Novel Synthesis of 3-Phenylazo-1,5-benzothiazepines, -1,5-benzoxazepines and -1,5-benzodiazepines *via* a One-Pot Reaction

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Novel polysubstituted -1,5-benzothiazepine, -1,5-benzoxazepine, and -1,5-benzodiazepine were prepared in good yields by the reaction of hydrazono derivatives with *o*-thioaminophenol, *o*-aminophenol and *o*-phenylenediamine *via* a one-pot reaction.

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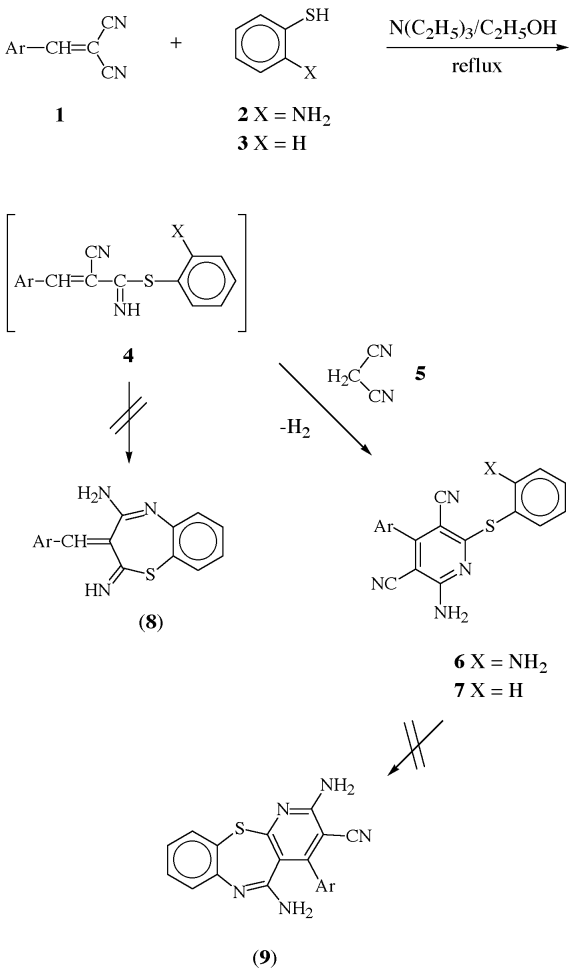
The benzylidenecyanoacetic esters and benzylidenemalononitriles have been widely applied as a precursor in the synthesis of heterocyclic compounds [1-6]. Kambe *et. al.* [1] reported the synthesis of substituted pyridines (**6, 7**), wherein an key intermediate (**4**) further reacted *in situ* with one mole of malononitrile. This reaction pathway [1] seems possible for us to construct the seven-membered rings (**8, 9**) (Scheme 1). In continuation of our interest to prepare seven-membered rings, [7-10] we report herein the reactivity of the hydrazono derivatives **11** and **18** which have not previously been used as a precursor for these compounds.

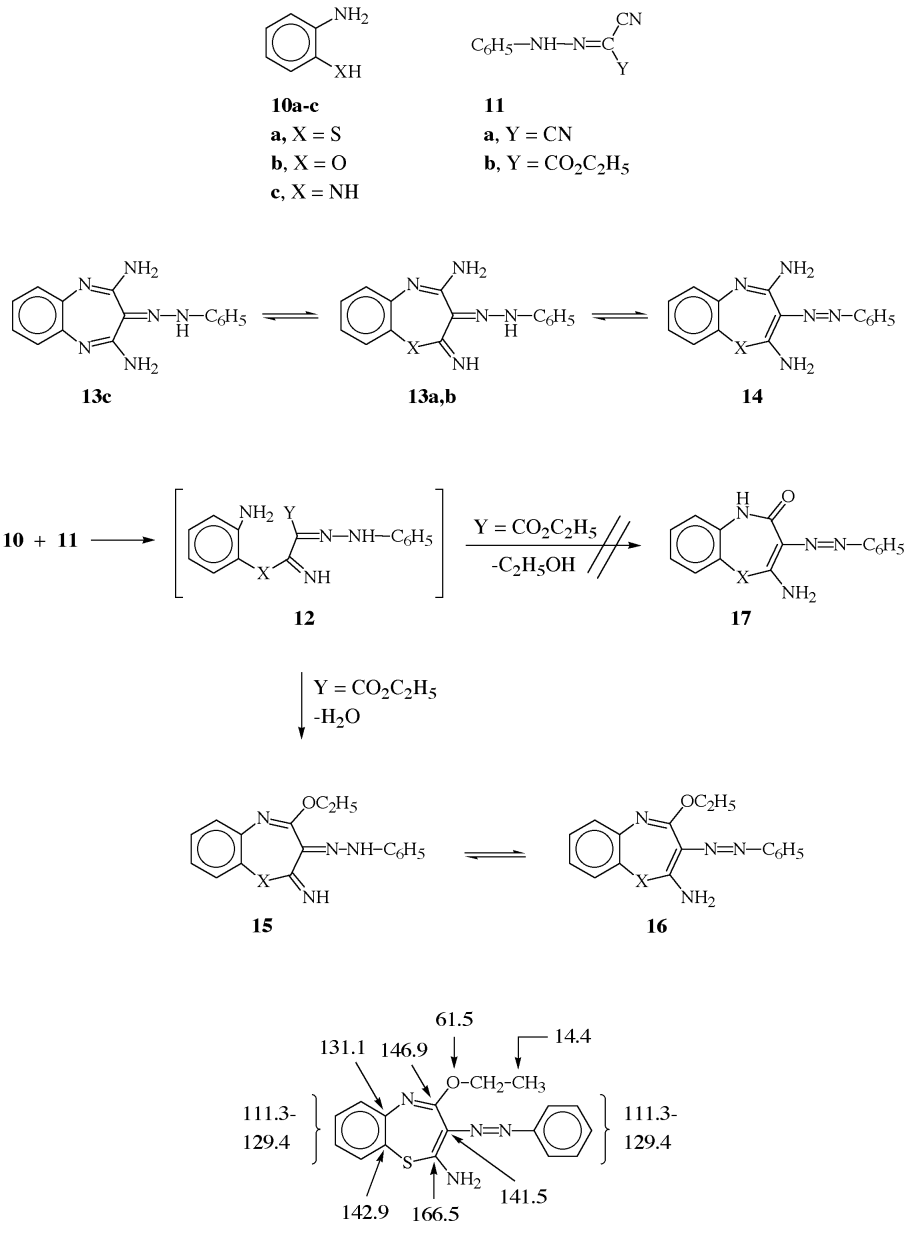
Scheme 1



Thus, phenylhydrazonomalononitrile **11a** and phenylhydrazonoethylcyanoacetate **11b** readily reacted with *o*-thioaminophenol **10a**, *o*-aminophenol **10b,** and *o*-phenylenediamine **10c** to give 2-amino-3-phenylazo-1,5-benzothiazepine, 2-amino-3-phenylazo-1,5-benzoxazepine and 2-amino-3-phenylazo-1,5-benzodiazepine derivatives **14** and **16**. The 4-amino-2-imino-3-phenylhydrazo-1,5-benzothiazepine **13a** seems to be formed *via* nucleophilic addition of the XH function of **10a** to the CN function of **11a** (Y= CN) to yield the intermediate **12**. Further cyclization through a similar addition of the NH_2 to the second CN function yielded finally **13a** which could isomerizes to 2,4-diamino-3-phenylazo-1,5-benzothiazepine **14a** (Scheme 2).

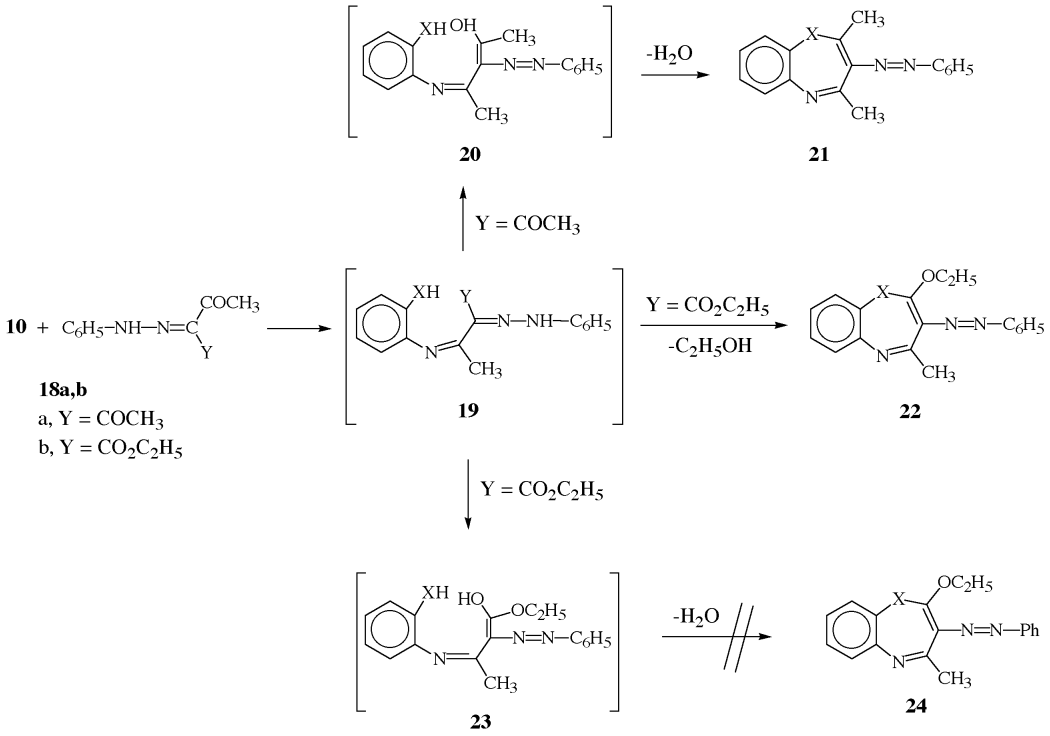
However, in the case of **11b** (Y= $CO_2C_2H_5$), it seems that the reaction proceeds *via* elimination of water from the intermediate **12** resulting in the formation of 4-ethoxy-2-imino-3-phenylhydrazo-1,5-benzothiazepine **15a** which might be present as 2-amino-4-ethoxy-3-phenylazo-1,5-benzothiazepine **16a**. The formation of compound **17** was ruled out based on spectral and elemental analytical data (Scheme 2). The IR (KBr, ν = cm^{-1}) spectra of **13** and **15** revealed absorption bands at 3350-3225, 3120 (NH_2, NH). The ^1H NMR ($CDCl_3$, δ = ppm) spectrum of **15a** showed triplet at 1.4, quartet at 4.4 assigned for the ethoxy, -multiplets at 7.1-7.9 for aromatic, singlet at 11.3 for NH and singlet at 15.0 ppm for NH protons, respectively. Also, the ^{13}C NMR spectrum of **15a** showed signals at δ 14.4 (OCH_2-CH_3), 61.5 (O-CH_2-CH_3), 111.3-129.4 (phenyl, and C-6 to C-9), 131.1 (C-5a), 141.5 (C-3), 142.9 (C-9a), 146.9 (C-4) and 166.5 (C-2), respectively. The quite high chemical shifts of the low field signals revealed the presence of strong hydrogen-bonded associations in the molecule. In the case of **15c** the solid state ir spectrum (KBr disk) showed an intense NH_2 absorption. However, the nmr spectrum ($CDCl_3$) lack the NH_2 signal and its integration value. From ^1H nmr and ir data the compound **15c** exist predominantly in solution in imino

Scheme 2



form, while the amino form is more common in the solid state. In general, the hydrazone structures **13** and **15** seem more predominant than the possible isomeric azo structures **14** and **16**. However, the phenylhydrazonoacetylacetone **18a** easily condensed with **10a** to yield the key intermediate **19** (Y= $COCH_3$), which in turn loses another molecule of water from the intermediate **20** to yield 2,4-dimethyl-3-phenylazo-1,5-benzothiazepine **21a**. The ^1H nmr spectrum showed two singlets at δ 2.3 and 2.4 ppm for two methyl groups. On the other hand, phenylhydrazonoethylacetoacetate **18b** (Y = $CO_2C_2H_5$) condensed with **10a** to yield the corresponding 2-hydroxy-4-methyl-3-phenylazo-1,5-benzothiazepine **22a** *via* loss of ethanol directly from the intermediate **19** (Y = $CO_2C_2H_5$). However, the possible structure **24** was ruled out based on spectral data, (Scheme 3). The IR, ^1H, ^{13}C nmr, and mass spectral data confirmed the absence of the ester group and the presence of only one methyl group, (^1H, δ 2.4 and ^{13}C, δ 11.8 ppm).

Scheme 3



EXPERIMENTAL

All melting points were measured on a Gallen-Kamp melting point apparatus and are uncorrected. IR spectra were recorded (potassium bromide, ν = cm^{-1}) were run on a Shimadzu 408 and a Pye Unicam Spectrophotometer. The ^1H, ^{13}C NMR spectra (deuterochloroform, δ = ppm) were recorded on a Bruker WM 300 MH_Z Spectrometer and tetramethylsilane was used as internal standard (Duisburg University, Germany). Mass spectra were recorded on a mass Spectrometer MS 9 (AET) EI Mode, and all the Microanalysis were carried out at Microanalytical Center, Cairo University, Egypt.

Synthesis of 4-Amino-2-imino-3-phenylhydrazo-1,5-benzothiazepine (**13a**), 4-Amino-2-imino-3-phenylhydrazo-1,5-benzoxazepine (**13b**) and 2,4-Diamino-3-phenylhydrazo-1,5-benzodiazepine (**13c**).

General Procedure.

A solution of *o*-aminothiophenol **10a** (0.24 g, 2 mmoles) and phenylhydrazonomalononitrile **11a** (0.34 g, 2 mmoles) in 20 mL of ethanol in the presence of 0.1 mL of piperidine was refluxed for 1-2 hours. The solvent was concentrated *in vacuo*, and the residue was triturated with 5 mL of methanol. The product so formed (**13a**) was collected by filtration, washed with methanol and recrystallized from ethanol. Compounds **11a** and **10b,c** were reacted similarly (2 mmoles each) under the same reaction conditions to yield **13b,c**.

Compound **13a** was obtained in 85 % yield, mp 235°; ir: ν 3350-3225, 3120 cm^{-1} (NH_2, NH); ^1H nmr: δ 7.1-7.9 (m, 9H, Ar-H), 9.9 (s, 2H, NH_2), 11.1 (s, 1H, NH), 14.6 (s, 1H, NH); ms: *m/z* (%) 295 (M^+, 8).

Anal. Calcd. for $C_{15}H_{13}N_5S$: C, 61.00; H, 4.44; N, 23.71; S, 10.85.Found: C, 60.82; H, 4.32; N, 23.53; S, 10.71.

Compound **13b** was obtained in 75 % yield; mp: 110° (MeOH); ir: 3340, 3220 cm^{-1} (NH_2, NH); ^1H nmr: δ 7.1-7.9 (m, 9H, Ar-H), 9.8 (s, 2H, NH_2), 11.2 (s, 1H, NH), 14.2 (s, 1H, NH); ms: *m/z* 279 (M^+ 10).

Anal.Calcd. for $C_{15}H_{13}N_5O$: C, 64.51; H, 4.69; N, 25.07. Found:C, 64.33; H, 4.56; N, 24.92.

Compound **13c** was obtained in 70 % yield, mp 130° (EtOH); ir: 3335-3220 cm^{-1} (NH_2, NH); ^1H nmr: δ 7.2-7.9 (m, 9H, Ar-H), 9.7 (s, 2H, NH_2), 9.9 (s, 2H, NH_2), 14.4 (s, 1H, NH); ms: *m/z* 278 (M^+, 55).

Anal. Calcd. for $C_{15}H_{14}N_{6:}$ C, 64.73; H, 5.07; N, 30.20. Found: C, 64.55; H, 4.97; N, 30.04.

Synthesis of 4-Ethoxy-2-imino-3-phenylhydrazo-1,5-benzothiazepine (**15a**), 4-Ethoxy-2-imino-3-phenylhydrazo-1,5-benzoxazepine (**15b**) and 2-Amino-4-ethoxy-3-phenylhydrazo-1,5-benzodiazepine (**15c**).

General Procedure.

To a solution of *o*-aminothiophenol **10a** (0.24 g, 2 mmoles) in 10 mL of ethanol was added a solution of compound **11b** (0.4g, 2 mmoles) in 15 mL of ethanol and 0.1 mL of piperidine.

The mixture was boiled under reflux for 2-4 hours. The solution was concentrated *in vacuo* and the residue was triturated with methanol. The product so formed **15a** was collected by filtration, washed with methanol and recrystallized from ethanol. Analogously, compounds **10b,c** were reacted with **11b** (2 mmoles each) under the same reaction conditions to yield **15b,c**. compound (**15a**): yield 62%, mp 150°; ir: 3250-3130 cm^{-1}, (NH_2); ^{1}H-nmr: δ 1.4 (t, 3H, CH_3), 4.4 (q, 2H, CH_2), 7.1-7.9 (m, 9H, Ar-H), 11.3 (s, 1H, NH), 15.0 (s, 1H, NH); ^{13}C-nmr: δ 14.4 (O-CH_2- *C*H_3), 61.5 (O-*C*H_2-CH_3), 111.3 - 129.4 (phenyl and C-6 to C-9), 131.1 (C-5a), 141.5 (C-3), 142.9 (C-9a), 146.9 (C-4) and 166.5 (C-2). ms, *m/z* 324 (M^+, 25).

Anal. Calcd. for $C_{17}H_{16}N_4OS$: C, 62.94; H, 4.97; N, 17.27; S, 09.88. Found: C, 62.78; H, 4.85; N, 17.10; S, 09.72.

Compound **15b** was obtained in 65 % yield, mp 130° (MeOH); ir: 3330-3235 cm^{-1} (NH); ^{1}H nmr:δ 1.3 (t, 3H, CH_3), 4.3 (q, 2H, CH_2), 7.1 -7.9 (m, 9H, Ar-H), 11.4 (s, 1H, NH), 15.1 (s, 1H, NH); ms: *m/z* 308 (M^+, 35).

Anal. Calcd. for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.05; H, 5.10; N, 18.01.

Compound **15c** was obtained in 60 % yield; mp 200° (MeOH); ir: 3335-3165 cm^{-1} (NH, NH_2); ^{1}H nmr: δ 1.4 (t, 3H, CH_3), 4.3 (q, 2H, CH_2), 7.1-7.9 (m, 10H, Ar-H + NH), 11.1 (s, 1H, NH), 15.1 (s, 1H, NH); ms: *m/z* 308 (M + 1, 55).

Anal. Calcd. for $C_{17}H_{17}N_5O$: C, 66.43; H, 5.57; N, 22.79. Found: C, 66.26; H, 5.46; N, 22.62.

Synthesis of 2,4-Dimethyl-3-phenylazo-1,5-benzothiazepine (**21a**), 2,4-Dimethyl-3-phenylazo-1,5-benzoxazepine (**21b**) and 2,4-Dimethyl-3-phenylazo-(1*H*)-1,5-benzodiazepine (**21c**).

General Procedure.

A mixture of **10a** (0.24 g, 2 mmoles) and **18a** (0.40 g, 2 mmoles) was refluxed in 20 mL of ethanol in the presence of 0.1 mL of piperidine for 2 hours. The solvent was concentrated *in vacuo*, and the residue was triturated with 5 mL of methanol. The product so formed **21a** was collected by filtration, washed with water and recrystallized from ethanol. In analogy, compound **18b** was reacted with **10b,c** (2 mmoles each) under the same reaction conditions to give **21b,c**.

Compound **21a** was obtained in 70 % yield, mp 100°; ^{1}H nmr: δ 2.3 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 7.0-7.8 (m, 9H, Ar-H); ms: *m/z* 293 (M^+, 60).

Anal. Calcd. for $C_{17}H_{15}N_3S$: C, 69.60; H, 5.15; N, 14.32; S 10.92. Found: C, 69.42; H, 5.05; N,14.16; S, 10.73.

Compound **21b** was obtained in 65 % yield, mp 110° (MeOH); ^{1}H nmr: δ 2.2 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 7.1-7.9 (m, 9H, Ar-H); ms: *m/z* 277 (M^+, 30).

Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.47; H, 5.32; N, 14.99.

Compound **21c** was obtained in 65 % yield, mp 135° (EtOH); ir: ν 3225 cm^{-1} (NH); ^{1}H nmr: δ 2.3 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 7.0-7.9 (m, 9H, Ar-H), 9.3 (s, 1H, NH); ms: *m/z* 276 (M^+, 25).

Anal.Calcd. for $C_{17}H_{16}N_4$: C, 73.89; H, 5.84; N, 20.27. Found: C, 73.71; H, 5.72; N, 20.09.

Synthesis of 2-Hydroxy-4-methyl-3-phenylazo-1,5-benzothiazepine (**22a**), 2-Hydroxy-4-methyl-3-phenylazo-1,5-benzoxazepine (**22b**) and 2-Hydroxy-4-methyl-3-phenylazo-1*H*-1,5-benzodiazepine (**22c**).

General Procedure.

A solution of ethanol (20 mL) containing **10a** (0.25 g, 2 mmoles), **18a** (0.46 g, 2 mmoles) and piperidine (0.1 mL) was refluxed for 4 hours. The solution was concentrated *in vacuo*. The residue was triturated with methanol. The product so formed (**22a**) was collected by filtration, washed with methanol and recrystallized from methanol. Similarly, compounds **10b,c** were reacted with **18b** (2 mmoles each) under the same reaction conditions to give **22b,c**.

Compound **22a** was obtained in 70 % yield, mp 160°; ir: 3450-3350 cm^{-1} (OH); ^{1}H nmr:δ 2.4 (s, 3H, CH_3), 7.1-7.9 (m, 9H, Ar-H), 13.6 (s, 1H, OH); ^{13}C nmr: δ 11.8 (CH_3), 128.9-115.9 (phenyl and C-6 to C-9), 129.7 (C-5a), 138.1 (C-9a), 141.2 (C-3), 148.6 (C-4), 157.5 (C-2); ms: *m/z* 296 (M + 1, 65).

Anal. Calcd. for $C_{16}H_{13}N_3OS$: C, 65.07; H, 4.44; N, 14.23; S, 10.85. Found: C, 64.82; H, 4.32; N, 14.04, S, 10.70.

Compound **22b** was obtained in 55 % yield, mp 110° (MeOH); ir: 3445-3360 cm^{-1} (OH); ^{1}H nmr: δ 2.3 (s, 3H, CH_3), 7.1-7.9 (m, 9H, Ar-H), 13.5 (s, 1H, OH); ms: *m/z* 279 (M^+, 75).

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05. Found: C, 68.63; H, 4.57; N, 14.89.

Compound **22c** was obtained in 53 % yield, mp 150° (MeOH); ir: 3445-3250 cm^{-1} (OH, NH); ^{1}H nmr: δ 2.4 (s, 3H, CH_3), 7.1-7.9 (m, 10H, Ar-H + NH), 13.6 (s, 1H, OH); ms: *m/z* 278 (M^+ 40).

Anal. Calcd. for $C_{16}H_{14}N_4O$: C, 69.05; H, 5.07; N, 20.13. Found: C, 68.88; H, 4.96; N, 19.95.

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