatives of the Baylis-Hillman adducts of acrylates. Similar derivatives resulting from Baylis-Hillman reaction of acrylonitrile furnishes the 3-arylemethylene-4,5-dihydro-3*H*-benzo[*b*][1,4] diazepin-2-ylamines via tandem conversion of the cyano group to imidates, acid-catalyzed rearrangement followed by intramolecular cyclization.

Melting points are uncorrected and were determined in capillary tubes on a hot stage apparatus containing silicon oil. IR spectra were recorded using a Perkin Elmer RX I FTIR spectrophotometer. ¹H NMR and ¹³C NMR spectra were recorded on either a 300 or a 200 MHz FT spectrometer, using TMS as an internal standard (chemical shifts in δ values, *J* in Hz). The FABMS were recorded on JEOL/SX-102 spectrometers and ESMS were recorded through direct flow injections in Merck M-8000 LCMS system. Elemental analyses were performed on a Carlo Erba 1108 microanalyzer or Elementar's Vario EL III microanalyzer. Since compounds **9a** and **12a** are known,^{5b} corresponding spectral data is not provided.

General Procedure for the preparation of compounds 2a-h and 16a-b,e- These compounds were prepared following the procedure published earlier.⁸

2-[(2-Amino-phenylamino)-phenyl-methyl]-acrylic acid ethyl ester (2a)

Yield: 63%; brown oil.

IR (neat): 1711 (CO₂Et), 3397 (NH and NH₂) cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ = 1.26 (t, 3H, *J*= 7.0 Hz, CH₂CH₃), 3.41 (brs, 2H, NH₂), 4.18 (q, 2H, *J*= 7.2 Hz, CH₂CH₃), 5.48 (s, 1H, =CH₂), 5.96 (s, 1H, CHNH), 6.32 (s, 1H, =CH₂), 6.55-6.62 (m, 1H, ArH), 6.71-6.83 (m, 3H, ArH), 7.30-7.39 (m, 5H, ArH).

MS (ES⁺): *m/z* 297.0 (M⁺+1).

Anal. Calcd. for C₁₈H₂₀N₂O₂: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.19; H, 6.86; N, 9.11.

2-[(2-Amino-phenylamino)-(2-chloro-phenyl)-methyl]-acrylic acid ethyl ester (2b)

Yield: 74%; brown oil.

IR (neat): 1705 (CO₂Et), 3431 (NH and NH₂) cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 1.27 (t, 3H, *J*= 8.2 Hz, CH₂CH₃), 2.94 (brs, 2H, NH₂), 4.23 (q, 2H, *J*= 7.3 Hz, CH₂CH₃), 5.76 (s, 1H, =CH₂), 5.91 (s, 1H, CHNH), 6.43 (s, 1H, =CH₂), 6.50-6.53 (m, 1H, ArH), 6.67-6.80 (m, 3H, ArH), 7.22-7.25 (m, 2H, ArH), 7.35-7.49 (m, 2H, ArH).

MS (ES⁺): *m/z* 331.0 (M⁺+1).

Anal. Calcd. for C₁₈H₁₉ClN₂O₂: C, 65.35; H, 5.79; N, 8.47. Found: C, 65.22; H, 5.58; N, 8.43.

2-[(2-Amino-phenylamino)-(2-fluoro-phenyl)-methyl]-acrylic acid ethyl ester (2c)

Yield: 86%; brown oil.

IR (neat): 1713 (CO₂Et), 3399 (NH and NH₂) cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ = 1.27 (t, 3H, *J*= 7.2 Hz, CH₂CH₃), 3.39 (brs, 2H, NH₂), 4.12 (q, 2H, *J*= 7.2 Hz, CH₂CH₃), 5.75 (s, 1H, CHNH), 5.84 (s, 1H, =CH₂), 6.40 (s, 1H, =CH₂), 6.54 (d, 1H, *J*= 7.3 Hz, ArH), 6.44-6.74 (m, 3H, ArH), 7.01-7.13 (m, 2H, ArH), 7.22-7.39 (m, 2H, ArH).

MS (ES⁺): *m/z* 315.1 (M⁺+1).

Anal. Calcd. for C₁₈H₁₉FN₂O₂: C, 68.77; H, 6.09; N, 8.91. Found: C, 68.51; H, 5.81; N, 8.77.

2-[(2-Amino-phenylamino)-(2,4-dichloro-phenyl)-methyl]-acrylic acid ethyl ester (2d)

Yield: 62%; brown oil.

IR (neat): 1714 (CO₂Et), 3365 (NH, NH₂) cm⁻¹.

¹H NMR (CDCl₃, 200 MHz): δ = 1.25 (t, 3H, *J*= 7.6 Hz, CH₂CH₃), 4.16 (q, 2H, *J*= 7.3 Hz, CH₂CH₃), 5.73 (s, 1H, =CH₂), 5.81 (s, 1H, CHNH), 6.26-6.46 (m, 2H, =CH₂ & ArH), 6.72-6.73 (m, 3H, ArH), 7.18-7.43 (m, 3H, ArH).

MS (ES⁺): *m/z* 365.0 (M⁺+1).

Anal. Calcd. for C₁₈H₁₈Cl₂N₂O₂: C, 59.19; H, 4.97; N, 7.67. Found: C, 58.91; H, 5.16; N, 7.49.

2-[(2-Amino-phenylamino)-p-tolyl-methyl]-acrylic acid ethyl ester (2e)

Yield: 84%; brown oil.

IR (neat): 1711 (CO₂Et), 3402 (NH and NH₂) cm⁻¹.

¹H NMR (CDCl₃, 200 MHz): δ = 1.22 (t, 3H, *J*= 7.3 Hz, CH₂CH₃), 2.33 (s, 3H, ArH), 3.34 (brs, 2H, NH₂), 4.16 (q, 2H, *J*= 7.3 Hz, CH₂CH₃), 5.38 (s, 1H, CHNH), 5.88 (s, 1H, =CH₂), 6.35 (s, 1H, =CH₂), 6.53 (d, 1H, *J*= 7.1 Hz, ArH), 6.68-6.79 (m, 3H, ArH), 7.13 (d, 2H, *J*= 8.0 Hz, ArH), 7.27 (d, 2H, *J*= 8.0 Hz, ArH).

MS (ES⁺): *m/z* 311.1 (M⁺+1).

Anal. Calcd. for C₁₉H₂₂N₂O₂: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.30; H, 7.01; N, 8.84.

2-[(2-Amino-phenylamino)-(4-chloro-phenyl)-methyl]-acrylic acid ethyl ester (2f)

Yield: 62%; brown oil.

IR (neat): 1714 (CO₂Et), 3365 (NH and NH₂) cm⁻¹.

^1H NMR (200 MHz, CDCl_3): δ = 1.25 (t, 3H, J = 7.6 Hz, CH_2CH_3), 4.16 (q, 2H, J = 7.3 Hz, CH_2CH_3), 5.73 (s, 1H, =CH₂), 5.81 (s, 1H, CHNH), 6.26-6.46 (m, 2H, =CH₂ & ArH), 6.72-6.73 (m, 3H, ArH), 7.18-7.43 (m, 3H, ArH).

MS (ES⁺): m/z 331.0 (M^+ +1).

Anal. Calcd. for $\text{C}_{18}\text{H}_{19}\text{Cl}_2\text{N}_2\text{O}_2$: C, 65.35; H, 5.79; N, 8.47. Found: C, 65.29; H, 5.70; N, 8.45.

2-[(2-Amino-phenylamino)-(4-bromo-phenyl)-methyl]-acrylic acid ethyl ester (2g)

Yield: 75%; brown oil.

IR (neat): 1710 (CO_2Et), 3350 (NH, NH_2) cm^{-1} .

^1H NMR (CDCl_3 , 300 MHz): δ = 1.27 (t, 3H, J = 7.2 Hz, CH_2CH_3), 4.20 (q, 2H, J = 7.2 Hz, CH_2CH_3), 5.40 (s, 1H, CHNH), 5.89 (s, 1H, =CH₂), 6.40 (s, 1H, =CH₂), 6.54 (d, 1H, J = 9.1 Hz, ArH), 6.72-6.78 (m, 3H, ArH), 7.29 (d, 2H, J = 9.0 Hz, ArH), 7.47 (d, 2H, J = 9.0 Hz, ArH).

MS (ES⁺): m/z 374.9 (M^+ +1).

Anal. Calcd. for $\text{C}_{18}\text{H}_{19}\text{BrN}_2\text{O}_2$: C, 57.61; H, 5.10; N, 7.47. Found: C, 57.79; H, 5.33; N, 7.48.

2-[(2-Amino-phenylamino-thiophen-2-yl-methyl)-acrylic acid ethyl ester (2h)

Yield: 74%; brown oil.

IR (neat): 1711 (CO_2Et), 3401 (NH, NH_2) cm^{-1} .

^1H NMR (CDCl_3 , 200 MHz): δ = 1.26 (t, 3H, J = 7.2 Hz, CH_2CH_3), 3.45 (brs, 2h, NH_2), 4.21 (q, 2H, J = 7.3 Hz, CH_2CH_3), 5.64 (s, 1H, CHNH), 5.90 (s, 1H, =CH₂), 6.36 (s, 1H, =CH₂), 6.58-6.61 (m, 1H, ArH), 6.74 (s, 3H, ArH), 6.97 (s, 2H, ArH), 7.22 (s, 1H, ArH).

MS (ES⁺): m/z 302.9 (M^+ +1).

Anal. Calcd. for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$: C, 63.55; H, 6.00; N, 9.26. Found: C, 63.76; H, 6.20; N, 8.92.

2-[(2-Amino-phenylamino)-phenyl methyl]-acrylonitrile (16a)

Yield: 52%; brown oil.

IR (neat): 2225 (CN), 3400 (NH and NH_2) cm^{-1} .

^1H NMR (CDCl_3 , 200 MHz): δ = 3.08 (brs, 2H, NH_2), 5.04 (s, 1H, CHNH), 6.05 (s, 1H, =CH₂), 6.11 (s, 1H, =CH₂), 6.55-6.58 (m, 1H, ArH), 6.74-6.81 (m, 3H, ArH), 7.39-7.43 (m, 5H, ArH).

MS (ES⁺): m/z 250.1 (M^+ +1).

Anal. Calcd. for $\text{C}_{16}\text{H}_{15}\text{N}_3$: C, 77.08; H, 6.06; N, 16.85. Found: C, 76.88; H, 6.21; N, 16.98.

2-[(2-Amino-phenylamino)-(2-chloro-phenyl)-methyl]-acrylonitrile (16b)

Yield: 63%; brown oil.

IR (neat): 2209 (CN), 3377 (NH and NH_2) cm^{-1} .

^1H NMR (CDCl_3 , 200 MHz): δ = 3.93 (brs, 2H, NH_2), 5.57 (s, 1H, CHNH), 6.01 (s, 1H, =CH₂), 6.11 (s, 1H, =CH₂), 6.47-6.49 (m, 1H, ArH), 6.71-6.77 (m, 3H, ArH), 7.28-7.33 (m, 2H, ArH), 7.43-7.53 (m, 2H, ArH).

MS (ES⁺): m/z 284.2 (M^+ +1).

Anal. Calcd. for $\text{C}_{16}\text{H}_{14}\text{ClN}_3$: C, 67.72; H, 4.97; N, 14.81. Found: C, 67.93; H, 5.04; N, 14.89.

2-[(2-Amino-phenylamino)-*p*-tolyl-methyl]-acrylonitrile (16e)

Yield: 56%; brown oil.

IR (neat): 2225 (CN), 3411 (NH and NH_2) cm^{-1} .

^1H NMR (CDCl_3 , 200 MHz): δ = 2.37 (s, 3H, CH_3), 3.39 (brs, 2H, NH_2), 3.84 (brs, 1H, CHNH), 5.04 (d, 2H, J = 3.6 Hz, CHNH), 6.04 (d, 1H, J = 1.0 Hz, =CH₂), 6.06 (s, 1H, =CH), 6.55-6.57 (m, 1H, ArH), 6.74-6.81 (m, 3H, ArH), 7.10 (d, 2H, J = 8.0 Hz, ArH), 7.31 (d, 2H, J = 8.0 Hz, ArH).

MS (ES⁺): m/z 264.2 (M^+ +1).

Anal. Calcd. for $\text{C}_{17}\text{H}_{17}\text{N}_3$: C, 77.54; H, 6.51; N, 15.96. Found: C, 77.75; H, 6.40; N, 16.09.

General procedure for the preparation of 3a-h,8a- To a stirred solution of appropriate compound (1.0 mmol) in dry THF (10 mL) was added sodium hydride as 60% suspension in oil (0.121 g, 2.5 mmol) and heated at reflux for 2h. On completion, the reaction mixture was extracted with EtOAc (3x20 mL) and 30 mL water. The organic layers were pooled, dried over Na_2SO_4 and concentrated to afford a residue, which was purified via silica gel chromatography using hexane: EtOAc (70:30, v/v) as eluent to yield the pure products.

3-Methylene-4-phenyl-1,3,4,5-tetrahydro-benzo[*b*][1,4]diazepin-2-one (3a)

Yield: 76%; light yellow solid; mp 175-176 °C.

IR (KBr): 1667 (CONH), 3428 (NH) cm^{-1} .

^1H NMR (CDCl_3 , 300 MHz): δ = 4.01 (s, 1H, NHCH), 5.18 (s, 2H, =CH₂ & NHCH), 5.99 (s, 1H, =CH₂), 6.78-6.96 (m, 4H, ArH), 7.23-7.37 (s, 5H, ArH), 7.93 (s, 1H, CONH).

^{13}C NMR (CDCl_3 +DMSO_d₆, 50 MHz): δ = 66.4, 121.1, 121.6, 121.7, 122.9, 124.9, 127.3, 128.0, 128.9, 138.4, 141.9, 144.9, 169.6.

MS (ES⁺): m/z 251.0 (M^+ +1).

Anal. Calcd. for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.80; H, 5.45; N, 10.87.

4-(2-Chloro-phenyl)-3-methylene-4-phenyl-1,3,4,5-tetrahydro-benzo[*b*][1,4] diazepin-2-one (3b)

Yield: 84%; yellow solid; mp 182-183 °C.

IR (KBr): 1668 (CONH), 3349 (NH) cm^{-1} .

^1H NMR (CDCl_3 , 300 MHz): δ = 4.18 (s, 1H, NHCH), 5.43 (s, 1H, =CH₂), 5.75 (s, 1H, CHNH), 6.14 (s, 1H, =CH₂), 6.82-6.84 (m, 1H, ArH), 6.90-6.97 (m, 2H, ArH), 7.20-7.23 (m, 2H, ArH), 7.28 (s, 1H, ArH), 7.36-7.39 (m, 1H, ArH), 7.50-7.52 (m, 1H, ArH), 8.08 (s, 1H, CONH);

^{13}C NMR (CDCl_3 , 50 MHz): δ = 63.8, 121.5, 121.7, 123.3, 125.1, 125.4, 127.6, 129.3, 129.6, 130.1, 133.2, 138.2, 139.1, 142.6, 169.7.

MS (ES⁺): m/z 285.1 (M^+ +1).

Anal. Calcd. for C₁₆H₁₃ClN₂O: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.67; H, 4.76; N, 9.64.

4-(2-Fluoro-phenyl)-3-methylene-4-phenyl-1,3,4,5-tetrahydro-benzo[*b*][1,4]diazepin-2-one (3c)

Yield: 75%; yellow solid; mp 160-162 °C.

IR (KBr): 1660 (CONH), 3316 (NH) cm⁻¹.

¹H NMR (CDCl₃, 200 MHz): δ= 4.07 (brs, 1H, NHCH), 5.39 (s, 1H, =CH₂), 5.63 (s, 1H, CHNH), 6.10 (s, 1H, =CH₂), 6.83-6.96 (m, 4H, ArH), 7.03-7.12 (m, 1H, ArH), 7.23-7.24 (m, 2H, ArH), 7.44-7.45 (m, 1H, ArH), 8.03 (s, 1H, CONH).

MS (ES+): *m/z* 269.2 (M⁺+1).

Anal. Calcd. for C₁₆H₁₃FN₂O: C, 71.63; H, 4.88; N, 10.44. Found: C, 71.48; H, 5.11; N, 10.25.

4-(2,4-Dichloro-phenyl)-3-methylene-1,3,4,5-tetrahydro-benzo[*b*][1,4]diazepin-2-one (3d)

Yield: 73%; yellow solid; mp 162-164 °C.

IR (KBr): 1650 (CONH), 3411 (NH) cm⁻¹.

¹H NMR (CDCl₃, 200 MHz): δ= 4.14 (d, 1H, *J*= 3.6 Hz, NHCH), 5.43 (s, 1H, =CH₂), 5.70 (d, 1H, *J*= 3.6 Hz, CHNH), 6.07 (s, 1H, =CH₂), 6.80-6.84 (m, 1H, ArH), 6.92-6.98 (m, 3H, ArH), 7.15-7.20 (dd, 1H, *J*₁= 1.8 Hz, *J*₂= 8.40 Hz, ArH), 7.38 (d, 1H, *J*= 1.8 Hz, ArH), 7.44-7.49 (m, 1H, ArH), 8.07 (s, 1H, CONH).

¹³C NMR (CDCl₃, 50 MHz) δ= 63.8, 121.7, 121.8, 123.6, 124.9, 125.7, 127.9, 129.9, 130.2, 133.8, 134.7, 137.7, 137.9, 142.3, 169.7.

MS (ES+): *m/z* 319.1 (M⁺+1).

Anal. Calcd. for C₁₆H₁₂Cl₂N₂O: C, 60.21; H, 3.79; N, 8.78. Found: C, 60.50; H, 3.95; N, 8.62.

4-(4-Methyl-phenyl)-3-methylene-4-phenyl-1,3,4,5-tetrahydro-benzo[*b*][1,4]diazepin-2-one (3e)

Yield: 74%; white solid; mp 192-194 °C.

IR (KBr): 1665 (CONH), 3421 (NH) cm⁻¹.

¹H NMR (CDCl₃, 200 MHz): δ= 2.32 (s, 3H, CH₃), 3.91 (brs, 1H, CHNH), 5.12 (s, 1H, =CH₂), 5.23 (s, 1H, CHNH), 6.02 (s, 1H, =CH₂), 6.80-6.91 (m, 2H, ArH), 6.93-7.08 (m, 1H, ArH), 7.09-7.12 (m, 2H, ArH), 7.15-7.29 (m, 3H, ArH), 8.01 (s, 1H, CONH).

¹³C NMR (CDCl₃, 50 MHz): δ= 21.0, 65.0, 120.5, 121.1, 121.86, 124.3, 126.9, 128.3, 129.0, 136.7, 138.3, 138.9, 145.0, 169.0.

MS (ES+) *m/z* 265.1 (M⁺+1).

Anal. Calcd. for C₁₇H₁₆N₂O: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.31; H, 5.88; N, 10.39.

4-(4-Chloro-phenyl)-3-methylene-4-phenyl-1,3,4,5-tetrahydro-benzo[*b*][1,4]diazepin-2-one (3f)

Yield: 78%; light yellow solid; mp 190-192 °C.

IR (KBr): 1658 (CONH), 3298 (NH) cm⁻¹.

¹H NMR (CDCl₃, 200 MHz): δ= 4.03 (s, 1H, CHNH), 5.26 (s, 2H, =CH₂ & NHCH), 5.97 (s, 1H, =CH₂), 6.82-

7.04 (m, 4H, ArH), 7.31 (s, 4H, ArH), 8.07 (s, 1H, CONH).

¹³C NMR (CDCl₃, 50 MHz): δ= 66.1, 121.3, 121.7, 122.2, 123.3, 125.2, 128.8, 129.1, 133.8, 138.0, 140.4, 144.5, 169.6.

MS (ES+): *m/z* 285.0 (M⁺+1), 287.0 (M⁺+3).

Anal. Calcd. for C₁₆H₁₃ClN₂O: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.60; H, 4.71; N, 10.01.

4-(4-Bromo-phenyl)-3-methylene-4-phenyl-1,3,4,5-tetrahydro-benzo[*b*][1,4]diazepin-2-one (3g)

Yield: 64%; light yellow solid; mp 196-198 °C.

IR (KBr): 1650 (CONH), 3312 (NH) cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ= 4.04 (brs, 1H, CHNH), 5.24 (s, 1H, =CH₂), 5.28 (s, 1H, CHNH), 6.00 (s, 1H, =CH₂), 6.84-7.05 (m, 4H, ArH), 7.28 (d, 2H, *J*= 8.4 Hz, ArH), 7.47 (d, 2H, *J*= 8.4 Hz, ArH), 7.78 (s, 1H, CONH).

¹³C NMR (CDCl₃+DMSO_d₆, 50 MHz): δ= 70.1, 125.8, 126.1, 126.3, 126.5, 127.6, 129.7, 133.4, 134.1, 136.5, 143.0, 146.3, 149.5, 174.1.

MS (ES+): *m/z* 329.1 (M⁺+1).

Anal. Calcd. for C₁₆H₁₃BrN₂O: C, 58.38; H, 3.98; N, 8.51. Found: C, 58.54; H, 4.10; N, 8.30.

3-Methylene-4-thiophene-1,3,4,5-tetrahydro-benzo[*b*][1,4]diazepin-2-one (3h)

Yield: 59%; brown solid; mp 182-184 °C.

IR (KBr): 1666 (CONH), 3418 (NH) cm⁻¹.

¹H NMR (CDCl₃+DMSO_d₆, 200 MHz): δ= 5.06 (b, 1H, CHNH), 5.16 (s, 1H, =CH₂), (s, 1H, =CH₂), 5.27 (d, 1H, *J*= 4.0 Hz, CHNH), 5.69 (s, 1H, ArH), 6.42-6.66 (m, 5H, ArH & 1 Het-H), 6.93 (d, 1H, *J*= 3.0 Hz, Het-H), 7.30 (s, 1H, Het-H), 9.01 (s, 1H, CONH).

¹³C NMR (CDCl₃, 50 MHz) δ= 65.4, 125.4, 126.0, 128.3, 129.4, 129.9, 130.7, 132.3, 133.6; 142.9, 149.3, 152.1, 172.8.

MS (ES+): *m/z* 257.0 (M⁺+1).

Anal. Calcd. for C₁₄H₁₂N₂OS: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.51; H, 4.79; N, 11.12.

2-[2-Amino-4,5-dichloro-phenylamino]-phenyl-methyl]-acrylic acid ethyl ester (8a)

Yield: 83%; white solid; mp 138-140 °C.

IR (KBr): 1655 (CONH), 3430 (NH) cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ= 2.19 (s, 6H, 2xCH₃), 3.85 (brs, 1H, CHNH), 5.19 (s, 2H, NHCH & =CH₂), 5.95 (s, 1H, =CH₂), 6.65 (d, 2H, *J*= 2.2 Hz, ArH), 7.31-7.42 (m, 5H, ArH), 7.42 (s, 1H, CONH).

¹³C NMR (CDCl₃, 50 MHz) δ= 19.3, 19.5, 60.8, 122.7, 123.4, 127.1, 127.6, 128.4, 129.2, 131.1, 133.9, 136.4, 142.2, 145.2, 170.3.

MS (ES+): *m/z* 279.2 (M⁺+1).

Anal. Calcd. for C₁₈H₁₈N₂O: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.80; H, 5.45; N, 10.97.

General procedure for the preparation of 4-6a- To a solution of appropriate acetate (1.0 mmol) in dry THF (15 mL) was added DABCO (1.02 g, 4.5 mmol) at room temperature and stirred for 10 minutes. Simultaneously, appropriate 2-nitro aniline was taken in dry THF (10 mL) in a separate flask and sodium hydride (0.121 g, 2.5 mmol) was added to it at room temperature under stirring. The mixture of DABCO with Baylis Hillman acetate was added dropwise to the nitro aniline mixture maintaining dry conditions. The reaction was allowed to proceed at ambient temperature for 1.5h. On completion, the reaction mixture was extracted with EtOAc (3x20) and 30 ml water. The organic layers were pooled, dried over Na₂SO₄ and concentrated in vacuo to afford the residue, which was purified by silica gel chromatography using hexane: EtOAc (95:5, v/v) to yield the pure products.

2-[(4,5-Methyl-2-nitro-phenylamino)-phenyl-methyl]-acrylic acid ethyl ester (5a)

Yield: 71%; yellow solid; mp 114-116 °C.

IR (KBr): 1717 (CO₂Et), 3377 (NH) cm⁻¹.

¹H NMR (CDCl₃, 200 MHz): δ= 1.23 (t, 3H, *J*= 7.2 Hz, CH₂CH₃), 2.16 (s, 3H, CH₃), 2.21 (s, 3H, CH₃), 4.20 (q, 2H, *J*= 7.2 Hz, CH₂CH₃), 5.67 (s, 1H, CHNH), 5.70 (s, 1H, CHNH), 5.82 (s, 1H, =CH₂), 6.41 (s, 1H, =CH₂), 6.54 (s, 1H, ArH), 7.28-7.38 (m, 5H, ArH), 7.95 (s, 1H, ArH).

¹³C NMR (CDCl₃, 50 MHz) δ= 14.4, 19.0, 21.2, 58.1, 61.6, 115.5, 125.7, 126.7, 126.9, 127.7, 128.5, 129.4, 130.9, 139.8, 140.27, 142.8, 147.6, 166.2.

MS (ES⁺): *m/z* 354.9 (M⁺+1).

Anal. Calcd. for C₂₀H₂₂N₂O₄: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.90; H, 6.39; N, 7.67.

2-[(4,5-Dichloro-2-nitro-phenylamino)-phenyl-methyl]-acrylic acid ethyl ester (6a)

Yield: 73%; orange solid; mp 114-116 °C.

IR (KBr): 1717 (CO₂Et), 3377 (NH) cm⁻¹.

¹H NMR (CDCl₃, 200 MHz): δ= 1.27 (t, 3H, *J*= 7.4 Hz, CH₂CH₃), 4.21 (q, 2H, *J*= 7.1 Hz, CH₂CH₃), 5.59 (s, 1H, CHNH), 5.63 (s, 1H, CHNH), 5.81 (s, 1H, =CH₂), 6.45 (s, 1H, =CH₂), 6.88 (s, 1H, ArH), 7.37-7.43 (m, 5H, ArH), 8.30 (s, 1H, ArH).

¹³C NMR (CDCl₃, 50 MHz): δ= 14.3, 58.6, 61.8, 116.3, 120.1, 127.2, 127.6, 128.1, 128.9, 129.6, 131.6, 138.6, 139.9, 141.6, 142.9, 165.8.

MS (ES⁺): *m/z* 394.7 (M⁺+1).

Anal. Calcd. for C₁₈H₁₆Cl₂N₂O₄: C, 54.70; H, 4.08; N, 7.09. Found: C, 54.88; H, 3.80; N, 6.90.

General procedure for the preparation of 9-11a- To a solution of appropriate compound (1.0 mmol) in methanol (10 mL) was added SnCl₂·2H₂O (1.73 g, 5.0 mmol) and the reaction mixture was heated at reflux with stirring at 80°C for 12h in a nitrogen atmosphere. On completion, methanol was evaporated and the residue was made alkaline with saturated NaHCO₃ and then EtOAc

(100 mL) was added. The suspension was passed through a bed of celite and the filtrate was partitioned in a separating funnel. The organic layer was separated, dried (Na₂SO₄) and concentrated to afford a residue, which was purified by silica gel chromatography using hexane: EtOAc (80:20, v/v) to yield pure product.

2-[(2-Amino-4,5-methyl-phenylamino)-methyl]-3-phenyl-acrylic acid ethyl ester (10a)

Yield: 72%; brown oil.

IR (neat): 1703 (CO₂Et), 3343 (NH and NH₂) cm⁻¹.

¹H NMR (CDCl₃, 200 MHz): δ= 1.34 (t, 3H, *J*= 7.2 Hz, CH₂CH₃), 2.08 (s, 3H, CH₃), 2.13 (s, 3H, CH₃), 3.40 (brs, 2H, NH₂), 4.08 (s, 2H, CH₂NH), 4.30 (q, 2H, *J*= 7.2 Hz, CH₂CH₃), 6.32 (s, 1H, ArH), 6.53 (s, 1H, ArH), 7.37-7.45 (m, 5H, ArH), 7.90 (s, 1H, =CH).

MS (ES⁺): *m/z* 325.1 (M⁺+1).

Anal. Calcd. for C₂₀H₂₄N₂O₂: C, 74.04; H, 7.46; N, 8.64. Found: C, 74.19; H, 7.44; N, 8.70.

2-[(2-Amino-4,5-dichloro-phenylamino)-methyl]-3-phenyl-acrylic acid ethyl ester (11a)

Yield: 68%; brown oil.

IR (neat): 1710 (CO₂Et), 3418 (NH and NH₂) cm⁻¹.

¹H NMR (CDCl₃, 200 MHz): δ= 1.32 (t, 3H, *J*= 7.2 Hz, CH₂CH₃), 3.40 (s, 2H, NH₂), 4.07 (s, 2H, CH₂), 4.27 (q, 2H, *J*= 7.2 Hz, CH₂CH₃), 6.45 (s, 1H, ArH), 6.54 (s, 1H, ArH), 7.36-7.40 (m, 5H, ArH), 7.92 (s, 1H, =CH).

MS (ES⁺): *m/z* 365.2 (M⁺+1).

Anal. Calcd. for C₁₈H₁₈Cl₂N₂O₂: C, 59.19; H, 4.97; N, 7.67. Found: C, 58.95; H, 5.10; N, 7.88

General procedure for the preparation of 12-14a

These compounds were prepared following the procedure described for 3a-h. (refer to ref. 5b).

3-Benzylidene-7,8-dimethyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one (13a)

Yield: 70%; white solid; mp 194-196 °C.

IR (KBr): 1632 (CONH), 3267 (NH) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ= 2.16 (s, 6h, 2xCH₃), 3.85 (brs, 1H, CHNH), 4.10 (s, 2H, CH₂), 6.55 (s, 1H, ArH), 6.65 (s, 1H, ArH), 7.34-7.37 (m, 5H, ArH), 7.79 (s, 1H, =CH), 7.92 (brs, 1H, CONH).

MS (ES⁺): *m/z* 279.2 (M⁺+1).

Anal. Calcd. for C, 77.67; H, 6.52; N, 10.06. Found: C, 77.32; H, 6.49; N, 10.22.

3-Benzylidene-7,8-dichloro-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one (14a)

Yield: 76%; white solid, mp 118-120 °C.

IR (KBr): 1657 (CONH), 3374 (NH and NH₂) cm⁻¹.

¹H NMR (CDCl₃, 200 MHz): δ= 4.12 (s merged with brs, 3H, CHNH & CH₂), 6.83 (s, 1H, ArH), 7.07 (s, 1H, ArH), 7.35-7.39 (m, 5H, ArH), 7.87 (s, 1H, =CH), 8.54 (s, 1H, CONH).

^{13}C NMR (DMSO- d_6 , 50 MHz): δ = 47.8, 124.3, 126.2, 126.8, 130.3, 132.7, 133.8, 134.6, 137.9, 140.4, 141.8, 145.2, 174.6.

MS (ES+): m/z 319.1 (M^+ +1).

Anal. Calcd. for $\text{C}_{18}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_4$: C, 60.21; H, 3.79; N, 8.78. Found: C, 60.40; H, 4.01; N, 8.55.

General procedure for the preparation of 2,7a- To a stirred solution of appropriate compound (1.0 mmol) in MeOH (10 mL) was added zinc powder (0.150 g, 1.5 mmol) followed by HCOONH_4 (0.289 g, 3.0 mmol) at room temperature. After completion (monitored by TLC), MeOH was evaporated in vacuo and the residue was dissolved in EtOAc (20 mL) this was then passed through a bed of celite. The filtrate was extracted with EtOAc (2x20 mL) and water 30 mL. The organic layers were combined, dried over Na_2SO_4 and evaporated to yield the crude product, which was purified through silica gel chromatography. Elution with hexane:EtOAc (80:20) afforded the pure compounds

2-[2-Amino-4,5-dichloro-phenylamino)-phenyl-methyl]-acrylic acid ethyl ester (7a)

Yield: 60%; brown oil.

IR (neat): 1748 (CO_2Et), 3407 (NH and NH_2) cm^{-1} .

^1H NMR (CDCl_3 , 200 MHz): δ = 1.22 (t, 3H, J = 7.2 Hz, CH_2CH_3), 2.12 (s, 6H, $2\times\text{CH}_3$), 3.80 (brs, 1H, NH), 4.15 (q, 2H, J = 7.0 Hz, CH_2CH_3), 5.37 (s, 1H, CHNH), 5.90 (s, 1H, = CH_2), 6.35 (d, 2H, J = 4.8 Hz, = CH_2 & ArH), 6.54 (s, 1H, ArH), 7.29-7.37 (m, 5H, ArH).

MS (ES+): m/z 325.2 (M^+ +1).

Anal. Calcd. for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 73.89; H, 7.65; N, 8.49.

General Procedure for the preparation of 18a-c- Through a solution of 1.0 mmol of the appropriate nitrile in 10 mL of dry dichloromethane and 0.12 mL of ethanol (1.0 mmol) was bubbled at 0 °C ca. 1.5 mmol of gaseous HCl. The reaction was kept at 0 °C for 3h after which it was allowed to warm to room temperature and continued for another 5h. The excess dichloromethane was removed under nitrogen, dry diethyl ether was added to the residue and the flask was left at 0 °C for 24h. The solid obtained on trituration was filtered and dried over P_2O_5 to afford the final compounds as the hydrochloride salt.

3-Benzylidene-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-ylamine (18a)

Yield: 70% as HCl salt; brown solid, mp 178-179 °C.

IR (KBr): 3408 (NH and NH_2) cm^{-1} ;

^1H NMR (CD_3OD , 300 MHz) δ = 3.35 (s, 2H, CH_2NH), 7.09-7.134 (m, 4H, ArH), 7.14-7.18 (m, 5H, ArH), 7.45 (s, 1H, =CH);

MS (ES+) m/z 250 (M^+ +1).

Anal. Calcd. for $\text{C}_{16}\text{H}_{16}\text{ClN}_3$: C, 67.25; H, 5.64; N, 14.70. Found: C, 66.96; H, 5.88; N, 14.47.

3-(2-chloro-benzylidene)-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-ylamine (18b)

Yield: 77% as HCl salt; white solid; mp 216-218 °C.

IR (KBr): 3410 (NH and NH_2) cm^{-1} .

^1H NMR (CD_3OD , 300 MHz): δ = 3.33 (s, 2H, CH_2NH), 7.17-7.20 (m, 4H, ArH), 7.17-7.20 (m, 6H, ArH & =CH);

MS (ES+): m/z 284 (M^+ +1).

Anal. Calcd. for $\text{C}_{16}\text{H}_{15}\text{Cl}_2\text{N}_3\cdot\text{H}_2\text{O}$: C, 56.82; H, 5.07; N, 12.42. Found: C, 57.13; H, 4.89; N, 12.35.

3-(4-Methyl-benzylidene)-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-ylamine (18e)

Yield: 74% as HCl salt; brown solid; mp 199-201 °C.

IR (KBr): 3420 (NH and NH_2) cm^{-1} .

^1H NMR (CD_3OD , 300 MHz): δ = 2.37 (s, 3H, CH_3), 3.32 (s, 1H, CH_2NH), 3.78 (d, 2H, J = 4.5 Hz, CH_2NH), 6.85-6.90 (m, 4H, ArH), 7.12-7.37 (m, 4H, ArH), 7.64 (s, 1H, =CH);

MS (ES+) m/z 264 (M^+ +1).

Anal. Calcd. for $\text{C}_{17}\text{H}_{18}\text{ClN}_3\cdot\text{H}_2\text{O}$: C, 64.25; H, 6.34; N, 13.22. Found: C, 64.38; H, 6.66; N, 12.97.

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