Cyclocondensation Reaction of 1,2-Diamino-4-methylbenzene and *p*-Substituted Acetophenones

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1,2-Diamino-4-methylbenzene **1** reacts in the presence of sulphuric acid with 4-substituted acetophenones **2a-e** yielding 2,4-diaryl-2,3-dihydro-2,8-dimethyl-1*H*-1,5-benzodiazepines **3a-e** and as minor component 2,4-diaryl-2,3-dihydro-2,7-dimethyl-1*H*-1,5-benzodiazepines **4a-e**. The ratio **3**:**4** is in the range of 7:3. The structure determination of the regioisomers was performed by NOE measurements.

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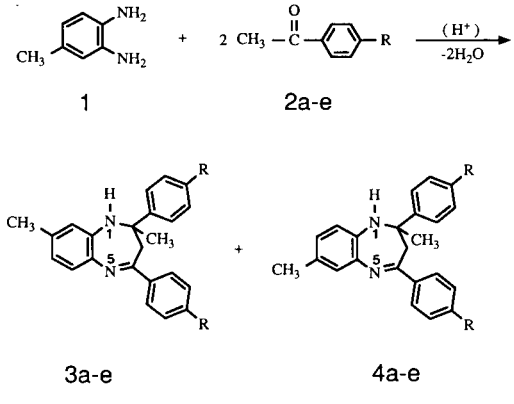
The reaction between 1,2-diamines and ketones with reactive methylene or methyl groups in the α-position is a very convenient and versatile method for the preparation of dihydrodiazepine systems [1-5]. Thus, derivatives of 1*H*-1,5-benzodiazepine can be obtained which possess interesting biological and pharmacological properties [5].

Unsymmetrically substituted 1,2-diaminobenzenes should lead to a regiospecific cyclocondensation reaction. We started this investigation with the weakly directing methyl group in 1,2-diamino-4-methylbenzene **1**. Refluxing **1** and the acetophenones **2a-e** in methanol in the presence of catalytic amounts of sulphuric acid yields the 2,4-diaryl-2,3-dihydro-2,8-dimethyl-1*H*-1,5-benzodiazepines **3** and the isomeric 2,4-diaryl-2,3-dihydro-2,7-dimethyl-1*H*-1,5-benzodiazepines **4**.

The structure of the obtained compounds **3** and **4** was determined by spectroscopic methods. Characteristic ir absorptions (measured in potassium bromide pellets) can be observed in the regions 3270-3380 cm^{-1} and 1580-1620 cm^{-1}, indicating N-H stretching vibrations and coupled

Scheme 1



	R	Total Yield [%]	Ratio 3 : 4
a	H	40	78 : 22
b	CH_3	31	68 : 32
c	Cl	68	62 : 38
d	Br	59	72 : 28
e	NO_2	89	77 : 23

Table 1

^{1}H NMR Data of 3a-e and 4a-e (δ Values in Deuteriochloroform, TMS as the Internal Standard, 400 MHz)

Compound	NH s	3-CH_2 AB	6-H d	7-H dd	8-H dd	9-H d	2-CH_3 s	7-CH_3 s	8-CH_3 s	Aryl-H m
3a	3.49	2.96/3.14	~7.2	6.83	—	6.64	1.75	—	2.32	7.15-7.61
4a	3.38	2.94/3.10	~7.2	—	6.88	6.74	1.74	2.32	—	7.15-7.61
3b	3.47	2.94/3.07	7.22	6.82	—	6.61	1.70	—	2.31	7.05/7.08/7.47/7.53
4b	3.41	2.88/3.01	7.12	—	6.86	6.72	1.69	2.29	—	~7.07, ~7.5
3c	3.40	2.87/3.07	~7.2	6.84	—	6.62	1.71	—	2.32	7.18/7.44/7.49
4c	3.27	2.84/3.01	7.11	—	6.89	6.73	1.70	2.33	—	~7.18/7.46/7.52
3d	3.40	2.86/3.06	7.18	6.84	—	6.62	1.70	—	2.31	7.33/7.35/7.42
4d	3.28	2.84/3.00	7.10	—	6.89	6.72	1.69	2.32	—	~7.35/7.46
3e	3.64	2.98/3.31	7.22	6.87	—	6.68	1.81	—	2.34	7.65/7.69/8.02/8.03
4e	3.46	2.95/3.22	7.14	—	6.96	6.79	1.80	2.33	—	7.66/7.76/~8.04

Table 2

^{13}C NMR Data of **3a-e** and **4a-e** (δ Values in Deuteriochloroform, TMS as Internal Standard, 100 MHz)

Compound	C-2	C-3	C-4	CH (arom) [a]	C_q (arom) [a]	2-CH_3	7/8-CH_3
3a	72.8	43.3	166.6	121.5/122.3/125.5/127.0/127.0/ 128.0/128.3/129.0/129.5	136.3/137.3/138.0/ 139.9/147.7	29.9	21.0
4a	73.7	42.9	167.7	121.5/122.3/125.5/127.1/128.0/ 128.3/128.7/129.0/129.7	131.3/135.5/139.6/ 140.4/147.7	29.7	20.5
3b	72.4	43.1	166.5	121.5/122.3/125.2/127.1/ 128.8/128.9/131.3	136.0/136.6/137.3/137.5/ 138.1/139.7/145.2	29.9	20.7/21.0/ 21.3 (CH_3)
4b	73.4	42.8	167.6	121.5/122.6/125.2/127.2/ 128.8/128.9/131.2	131.9/136.7/137.0/138.5/ 139.9/140.6/146.5	29.8	20.6/20.7 21.3 (CH_3)
3c	72.5	43.1	164.9	121.5/122.6/127.0/128.2/ 128.3/128.3/128.9	133.0/135.8/136.4/137.0/ 137.5/138.0/145.9	29.9	21.0
4c	73.5	42.8	166.1	121.5/122.6/127.3/128.2/ 128.3/128.3/128.7	131.6/135.0/136.0/136.6/ 137.8/140.2/146.0	29.5	20.5
3d	72.6	43.1	164.9	121.5/122.7/127.4/128.4/ 129.0/131.2/131.3	121.1/124.3/136.7/137.0/ 137.5/138.5/146.4	29.9	21.0
4d	73.6	42.8	166.2	121.5/122.7/127.3/128.5/ 128.7/131.2/131.3	121.1/124.5/131.7/135.0/ 138.2/140.1/146.5	29.5	20.5
3e	72.2	43.2	162.5	121.2/122.9/123.4/123.5/ 126.7/127.4/130.1	135.9/137.2/138.1/145.0/ 147.0/148.3/154.1	30.4	21.1
4e	73.6	42.9	164.0	121.4/123.3/123.5/126.7/ 127.5/128.5/129.5	132.0/134.6/139.4/144.6/ 147.0/148.4/154.2	29.9	20.5

[a] Some signals of the minor component **4** are overlapping with signals of the major component **3**.

stretching vibrations of the C=N and C···C bonds in the bicyclic ring skeleton. The ^1H and ^{13}C nmr data are summarized in Tables 1 and 2. The methylene groups in **3** and **4** cause proton signals due to AB spin patterns with $^2J \approx -13$ Hz. The benzene ring protons obey the sequence δ (9-H) < δ (7-H) < δ (6-H) in **3** and δ (9-H) < δ (8-H) < δ (6-H) in **4**. The proton 9-H shows for the compounds **3** a stronger high-field shift than for the isomers **4**. This effect is due to the neighborhood of the methyl group and can be taken as a hint for the structure correlation. Whereas 9-H gives rise to a doublet with $^4J \approx 1.5$ Hz for **3**, it leads to a doublet with $^3J \approx 7.5$ Hz for **4**. Doublets of doublets with $^3J \approx 7.5$ Hz and $^4J \approx 1.5$ Hz are observed for 7-H in **3** and 8-H in **4**. However, an exact structure determination for **3** and **4** was only possible on the basis of NOE measurements. The difference spectra reveal the neighborhood of 9-H and NH and simultaneously the neighborhood of NH and 2-CH_3. The isomer **3** is the major product in all investigated examples **a-e**. The ratios **3**:**4** in Scheme 1 were calculated by the integration of the proton signals.

EXPERIMENTAL

Melting points were determined on a Büchi melting point apparatus. The PFT-^1H and ^{13}C nmr spectra were recorded in deuteriochloroform on a Bruker AM 400 spectrometer. The mass spectra were obtained on a Finnigan M 95 instrument operating at 70 eV.

Synthesis of 2,3-Dihydro-2,8-dimethyl-2,4-diphenyl-1*H*-1,5-benzodiazepine **3a** and 2,3-Dihydro-2,7-dimethyl-2,4-diphenyl-1*H*-1,5-benzodiazepine **4a**.

A solution of 0.5 g (4.1 mmoles) of 1,2-diamino-4-methylbenzene **1** and 0.98 g (8.2 mmoles) of acetophenone **2a** in 20 ml of methanol and 40 mg of concentrated sulphuric acid is refluxed for 18 hours. The yellow precipitate formed by cooling is filtered off and recrystallized from methanol, 0.53 g (40%) of **3a**/**4a** can be isolated, mp 110-112°; ms: m/z (%) 326 (19, $M^{+\cdot}$), 311 (15, $M^{+\cdot}$ -CH_3), 249 (11, $M^{+\cdot}$ -C_6H_5), 209 (39), 208 (100, $M^{+\cdot}$ -C_8H_8N), 207 (20), 103 (17), 77 (13).

Anal. Calcd. for $C_{23}H_{22}N_2$: C, 84.63; H, 6.79; N, 8.58. Found: C, 84.50; H, 6.80; N, 8.44.

The compounds **3b-e**/**4b-e** can be prepared analogously.

2,3-Dihydro-2,8-dimethyl-2,4-bis(4-methylphenyl)-1*H*-1,5-benzodiazepine **3b** and 2,3-Dihydro-2,7-dimethyl-2,4-bis(4-methylphenyl)-1*H*-1,5-benzodiazepine **4b**.

The yield was 31%, yellow crystals of mp 104-106°, ms: m/z (%) 354 (16, $M^{+\cdot}$), 339 (12, $M^{+\cdot}$ -CH_3), 263 (7, $M^{+\cdot}$ -C_7H_7), 223 (36), 222 (100, $M^{+\cdot}$ -$C_9H_{10}N$), 221 (14), 117 (12), 91 (6).

Anal. Calcd. for $C_{25}H_{26}N_2$: C, 84.70; H, 7.39; N, 7.90. Found: C, 84.37; H, 7.01; N, 7.93.

2,4-Bis(4-chlorophenyl)-2,3-dihydro-2,8-dimethyl-1*H*-1,5-benzodiazepine **3c** and 2,4-Bis(4-chlorophenyl)-2,3-dihydro-2,7-dimethyl-1*H*-1,5-benzodiazepine **4c**.

The yield was 68%, yellow crystals of mp 123-124°; ms: m/z (%) 398/396/394 (12, $M^{+\cdot}$, Cl_2 pattern), 383/381/379 (10, $M^{+\cdot}$ -CH_3, Cl_2 pattern), 285/283 (7, $M^{+\cdot}$ -C_6H_4Cl, Cl pattern), 245 (11), 244 (37), 243 (38), 242 (100, $M^{+\cdot}$ -C_8H_7ClN), 241 (16), 137 (13).

Anal. Calcd. for $C_{23}H_{20}Cl_2N_2$: C, 69.87; H, 5.09; N, 7.08. Found: C, 70.07; H, 5.29; N, 6.95.

2,4-Bis(4-bromophenyl)-2,3-dihydro-2,8-dimethyl-1*H*-1,5-benzodiazepine **3d** and 2,4-Bis(4-bromophenyl)-2,3-dihydro-2,7-dimethyl-1*H*-1,5-benzodiazepine **4d**.

The yield was 59%, yellow crystals of mp 152-153°; ms: m/z

(%) 486/484/482 (16, $M^{+\cdot}$, Br_2 pattern), 471/469/467 (11, $M^{+\cdot}$ $-CH_3$), 329/327 (9, $M^{+\cdot}$ $-C_6H_4Br$, Br pattern), 289 (29), 288 (98), 287 (42), 286 (100, $M^{+\cdot}$ $-C_8H_7BrN$), 207 (10), 183 (9), 181 (9), 147 (9), 102 (20).

Anal. Calcd. for $C_{23}H_{20}Br_2N_2$: C, 57.04; H, 4.16; N, 5.78. Found: C, 56.90; H, 4.26; N, 5.88.

2,3-Dihydro-2,8-dimethyl-2,4-bis(4-nitrophenyl)-1*H*-1,5-benzodiazepine **3e** and 2,3-Dihydro-2,7-dimethyl-2,4-bis(4-nitrophenyl)-1*H*-1,5-benzodiazepine **4e**.

The yield was 89%, red crystals of mp 150-152°; ms: m/z (%) 416 (19, $M^{+\cdot}$), 401 (16, $M^{+\cdot}$ $-CH_3$), 294 (14, $M^{+\cdot}$ $-C_6H_4NO_2$), 254 (23), 253 (100, $M^{+\cdot}$ $-C_8H_7N_2O_2$), 208 (12), 207 (20).

Anal. Calcd. for $C_{23}H_{20}N_4O_4$: C, 66.34; H, 4.84; N, 13.45. Found: C, 65.99; H, 4.80; N, 13.55.

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