Chemistry of Heterocyclic Compounds, Vol. 42, No. 7, 2006

SYNTHESIS OF NOVEL SUBSTITUTED DIARYL-1,4-DIAZEPINES

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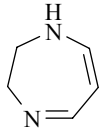
In this paper a convenient route to new 2,3-diaryl-substituted 1,4-diazepines is described through cyclization of ethanedione derivatives and 1,3-propanediamine. The ethanedione derivatives required were synthesized by microwave-assisted oxidation from ethanones.

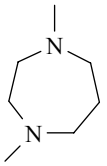
Keywords: diaryl diazepines, ethanedione, ethanone.

Seven-membered heterocycles with two heteroatoms in the 1,4-position are well known because of their unique pharmacological activity towards the central nervous system as observed in the case of 1,4-benzodiazepines [1]. These properties strongly depend on the nature of the heterocyclic core, particularly on the relative positions of the two nitrogen atoms and the type of ring fused to the seven-membered ring. In recent years a variety of 1,4-diazepines was reported for inhibition of platelet aggregation [2], peptidoglycan synthesis inhibition [3], 5-HT antagonists [4,5], H_3 receptor antagonists [6], as peptidomimetic scaffolds [7], biological tools [8], protein kinase inhibitors [9], matrix metalloproteinase inhibitors [10] (MMPs), and anti-HIV agents [11]. The DNA strand breaking activity was reported [12] for diaryl diazepine. Up to this time there was only one study regarding the synthesis of 2,3-diaryl-6,7-dihydro-5H-1,4-diazepine [12] by reacting cheaply available benzil and 1,3-diaminopropane.

Although reports on fused 1,4-diazepines exist, simple monocyclic 1,4-diazepines have been less reported with the exception of 2,3-dihydro-1H-1,4-diazepine **I** [13] and the homopiperazine system **II** [14]. Looking to these aspects it was planned to synthesize some substituted diaryl diazepines **III** which are unexplored as yet.



I



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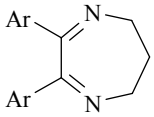

III

Previously, in our laboratory, synthesis of diaryl systems with a five- and six-membered heterocyclic core was carried out to obtain selective COX II inhibitors for anti-inflammatory action. In this paper our efforts towards the synthesis of 2,3-substituted diaryl-6,7-dihydro-5H-1,4-diazepines **III** from ethane-1,2-dione derivatives are presented.

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0009-3122/06/4207-0901

Expensive phenylacetic acid derivatives were synthesized by the Wilgerodt method and hydrolysis of benzyl cyanide derivatives. Friedel–Crafts reaction of substituted phenylacetic acid with substituted aromatic compounds gave ethanone derivatives in good yield. The IR spectrum showed an intense peak at 1685-1690 cm^{-1} due to carbonyl stretching. Unlike conventional methods, microwave-assisted selenium dioxide oxidation of ethanone derivatives using DMSO as a solvent simplifies the workup procedure and reduction of the reaction time. Some ethanedione derivatives obtained as either oily or sticky compounds were used in the next step without purification. The α-dicarbonyl (ethanedione) compounds exhibited in the IR spectrum a peak at 1650-1670 cm^{-1}.

The ethanedione derivatives **2a-q** and 1,3-propanediamine in equimolar amounts in the presence of glacial acetic acid in ethanol under reflux conditions afforded the cyclized product. It is clearly stated in the literature [15] that the synthesis of these analogs is difficult and occasionally unsuccessful. The yield of the cyclized compound is low to moderate due to the formation of the undesired uncyclized product and a partial recovery of the starting material.

The IR spectrum of the uncyclized product obtained shows an intense peak at 1670 cm^{-1}, which may be due to multiple condensation of ethanedione with 1,3-propanediamine even when equimolar quantities of ethanedione and 1,3-propanediamine are reacted [12].

The formation of cyclized products is confirmed by the appearance of C=N stretching in the IR spectrum at 1590-1610 cm^{-1} and the absence of carbonyl stretching. The ^1H NMR spectra show a broad hump for the methylene protons around δ 3.5 ppm, adjacent to the imine (4H, =N–C<u>H</u>$_2$–CH$_2$). This may be due to temperature coalescence or ring flip. The methylene protons adjacent to the imine of compounds **3n** and **3o** appear clearly as a multiplet (triplet). This clearly indicates that the hump is due to the ring flip [16]. The presence of the 2-chloro substituent does not allow the ring flip. This was confirmed by the NMR spectra of the cyclized compound **3q** formed from the change in the position of the substituent in phenylacetic acid, i.e., 3-chlorophenylacetic acid. A broad hump was observed in the NMR spectra for the methylene protons adjacent to the imine of the compound **3q.** Other methylene protons (2H, =N–CH$_2$–C<u>H</u>$_2$) appear as a multiplet at δ 2.32-2.39 ppm. The mass spectrum shows the [M+1] peak for all compounds. An [M+2] peak is observed for all halo compounds in the mass spectrum. The synthesis is depicted in the scheme below:

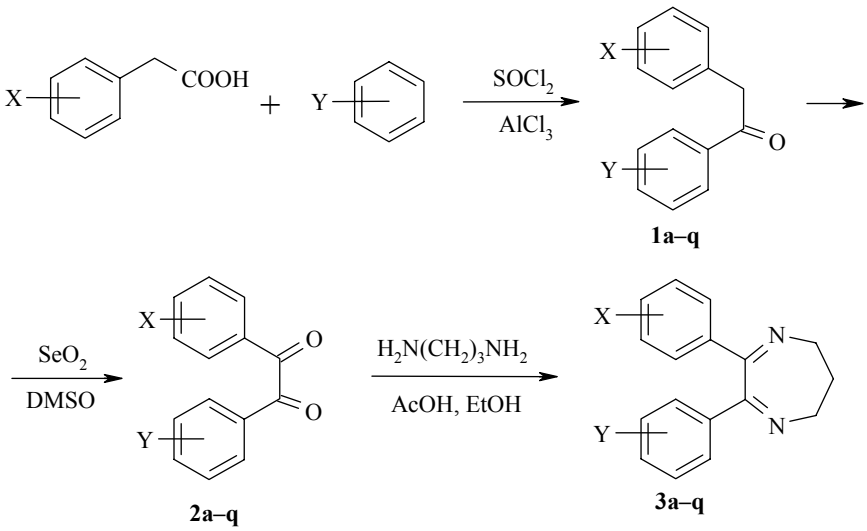

TABLE 1. Characteristics of Compounds **1a-q** and **2a-q**

Entry	X	Y	Compound **1**		Compound **2**		
			Mp, °C	Yield, %	Reaction time, s	Mp, °C	Yield,%
a	H	Me	109-111	58	30	Oil	77
b	H	4-Br	106-108	59	95	85-87	57
c	H	4-F	71-73	62	80	66-68	75
d	H	4-OMe	75-77	45	35	Sticky comp.	85
e	H	4-SMe	101-103	60	35	61-63	81
f	4-Cl	4-Me	116-118	77	50	126-128	81
g	4-Cl	4-Cl	115-117	59	100	196-198	51
h	4-Cl	4-F	124-126	79	80	144-146	73
i	4-Cl	4-SMe	160-162	29	115	134-136	74
j	4-Cl	H	137-139	72	55	79-81	90
k	4-Cl	4-Br	130-132	60	155	206-208	68
l	4-NO_2	H	135-137	42	20	142-144	76
m	4-NO_2	4-Me	114-116	80	35	185-186	74
n	2-Cl	4-Cl	93-95	77	40	103-105	51
o	2-Cl	4-SMe	89-92	28	40	101-103	52
p	4-Me	4-Me	106-109	54	40	101-103	94
q	3-Cl	4-Me	84-85	66	55	Sticky comp.	63

EXPERIMENTAL

Melting points were determined in capillaries using a Toshniwal melting point apparatus and are uncorrected. IR (in cm^{-1}) spectra were obtained on a Shimadzu 8300 instrument in KBr pellets. ^1H NMR spectra were recorded in $CDCl_3$ on a Bruker spectrometer (300 or 400 MHz), using TMS as an internal standard. Elemental analyses were recorded on a Perkin–Elmer PE 2400 CHNS analyzer. Mass spectra were recorded on APISciEX mass spectrometer equipped with an electrospray ionization (ESI) interface. Column chromatography was carried out using silica gel (100-200 mesh). Thin-layer chromatography (TLC) was performed on pre-coated silica gel Merck plates. Compounds were visualized by illuminating with UV light (254 nm) or exposure to iodine vapor. Solvents were purified using standard methods.

Synthesis of Ethanone Derivatives 1a-q (General Procedure). The substituted phenylacetic acid (1 mol) was dissolved in an excess quantity of thionyl chloride (2 mol) and allowed to reflux on a steam bath for 3 h. The excess of thionyl chloride was removed under vacuum. The resulting acid chloride solution was cooled and added dropwise to the cooled mixture of $AlCl_3$ (1.5 mol) and substituted aromatic compound. The reaction mixture was stirred for 45 min at room temperature. The reaction mixture was quenched with cold HCl, extracted with chloroform (3 × 20 ml). The combined organic extracts were washed with sodium bicarbonate solution, and water, and dried over anhydrous sodium sulfate. Recrystallization from methanol after solvent removal gave the ethanone derivatives. The results are summarized in Table 1.

Synthesis of Ethanedione Derivatives 2a-q (General Procedure). Selenium dioxide (0.15 mol) was added to the solution of ethanone derivative (0.1 mol) in DMSO (15 ml) and irradiated in the microwave oven for the specified time as given in Table 1. The hot mixture was filtered to remove the selenium metal and the filtrate was poured over crushed ice. The resulting precipitate was filtered, dried, and recrystallized from methanol to obtain the ethanedione derivative. The results are summarized in Table 1.

Synthesis of Diaryl Diazepines 3a-q (General Procedure). An equimolar mixture of the ethanedione derivative, 1,3-propanediamine, and glacial acetic acid (1:1:1) was dissolved in ethanol (30 ml). The mixture was allowed to reflux for 24-30 h. The reaction was monitored throughout by TLC, and the solvent was evaporated under vacuum after completion. The resulting sticky compound was stripped with silica gel, and chromatography with benzene gave a liquid product, with partial recovery of starting material, which on trituration with petroleum ether gave a solid product. This was recrystallized from a suitable solvent to afford the desired compounds **3a-q**.

3-(4-Methylphenyl)-2-phenyl-6,7-dihydro-5H-1,4-diazepine (3a). Yield 23%; mp 82-84°C (brown crystals from MeOH). IR, ν_{max}, cm^{-1}: 1608, 1592 (C=N), 1510, 1332, 1272, 825, 780. ^{1}H NMR, δ, ppm (400 MHz): 2.32 (3H, s, CH_3); 2.34-2.41 (2H, m, $NCH_2C\underline{H}_2$); 3.5 (4H, br. s, $NC\underline{H}_2CH_2$); 7.1-7.6 (9H, m, ArH). Mass-spectrum, *m/z*: 263 [MH^+]. Found, %: C 82.28; H 7.02; N 10.84. $C_{18}H_{18}N_2$. Calculated, %: C 82.41; H 6.92; N 10.68.

3-(4-Bromophenyl)-2-phenyl-6,7-dihydro-5H-1,4-diazepine (3b). Yield 6%; mp 93-95°C (white crystals from petr. ether). IR, ν_{max}, cm^{-1}: 1598 (C=N), 1585, 1392, 1272, 1068, 945, 825. ^{1}H NMR, δ, ppm (300 MHz): 2.33-2.41 (2H, m, $NCH_2C\underline{H}_2$); 3.5 (4H, br. s, $NC\underline{H}_2CH_2$); 7.1-7.6 (9H, m, ArH). Mass-spectrum, *m/z*: 329 [M+2]. Found, %: C 62.56; H 4.60; N 8.24. $C_{17}H_{15}BrN_2$. Calculated, %: C 62.4; H 4.62; N 8.56.

3-(4-Fluorophenyl)-2-phenyl-6,7-dihydro-5H-1,4-diazepine (3c). Yield 13%; mp 77-78°C (white crystals from petr. ether). IR, ν_{max}, cm^{-1}: 1598 (C=N), 1587, 1506, 1288, 1159, 1080, 943, 850, 783. ^{1}H NMR, δ, ppm (300 MHz): 2.31-2.40 (2H, m, $NCH_2C\underline{H}_2$); 3.5 (4H, br. s, $NC\underline{H}_2CH_2$); 6.9-7.6 (9H, m, ArH). Found, %: C 76.74; H 5.72; N 10.56. $C_{17}H_{15}FN_2$. Calculated, %: C 76.67; H 5.68; N 10.52.

3-(4-Methoxyphenyl)-2-phenyl-6,7-dihydro-5H-1,4-diazepine (3d). Yield 13%; mp 106-108°C (white crystals from MeOH–petr. ether). IR, ν_{max}, cm^{-1}: 1600 (C=N), 1570, 1508, 1247, 1174, 1029, 945, 813, 786. ^{1}H NMR, δ, ppm (400 MHz): 3.77 (3H, s, OCH_3); 2.31-2.38 (2H, m, $NCH_2C\underline{H}_2$); 3.2 (4H, br. s, $NC\underline{H}_2CH_2$); 6.8-7.3 (9H, m, ArH). Found, %: C 77.84; H 6.38; N 10.0. $C_{18}H_{18}N_2O$. Calculated, %: C 77.67; H 6.52; N 10.06.

3-(4-Methylsulfanylphenyl)-2-phenyl-6,7-dihydro-5H-1,4-diazepine (3e). Yield 29%; mp 115-117°C (brownish-white crystals from petr. ether). IR, ν_{max}, cm^{-1}: 1600, 1593 (C=N), 1550, 1247, 1180, 1097, 960, 823, 785. ^{1}H NMR, δ, ppm (400 MHz): 2.4 (3H, s, SCH_3); 2.34-2.37 (2H, m, $NCH_2C\underline{H}_2$); 3.5 (4H, br. s, $NC\underline{H}_2CH_2$); 7.1-7.5 (9H, m, ArH). Found, %: C 73.14; H 6.08; N 9.42. $C_{18}H_{18}N_2S$. Calculated, %: C 73.43; H 6.16; N 9.51.

2-(4-Chlorophenyl)-3-(4'-methylphenyl)-6,7-dihydro-5H-1,4-diazepine (3f). Yield 34%; mp 102-104°C (white crystals from MeOH). IR, ν_{max}, cm^{-1}: 1610 (C=N), 1600, 1593, 1400, 840, 821, 761. ^{1}H NMR, δ, ppm (300 MHz): 2.3 (3H, s, CH_3); 2.32-2.39 (2H, m, $NCH_2C\underline{H}_2$); 3.4 (4H, br. s, $NC\underline{H}_2CH_2$); 7.1-7.5 (8H, m, ArH). Found, %: C 72.83; H 5.62; N 9.49. $C_{18}H_{17}ClN_2$. Calculated, %: C 72.84; H 5.77; N 9.44.

2,3-Di-(4,4'-dichlorophenyl)-6,7-dihydro-5H-1,4-diazepine (3g). Yield 17%; mp 111-113°C (white crystals from MeOH). IR, ν_{max},cm^{-1}: 1614 (C=N), 1591, 1467, 1398, 1080, 840, 769. ^{1}H NMR, δ, ppm (300 MHz): 2.31-2.40 (2H, m, $NCH_2C\underline{H}_2$); 3.5 (4H, br. s, $NC\underline{H}_2CH_2$); 7.2-7.5 (8H, m, ArH). Found, %: C 64.24; H 4.35; N 8.98. $C_{17}H_{14}Cl_2N_2$. Calculated, %: C 64.37; H 4.45; N 8.83.

2-(4-Chlorophenyl)-3-(4'-fluorophenyl)-6,7-dihydro-5H-1,4-diazepine (3h). Yield 41%; mp 104-106°C (white crystals from MeOH). IR, ν_{max}, cm^{-1}: 1614 (C=N), 1587, 1272, 1090, 945, 850, 763. ^{1}H NMR, δ, ppm (400 MHz): 2.32-2.39 (2H, m, $NCH_2C\underline{H}_2$); 3.5 (4H, br. s, $NC\underline{H}_2CH_2$); 6.98-7.31 (8H, m, ArH). Found, %: C 68.12; H 4.66; N 9.54. $C_{17}H_{14}ClFN_2$. Calculated, %: C 67.89; H 4.69; N 9.31.

2-(4-Chlorophenyl)-3-(4'-methylsulfanylphenyl)-6,7-dihydro-5H-1,4-diazepine (3i). Yield 13%; mp 120-122°C (white crystals from petr. ether). IR, ν_{max}, cm^{-1}: 1610 (C=N), 1589, 1396, 1274, 1095, 941, 835, 815. ^{1}H NMR, δ, ppm (400 MHz): 2.45 (3H, s, SCH_3); 2.28-2.43 (2H, m, $NCH_2C\underline{H}_2$); 3.51 (4H, br. s, $NC\underline{H}_2CH_2$); 7.1-7.7 (8H, m, ArH). Found, %: C 65.91; H 5.15; N 8.82. $C_{18}H_{17}ClN_2S$. Calculated, %: C 65.74; H 5.21; N 8.52.

2-(4-Chlorophenyl)-3-phenyl-6,7-dihydro-5H-1,4-diazepine (3j). Yield 38%; mp 72-74°C (white crystals from MeOH). IR, ν_{max}, cm^{-1}: 1611, 1592 (C=N), 1456, 1338, 1272, 1092, 1013, 944, 835, 786. ^{1}H NMR, δ, ppm (300 MHz): 2.32-2.41 (2H, m, $NCH_2C\underline{H}_2$); 3.5 (4H, br. s, $NC\underline{H}_2CH_2$); 7.2-7.6 (9H, m, ArH).

Mass-spectrum, *m/z*: 283 [MH^+]. Found, %: C 72.04; H 5.62; N 9.72. $C_{17}H_{15}ClN_2$. Calculated, %: C 72.21; H 5.35; N 9.91.

3-(4'-Bromophenyl)-2-(4-chlorophenyl)-6,7-dihydro-5H-1,4-diazepine (3k). Yield 16%; mp 140-142°C (pale yellow flakes from MeOH). IR, ν_{max}, cm^{-1}: 1612 (C=N), 1585, 1490, 1310, 1174, 1068, 943, 827, 769. ^1H NMR, δ, ppm (300 MHz): 2.3-2.4 (2H, m, $NCH_2C\underline{H}_2$); 3.5 (4H, br. s, $NC\underline{H}_2CH_2$); 7.2-7.5 (8H, m, ArH). Found, %: C 56.50; H 3.83; N 7.81. $C_{17}H_{14}BrClN_2$. Calculated, %: C 56.46; H 3.90; N 7.75.

2-(4-Nitrophenyl)-3-phenyl-6,7-dihydro-5H-1,4-diazepine (3l). Yield 11%; mp 99-101°C (brown crystals from MeOH). IR, ν_{max}, cm^{-1}: 1608, 1600 (C=N), 1574, 1520, 1347, 854, 794. ^1H NMR, δ, ppm (300 MHz): 2.3-2.4 (2H, m, $NCH_2C\underline{H}_2$); 3.5 (4H, br. s, $NC\underline{H}_2CH_2$); 7.2-7.5 (9H, m, ArH). Mass-spectrum, *m/z*: 293 [M^+]. Found, %: C 69.94; H 5.03; N 14.10. $C_{17}H_{15}N_3O_2$. Calculated, %: C 69.61; H 5.15; N 14.33.

3-(4'-Methylphenyl)-2-(4-nitrophenyl)-6,7-dihydro-5H-1,4-diazepine (3m). Yield 17%; mp 161-163°C (yellow crystals from MeOH). IR, ν_{max}: 1595 (C=N), 1514, 1344, 1259, 1160, 1090, 973, 850 cm^{-1}. ^1H NMR, δ, ppm (300 MHz): 2.33 (3H, s, CH_3); 2.34-2.40 (2H, m, $NCH_2C\underline{H}_2$); 3.58 (4H, br. s, $NC\underline{H}_2CH_2$); 7.1-8.1 (8H, m, ArH). Found, %: C 70.2; H 5.72; N 13.88. $C_{18}H_{17}N_3O_2$. Calculated, %: C 70.34; H 5.58; N 13.67.

2-(2-Chlorophenyl)-3-(4'-chlorophenyl)-6,7-dihydro-5H-1,4-diazepine (3n). Yield 8%; mp 115-116°C (white crystals from MeOH). IR, ν_{max}, cm^{-1}: 1608 (C=N), 1589, 1562, 1490, 1320, 1100, 1060, 945, 850, 775. ^1H NMR, δ, ppm (300 MHz): 2.43-2.52 (2H, m, $NCH_2C\underline{H}_2$); 3.58-3.62 (2H, t, J = 12, $NC\underline{H}_2CH_2$); 3.70-3.74 (2H, t, J = 12, $NC\underline{H}_2CH_2$); 7.2-8.6 (8H, m, ArH). Found, %: C 64.55; H 4.32; N 9.12. $C_{17}H_{14}Cl_2N_2$. Calculated, %: C 64.37; H 4.45; N 8.83.

2-(2-Chlorophenyl)-3-(4'-methylsulfanylphenyl)-6,7-dihydro-5H-1,4-diazepine (3o). Yield 11%; mp 119-121°C (white crystals from MeOH–petr. ether). IR, ν_{max}, cm^{-1}: 1610 (C=N), 1589, 1565, 1490, 1309, 1274, 1184, 1097, 943, 856, 750. ^1H NMR, δ, ppm (400 MHz): 2.43 (3H, s, SCH_3); 2.46-2.49 (2H, m, $NCH_2C\underline{H}_2$); 3.60-3.63 (2H, t, J = 12, $NC\underline{H}_2CH_2$); 3.70-3.73 (2H, t, J = 12, $NC\underline{H}_2CH_2$); 7.1-7.3 (8H, m, ArH). Found, %: C 65.94; H 5.16; N 8.48. $C_{18}H_{17}ClN_2S$. Calculated, %: C 65.74; H 5.21; N 8.52.

2,3-Di-(4,4'-dimethylphenyl)-6,7-dihydro-5H-1,4-diazepine (3p). Yield 16%; mp 94-95°C (white crystals from petr. ether). IR, ν_{max}, cm^{-1}: 1608 (C=N), 1593, 1566, 1319, 1278, 1176, 1083, 945, 852, 800. ^1H NMR, δ, ppm (400 MHz): 2.32 (6H, s, $(CH_3)_2$); 2.34-2.37 (2H, m, $NCH_2C\underline{H}_2$); 3.5 (4H, br. s, $NC\underline{H}_2CH_2$); 7.11-7.52 (8H, m, ArH). Found, %: C 82.72; H 7.12; N 10.32. $C_{19}H_{20}N_2$. Calculated, %: C 82.57; H 7.29; N 10.14.

2-(3-Chlorophenyl)-3-(4'-methylphenyl)-6,7-dihydro-5H-1,4-diazepine (3q). Yield 38%; mp 119-121°C (white crystals from petr. ether). IR, ν_{max}, cm^{-1}: 1608 (C=N), 1595, 1564, 1471, 1255, 1091, 943, 829, 802, 761. ^1H NMR, δ, ppm (400 MHz): 2.33 (3H, s, CH_3); 2.35-2.40 (2H, m, $NCH_2C\underline{H}_2$); 3.53 (4H, br. s, $NC\underline{H}_2CH_2$); 7.1-7.7 (8H, m, ArH). Found, %: C 72.62; H 5.72; N 9.52. $C_{18}H_{17}ClN_2$. Calculated, %: C 72.84; H 5.77; N 9.44.

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