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Part 6: Synthesis of Spiro 1,5-Benzodiazepine Attached with Different Heterocyclic Moeities

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Abstract: 3-Oxime-4-phenyl-1(H)(l,5)benzodiazepin-2-one **2** was prepared and treated with malononitrile, arylidenenitriles, and bidentates to give the corresponding spiro-3,3′-isoxazolo-, thiadiazino-, and triazino-1,5-benzodiazepines **3**–**7**. 3-Bromo-3-cyano-4-phenyl-l(H)(l,5)benzodiazepin-2-one **9a** and 3-bromo-3-cyano-4-(4′-bromophenyl)-1(H)(l,5)benzodiazepin-2-one **9b** were synthesized via the bromination of 3-cyano-4-phenyl-1(H)(l,5)benzodiazepin-2-one **8**. Compounds **9a,b** were reacted with bidentates or cyclopentanone to afford spiro piprazine, quinoxaline, thiazine, thiadiazine, imidazole, and cyclopentafuran derivatives **10**–**16**. Treatment of compound **1** with *p*-tolyldiazonium chloride gave 3-(*p*-tolylazo)-4-phenyl-1(H)(1,5)-benzodiazepin-2-one **17**, which in turn treated with nitriles, cyclopentanone, and S,S-acetal derivative to give the corresponding spiro pyrazole, cyclopentapyrazole, and thiadiazole derivatives **18**–**21**.

Keywords: 3-bromo-3-cyano-4-phenyl-l(H)(1,5)benzodiazepin-2-one, 3-oxime-4-phenyl-1(H)(1,5)benzodiazepin-2-one, PTC, 3-(*p*-tolylazo)-4-phenyl-1(H)(1,5)benzodiazepin-2-one

1,5-Benzodiazepines are one of the most important classes of the therapeutic agents.[1] It has anti-inflammatory,[2] analgesic,[2,3] antagonists,[4] and antipyretic[5] properties. All these findings prompted us to continue our previous work on the synthesis of fused and spiro-1,5 benzodiazepines.[6–10]

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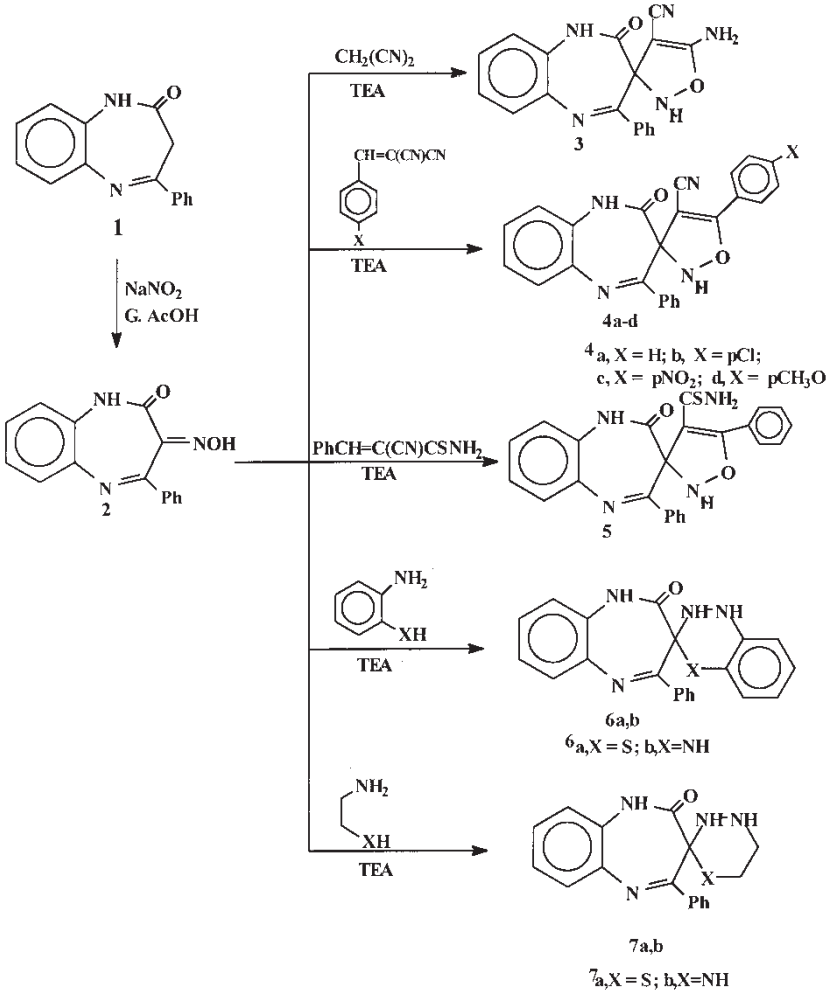
RESULTS AND DISCUSSION

Nitrosation of 1,3-dihydro-4-phenyl-1,5-benzodiazepin-2-one **1**[11] with sodium nitrite in acetic acid gave 3-oxime-4-phenyl-1(H)(1,5)-benzodiazepin-2-one **2**. ^{1}H NMR spectrum (δ, ppm) showed the following signals: 11.40 (s, 1H, NH); 10.3 (s, 1H, OH); 7.90–6.65 (m, 9H, arom.).

The action of active nitriles on compound **2** was studied. So, on treating compound **2** with malononitrile in the presence of triethylamine, spiro[2-oxo-4-phenyl-1(H)(1,5)benzodiazepine-3,3′-(5′-amino-cyano-2′(H)isoxazole)] **3** was obtained. IR spectrum showed the following absorption bands at 3400–3300 (br, 2NH), 3190, 3100 (NH_2, 2215 (CN), and 1675 (CO). The formation of compound **3** is believed to be via the addition of the active CH_2 group to the -C═N_{oxime} bond followed by a nucleophilic attack of the OH_{oxmine} group to one of the cyano group. Similarly, compound **2** was allowed to react with different arylidenenitriles, namely benzylidene(*p*-chlorobenzylidene, *p*-nitrobenzylidene, *p*-methoxybenzylidene)malononitrile, and benzyl-idenecyanothioacetamide in the presence of triethylamine to afford spiro[2-oxo-4-phenyl-l(H)(1,5)benzodiazepine-3,3′-(4′-cyano-5-phenyl-2′(H)- isoxazole)] **4$_a$**, spiro[2-oxo-4-phenyl-1(H)(1,5)benzo-diazepine-3,3′-(4′-cyano-5′-(*p*-chlorophenyl)-2′(H)-isoxazole)] **4$_b$**, spiro[2-oxo-4-phenyl-l(H)(1,5)benzodiazepine-3,3′-(4′-cyano-5′-(*p*-nitropheny1)-2′(H)-isoxazole)] **4$_c$**, spiro[2-oxo-4-phenyl-1(H)(1,5)-benzodiazepine-3,3′-(4′-cyano-5′-(*p*-methoxypheny1)-2′(H)-isoxazole)] **4$_d$**, and spiro[2-oxo-4-phenyl-1(H)(l,5) benzodiazepine-3,3′-(5′-phenyl-4′-thiocarboxamide-2′(H)isoxazole)] **5**, respectively. The reaction pathway was assumed to proceed via a nucleophilic attack of the OH_{oxime} group to the C═C bond of the arylidene derivative followed by addition of the CH-Ar group to the C═N_{oxime} with elimination of HCN molecule (cf. Scheme 1, Table 1)

Compound **2** is a good starting material for the synthesis of spiro heterocyclic systemes attached to the benzodiazepine moiety, where it was treated with a variety of bidentates, namely *o*-aminothiophenol, *o*-phenylenediamine, cystamine, and ethylenediamine, using triethylamine as a basic catalyst to yield spiro[2-oxo-4-phenyl-1(H)(1,5)benzodiazepine-3,2′-(3′,4′-dihydro(1′,3′,4′)benzothiadiazine)] **6$_a$** spiro[2-oxo-4-phenyl-1(H)(1,5)benzodiazepine-3,3′-(1′,2′,4′-trihydro(1′,2′,4′)-benzotriazine)] **6$_b$**, spiro[2-oxo-4-phenyl-1(H)(1,5)benzodiazepine-3,2′-(3′,4′,5′,6′-tetrahydro(1′,3′,4′)-thiadiazine)] **7$_a$**, and spiro [2-oxo-4-phenyl-1(H)(1,5)benzodiazepine-3,3′-(1′,2′,4′, 5′,6′-pentahydro(1′,2′,4′)triazine)] **7$_b$**, respectively (cf. Scheme 1, Table 1) Formation of compounds **6$_{a,b}$** and **7$_{a,b}$** was attributed to the nucleophilic attack of the SH group or NH_2 group to the C═N_{oxime} bond followed by elimination of a water molecule.

Treatment of 3-bromo-4-phenyl-1(H)(1,5)benzodiazepin-2-one[8] with potassium cyanide in dimethylsulfoxide as a solvent at 90°C afforded 3-cyano-4-phenyl-l(H)(1,5)benzodiazepin-2-one **8**. The IR spectrum showed an absorption band corresponding to CN at 2210 cm^{-1}. Bromination of



Scheme 1.

compound **8** with an equimolar amount of bromine, gave a mixture of 3-bromo-3-cyano-4-phenyl-1(H)(l,5)benzo-diazepin-2-one $\mathbf{9_a}$ and 3-bromo-3-cyano-4-(4′-bromophenyl)-1(H)(1,5)benzodiazepin-2-one $\mathbf{9_b}$, respectively. Compounds $\mathbf{9_{a,b}}$ were tested as starting material for the synthesis of spiro heterocyclic systems attached to benzodiazepine moeity. So, compounds $\mathbf{9_{a,b}}$ were treated with ethylenediamine, *o*-phenylenediamine, *o*-aminothiophenol, cystamine, thiosemicarbazide, guanidine, or cyclopentanone to give spiro[2-oxo-4-phenyl- 1(H)(1,5)-benzodiazepine-3,2′-(3′-amino-1′,5′,6′-trihydro(l′,4′)piprazine)] **10**, spiro[2-oxo-4-(*p*-bromopheny1)-1(H)(1,5)benzodiazepine-3,2′-(3′-amino-1′(H)quinoxaline)] **11**, spiro[2-oxo-4-phenyl-1(H)

Table 1. Analytical and spectral data of the new compounds

Product no.	M. P. (°C)[a]	Yield (%)	Mole. form. (Mol.wt.)	Analytical data[b] cal./found				IR (cm^{-1})[c]	^{1}H-NMR ∂ (ppm)[d]
				C	H	N	S		
2	244 acetic acid	90	$C_{15}H_{11}N_3O_2$ (265.27)	67.92 67.66	4.18 4.22	15.84 15.99		3485 (OH); 3192 (NH); 1673 (CO)	11.40 (s, 1H, NH); 10.35 (s, 1H, OH); 7.90–6.65 (m, 9H, arom.)
3	251 dioxane	70	$C_{18}H_{13}N_5O_2$ (331.33)	65.25 65.5	3.95 3.82	21.14 21.36		3400–3300 (br, 2NH); 3190, 3100 (NH_2); 2215 (CN); 1675 (CO)	10.00 (s, 1H, NH); 8.15 (s, 1H, NH); 7.90–6.40 (m, 9H, arom.); 4.35–3.75 (br, 2H, NH_2)
4_a	148 ethanol	30	$C_{24}H_{16}N_4O2$ (392.41)	73.46 73.49	4.11 4.35	14.28 14.08		3320, 3192 (2NH); 2206 (CN); 1678 (CO)	12.60 (s, 1H, NH); 11.70 (s, 1H, NH); 8.00–6.80 (m, 14H, arom.)
4_b	262 ethanol	86	$C_{24}H_{15}N_4O2Cl$ (426.86)	67.53 67.80	3.54 3.32	13.12 13.25		3340, 3183 (2NH); 2220 (CN); 1674 (CO)	12.85 (s, 1H, NH); 11.60 (s, 1H, NH); 8.40–7.20 (m, 13H, arom.)
4_c	125 methanol	55	$C_{24}H_{15}N_5O_4$ (437.41)	65.9 65.98	3.45 3.64	16.01 16.30		3328, 3198 (2NH); 2202 (CN); 1688(CO)	8.60 (s, 1H, NH); 8.50 –7.25 (m, 13H, arom.); 6.70 (s, 1H, NH)
4_d	212 ethanol	63	$C_{25}H_{18}N_4O_3$ (422.43)	71.10 71.31	4.29 4.50	13.26 13.04		3305, 3174 (2NH); 2920 ($CH_{aliph.}$); 2207 (CN); 1697 (CO)	12.30 (s, 1H, NH); 11.00 (s, 1H, NH); 8.20–7.00 (m, 13H, arom.); 3.45 (s, 3H, CH_3)
5	230 ethanol	82	$C_{24}H_{18}N_4O_2S$ (426.49)	67.59 67.40	4.25 4.00	13.14 13.35	7.52 7.70	3430, 3340, 3210, 3176 (2NH, NH_2); 1671 (CO)	12.85 (s, 1H, NH); 11.70 (s, 1H, NH); 8.90–6.60 (m, 14H, arom.); 4.45–4.15 (br, 2H, NH_2)

6_a	288 benzene	74	$C_{21}H_{16}N_4OS$ (372.44)	67.72 67.99	4.33 4.10	15.04 15.12	8.61 8.40	3373, 3289, 3180 (3NH); 1672 (CO)	12.75 (s, 1H, NH); 11.60 (s, 1H, NH); 8.60 (s, 1H, NH); 8.25–6.40 (m, 13H, arom.)
6_b	290 benzene	79	$C_{21}H_{17}N_5O$ (355.39)	70.97 70.77	4.82 4.60	19.71 19.51		3430, 3390, 3280, 3200 (4NH); 1670 (CO)	12.40 (s, 1H, NH); 11.15 (s, 1H, NH); 8.10–6.90 (m, 13H, arom.); 6.70 (s, 1H, NH); 6.50 (s, 1H, NH)
7_a	278 ethanol	63	$C_{17}H_{16}N_4OS$ (324.40)	62.94 62.99	4.97 4.88	17.27 17.35	9.88 9.96	3420, 3360, 3191 (3NH); 2906 ($CH_{aliph.}$); 1672 (CO)	12.55 (s, 1H, NH); 11.60 (s, 1H, NH); 8.90 (s, 1H, NH); 8.55 – 7.30 (m, 9H, arom.); 2.60–1.80 (br, 4H, $2CH_2$)
7_b	258 dioxane	68	$C_{17}H_{17}N_5O$ (307.35)	66.43 66.55	5.57 5.62	22.79 22.91		3440, 3380, 3188, 3150 (4NH); 2906 ($CH_{aliph.}$); 1672 (CO)	8.90 (s, 1H, NH); 8.25 –6.90 (m,10H, arom.+ NH); 6.20 – 5.55 (br, 2H, 2NH); 3.70–3.15 (m, 4H, $2CH_2$)
8	150 ethanol	96	$C_{16}H_{11}N_3O$ (261.28)	73.55 73.35	4.24 4.52	16.08 16.18		3206 (NH); 2214 (CN); 1715 (CO)	10.60 (s, 1H, NH); 8.00–6.40 (m, 9H, arom.); 6.10 (s, 1H, CH)
9_a	84 $CHCl_3$	53	$C_{16}H_{10}N_3OBr$ (340.18)	56.49 56.52	2.96 2.84	12.35 12.55		3196 (NH); 2208 (CN); 1697 (CO); 697 (C–Br)	10.40 (s, 1H, NH); 8.30–6.85 (m, 9H, arom.)
9_b	132 $CHCl_3$	40	$C_{16}H_9N_3OBr_2$ (419.07)	45.86 45.9	2.16 2.31	10.03 10.22		3198 (NH); 2217 (CN); 1689 (CO); 692 (C–Br)	11.00 (s, 1H, NH); 8.60–6.70 (m, 8H, arom.)
10	158 ethanol	71	$C_{18}H_{17}N_5O$ (319.36)	67.7 67.82	5.37 5.12	21.93 21.80		3421, 3360, 3165, 3065 (2NH, NH_2); 2980 ($CH_{aliph.}$); 1695 (CO)	11.35 (s, 1H, NH); 8.30–7.30 (m, 9H, arom.); 7.20 (s, 2H, NH_2); 7.00 (s, 1H, NH); 2.60–2.20 (m, 4H, $2CH_2$)

(*continued*)

Table 1. Continued

Product no.	M. P. (°C)[a]	Yield (%)	Mole. form. (Mol.wt.)	Analytical data[b] cal./found C	H	N	S	IR (cm^{-1})[c]	^{1}H-NMR ∂ (ppm)[d]
11	149 methanol	73	$C_{22}H_{16}N_5OBr$ (446.31)	59.21 59.15	3.61 3.82	15.69 15.87		3422, 3260, 3179, 3100 (2NH, NH_2); 1710 (CO)	11.90 (s, 1H, NH); 8.50–6.20 (m, 13H, arom.+ NH); 3.80–3.20 (br, 2H, NH_2)
12	Sub. at 320 $CHCl_3$	81	$C_{22}H_{16}N_4OS$ (384.45)	68.73 68.60	4.19 4.22	14.57 14.32	8.34 8.45	3260, 3165, 3100 (NH, NH_2); 1694 (CO)	11.15 (s, 1H, NH); 8.30–6.35 (m, 13H, arom.); 4.15–3.35 (br, 2H, NH_2)
13	140 dioxane	62	$C_{18}H_{16}N_4OS$ (336.41)	64.27 64.30	4.79 4.83	16.65 16.34	9.53 9.56	3400, 3350, 3166 (NH, NH_2); 2926, 2861 ($CH_{aliph.}$); 1699 (CO)	11.60 (s, 1H, NH); 8.40–6.70 (m, 9H, arom.); 6.45–6.00 (br, 2H, NH_2); 3.65–2.35 (m, 4H, $2CH_2$)
14	170 benzene	50	$C_{17}H_{13}N_6OSBr$ (429.31)	47.56 47.69	3.05 3.18	19.58 19.37	7.47 7.66	3350, 3300, 3290, 3240, 3200 (NH, $2NH_2$); 1715 (CO)	11.00 (s, 1H, NH); 8.25–6.75 (m, 8H, arom.); 3.80–3.20 (m, 4H, $2NH_2$)
15	170 benzene	60	$C_{17}H_{13}N_6OBr$ (397.24)	51.40 51.46	3.30 3.50	21.16 21.39		3300, 3250, 3220, 3180, 3100 (3NH, NH_2); 1720 (CO)	11.25 (s, 1H, NH); 10.00 (s, 1H, NH); 8.15–7.30 (m, 8H, arom.); 7.20 (s, 1H, NH); 4.50–4.25 (br, 2H, NH_2)
16	193 ethanol	66	$C_{21}H_{17}N_3O2$ (343.38)	73.45 73.25	4.99 4.86	12.24 12.31		3290, 3180 (2NH); 2973, 2920 ($CH_{aliph.}$); 1685 (CO)	10.15 (s, 1H, NH); 7.90–6.75 (m, 9H, arom.); 6.00 (s, 1H, NH); 2.70–2.10 (m, 4H, $2CH_2$); 1.30–0.85 (m, 2H, CH_2)

17	170 Acetic acid	87	$C_{22}H_{18}N_4O$ (354.41)	74.56 74.26	5.12 5.23	15.81 16.01		3220, 3183(2NH); 2865 ($CH_{aliph.}$); 1682 (CO)	11.30 (s, 1H, NH); 10.80 (s, 1H, NH); 8.60–7.15 (m, 13H, arom.); 2.55 (s, 3H, CH_3)
18	218 ethanol	70	$C_{25}H_{20}N_6O$ (420.47)	71.41 71.6	4.79 4.99	19.99 19.7		3441, 3320, 3203, 3110 (2NH, NH_2); 2919 ($CH_{aliph.}$); 2201 (CN); 1672 (CO)	10.80 (s, 1H, NH); 7.65–7.10 (m, 13H, arom.); 6.90 (s, 1H, NH); 4.00 (s, 2H, NH_2); 2.50 (s, 3H, CH_3)
19	205 benzene	66	$C_{25}H_{21}N_7O$ (435.49)	68.95 68.85	4.86 4.59	22.51 22.72		3447, 3300, 3190 (3NH); 2914 ($CH_{aliph.}$); 1662 (CO)	11.00 (s, 1H, NH); 8.50–7.10 (m, 14H, arom. +NH); 3.65 (s, 2H, CH_2); 3.40 (s, 1H, NH); 2.60 (s, 3H, CH_3)
20	222 benzene	53	$C_{27}H_{24}N_4O$ (420.51)	77.12 77.33	5.75 5.83	13.32 13.50		3300, 3198 (2NH); 2910 ($CH_{aliph.}$); 1660 (CO)	10.50 (s, 1H, NH); 7.70–7.05 (m, 13H, arom.); 6.85 (s, 1H, NH); 2.60 (s, 3H, CH_3); 2.0–0.90 (m, 6H, $CH_{2cyclic}$)
21	200 dioxane	79	$C_{26}H_{18}N_6OS$ (462.53)	67.52 67.77	3.92 3.7	18.17 18.33	6.93 6.98	3300, 3198 (2NH); 2210 (CN); 1670 (CO)	10.1 (s, 1H, NH); 7.70–7.05 (m, 13H, arom.); 6.2 (s, 1H, NH); 2.60 (s, 3H, CH_3)

[a]Uncorrected.
[b]Satisfactory microanalysis obtained C; ± 0.35, H; ± 0.4, N; ± 0.2, S; ± 0. 2.
[c]Measured by Nicolet FT-IR 710 Spectrophotometer.
[d]Measured by a Varian EM 360 L spectrometer at 60 MHZ using TMS as internal standard and DMSO as a solvent.

(1,5)benzodiazepine-3,2′-(3′-amino(1′,4′)benzothiazine)] **12**, spiro[2-oxo-4-phenyl-1(H)(1,5)-benzodiazepine-3,2′-(3′-amino-5′,6′-dihydro(1′,4′) thiazine)] **13**, spiro[2-oxo-4-(*p*-bromopheny1)-1 (H)(1,5)benzo diazepine-3,6′-(2′,5′-diamino-(1′,3′,4′)thiadiazine)] **14**, spiro [2-oxo-4-(*p*-bromopheny1)-1 (H)(1,5)-benzodiazepine-3,5′-(4′-amino-2′-imino-1′(H)imidazole)] **15**, and spiro[2-oxo-4-pheny1-1(H)(1,5)-benzodiazepine-3,3′-(2′-imino-4′,5′,6′-trihydrocyclopentafuran)] **16**, respectively (cf. Scheme 2, Table 1). The reaction pathway of the formation of compounds **10**–**15** was assumed to proceed via a nucleophilic attack of the NH_2 or the SH groups at the C-Br bond with elimination of the HBr molecule, followed by intramolecular cyclization through the nucleophilic addition of the NH_2 group at the CN group.

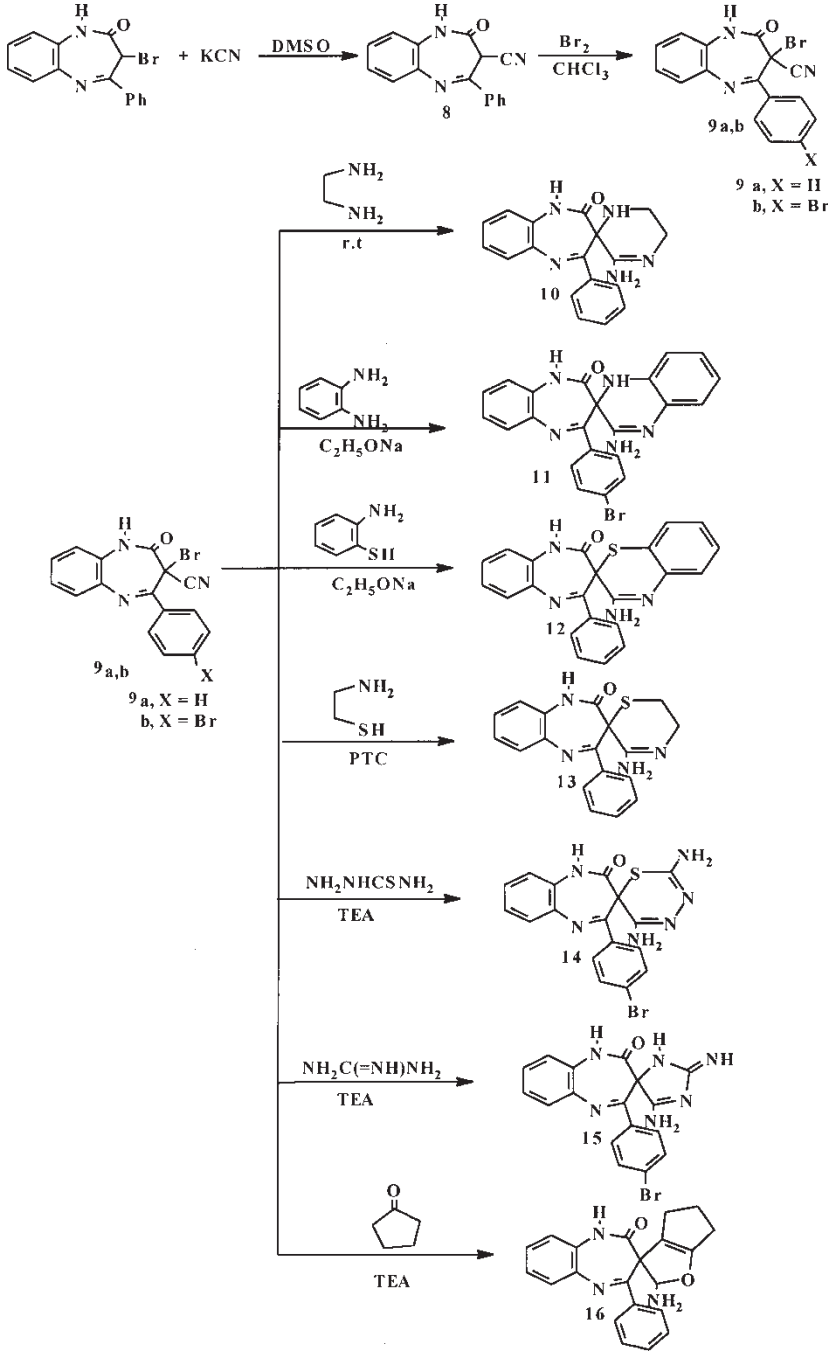
Compound **1** was reacted with *p*-tolyldiazonium chloride to give 3-(*p*-tolylazo)-4-phenyl-1(H)(1,5)benzodiazepin-2-one **17**. The reaction of compound **17** with active nitriles, namely malononitrile, cyanoacetamide, or cyanothioacetamide, gave the same product: spiro [2-oxo-4-phenyl-1(H)(1,5)benzodiazepine-3,3′-(5′aino-4′-cyano-1′-(p-tolyl)-2′(H)-pyrazole)] **18**. Treatment of compound **17** with cyanoacetohydrazide afforded spiro[2-oxo-4-phenyl-1(H)(1,5)benzodiazepine-3,3′-(2′,6′-dihydro-5′-imino-4′-(*p*-tolyl) pyrazole][4′,3′-b]pyrazole)] **19**. Moreover, the reaction of compound **17** with cyclopentanone and TEA in dioxane yielded spiro[2-oxo-4-phenyl-1(H)(1,5)benzodiazepine-3,3′-(1′-(*p*-tolyl)-2′,4′,5′,6′-tetrahydrocyclopentapyrazole)] **20** (cf. Scheme 3, Table 1). The reaction pathway of compound **18** was assumed to follow a preliminary formation of carbanion of the active methylene group, which was added at the -C═N-$bond_{benzodiazepine}$ followed by a nucleophilic attack of the NH group at the CN, CO, and CS groups with the elimination of the water molecule in the case of cyanoacetamide or the H_2S molecule in the case of cyanothioacetamide.

The reaction of compound **17** with CS_2 and malononitrile in 1:1:1 molar ratio under phas-transfer-catalysis (PTC) conditions [dioxane/potassium carbonate/tetrabutylammonium bromide (TBAB)] gave spiro[2-oxo-4-phenyl-1(H)(1,5)benzodiazepine-3,2′-(4′-(*p*-tolyl)-3′ (H)(1′,3′,4′)-thiadiazol-5′-ylidenemalononitrile)] **21** (cf. Scheme 3, Table 1). The reaction pathway was assumed to proceed via the addition of the SH group to the -C═N-NH-Ar bond followed by a nucleophilic attack of the NH group to the ethylenic bond of the dithioacetal with elimination of the H_2S molecule.

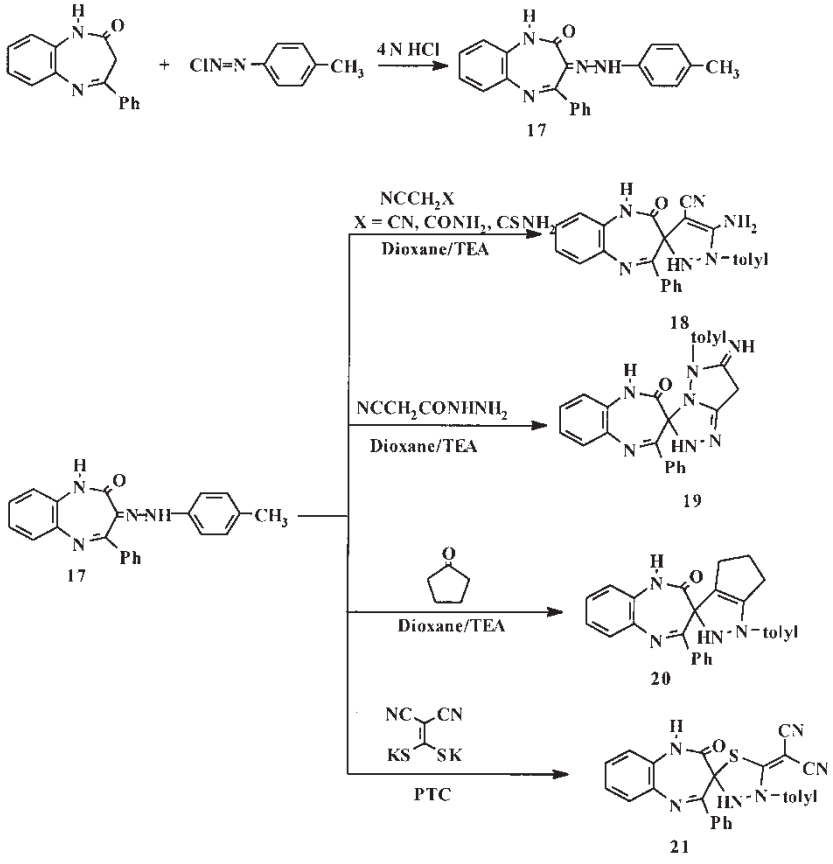
EXPERIMENTAL

Synthesis of Compound 2

To a stirred cold solution of compound **1** (0.01 mol, 2.36 g) in glacial acetic acid (20 mL), sodium nitrite (0.012 mol, 0.83 g) was added over 10 min. The stirring was continued for 30 min in an ice bath and for 2 h at room



Scheme 2.



Scheme 3.

temperature. The solid precipitate was filtered off, washed with water, dried, and crystallized (cf. Scheme 1, Table 1).

Synthesis of Compounds 3–5

Compound **2** (0.002 mol, 0.7 g) was added to a solution of the active nitrile (0.002 mol), namely malononitrile (0.13 g), benzylidenemalononitrile (0.3 g), *p*-chlorobenzylidenemalononitrile (0.37 g), *p*-nitro-benzylidenemalononitrile (0.39 g), *p*-methoxybenzyl-idenemalononitrile (0.36 g), or benzylidenecyanothioacetamide (0.37 g), along with a catalytic amount of triethylamine in dioxane (20 mL). The reaction mixture was refluxed for 4 h, and the solvent was evaporated in vacuo. The formed solid was filtered off and crystallized from the proper solvent (cf. Scheme 1, Table 1).

Synthesis of Compounds $6_{a,b}$ and $7_{a,b}$

To a stirred solution of compound **2** (0.02 mol, 0.53 g) in dioxane (20 mL), the appropriate bidentate reagent (0.02 mol) [namely *o*-aminothiophenol (0.22 mL), *o*-phenelenediamine (0.21 g), cystamine hydrochloride (0.22 g), or ethylenediamine (0.13 g)] and a catalytic amount of triethylamine were added. The reaction mixture was refluxed for 4 h and evaporated in vacuo, and the solid product was crystallized from the suitable solvent (cf. Scheme 2, Table 1). Note: In case of cystamine hydrochloride, triethylamine (3 mL, 0.022 mol) was added.

Synthesis of Compound 8

To a stirred suspension of potassium cyanide (0.002 mol, 0.156 g) in dimethylsulfoxide (10 mL), 3-bromo-1,3-dihydro-4-phenyl-1,5-benzodiazepin-2-one (0.002 mol, 0.63 g) was added dropwise at 90°C. The reaction mixture was further stirred for 30 min and poured into a mixture of ice-cold water (100 mL). The separated solid was collected by filtration and crystallized (cf. Scheme 2, Table 1).

Synthesis of Compounds $9_{a,b}$

To a stirred solution of compound **8** (0.02 mol, 5.22 g) in chloroform (50 mL), a solution of bromine (0.02 mol, 1.03 mL) in chloroform (15 mL) was added dropwise. The stirring was continued until the evolution of HBr gas ceased. The precipitated solid was filtered off, washed with dilute sodium bicarbonate solution (20 mL), and crystallized to give compound $\mathbf{9_a}$. The filtrate was evaporated in vacuo, and the residual solid was washed with water and crystallized to give compound $\mathbf{9_b}$ (cf. Scheme 2, Table 1).

Synthesis of Compound 10

To a solution of compound $\mathbf{9_a}$ (0.01 mol, 3.4 g) in dioxane (20 mL), ethylenediamine (0.01 mol, 0.67 mL) was added at room temperature. The reaction mixture was stirred for 4 h, the solvent was evaporated in vacuo, and the residual mass was treated with water. The separated solid was filtered off and crystallized (cf. Scheme 2, Table 1).

Synthesis of Compound 11

To a suspension of compound $\mathbf{9_b}$ (0.01 mol, 4.19 g) in sodium ethoxide solution (0.30 g of Na in 30 mL of absolute ethanol), *o*-phenylenediamine

(0.01 mol, 1.08 g) was added. The reaction mixture was refluxed for 2 h; the solid that formed after cooling was collected by filtration, washed with water, and crystallized (cf. Scheme 2, Table 1).

Synthesis of Compound 12

To a suspension of compound **9$_a$** (0.01 mol, 3.4 g) in sodium ethoxide solution (0.3 g of Na in 30 mL of absolute ethanol), *o*-aminothiophenol (0.01 mol, 1.07 mL) was added. The reaction mixture was refluxed for 4 h wand worked up as before (cf. Scheme 2, Table 1).

Synthesis of Compound 13

A mixture of a compound **9$_a$** (0.01 mol, 3.4 g), cystamine hydrochloride (0.01 mol, 1.13 g), anhydrous potassium carbonate (3 g), a catalytic amount of tetrabutyl ammounium bromide (TBAB), and dioxane (20 mL) was stirred for 40 min at rt. The reaction mixture was further stirred for 4 h at 60°C and filtered off, and the organic layer was evaporated in vacuo. The residual solid was washed with water, collected by filtration, and crystallized (Scheme 2, Table 1).

Synthesis of Compounds 14 and 15

To a stirred solution of compound **9$_b$** (0.01 mol, 4.19 g) in dioxane (20 mL), thiosemicarbazide (0.01 mol, 0.91 g) or guanidine hydrochloride (0.01 mol, 0.95 g) along with a catalytic amount of triethylamine were added. The reaction mixture was refluxed for 4 h and evaporated in vacuo, and the residual solid was collected by filtration and crystallized from the proper solvent (cf. Scheme 2, Table 1). Note: In case of guanidine hydrochloride, triethylamine (1.5 mL, 0.011 mol) was added.

Synthesis of Compound 16

To a stirred solution of compound **9$_a$** (0.01 mol, 3.4 g) in dioxane (15 mL), cyclopentanone (0.01 mol, 0.86 mL) and a catalytic amount of triethylamine were added. The reaction mixture was refluxed for 4 h and worked up as before (cf. Scheme 2, Table 1).

Synthesis of Compound 17

To a cold mixture of compound **1** (0.01 mol, 2.36 g) and HC1 (4N, 40 mL), a solution of p-tolyldiazonium chloride (a mixture of 0.01 mol, 1.07 g of

p-toluidine in 10 mL HCl and 0.7 g of $NaNO_2$ in 5 mL of H_2O) was added dropwise with stirring over 15 min. The stirring continued for 30 min, and the reaction mixture was allowed to stand for 2 h at room temperature. The precipitated solid was collected by filtration, washed with water, and crystallized (cf. Scheme 3, Table 1).

Synthesis of Compounds 18–20

To a solution of compound **17** (0.002 mol, 0.71 g) in dioxane (20 mL), the appropriate active methylene (0.002 mol) [namely malononitrile (0.13 g), cyanoacetamide (0.17 g), cyanothioacetamide (0.2 g), cyanoacetohydrazide (0.19 g), or cycloheptanone (0.17 mL)] and two drops of triethylamine were added. The reaction mixture was refluxed for 3 h and cooled to room temperature. The precipitated solid was collected by filtration and crystallized from the proper solvent (cf. Scheme 3, Table 1).

Synthesis of Compound 21

A mixture of malononitrile (0.04 mol, 2.64 g), CS_2 (0.045 mol, 2.7 mL), anhydrous potassium carbonate (3 g), a catalytic amount of TBAB, and dioxane (20 mL) was stirred for 40 min at 60°C. Compound **17** (0.02 mol, 0.71 g) was added to the dianionic ambident. The reaction mixture was stirred for 6 h at 40°C and filtered. The solvent was evaporated in vacuo. The residual solid was washed with water, collected by filtration, and crystallized (cf. Scheme 3, Table 1).

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