HETEROCYCLES, Vol. 76, No. 2, 2008, pp. 1007 - 1010. © The Japan Institute of Heterocyclic Chemistry
Received, 26th March, 2008, Accepted, 13th May, 2008, Published online, 19th May, 2008. COM-08-S(N)63

FACILE AND EFFICIENT SYNTHESIS OF 1,4-BENZODIAZEPINES FROM 1,4-NAPHTHOQUINONES

Vishnu K. Tandon* and Hardesh K. Maurya

Department of Chemistry, University of Lucknow, Lucknow – 226 007, India

E. mail: *vishnutandon@yahoo.co.in*

Dedicated to Professor Dr. Ryoji Noyori on occasion of his 70th birthday.

Abstract — Concise intramolecular cyclization reaction of 2,3-diamino-1,4-dihydro-naphthalenediones **4** and **7** in anhydrous K_2CO_3 /Et_3N and EtOH yielded novel 1,4-benzodiazepines **5** and **6** fused with 1,4-naphthoquinone nucleus.

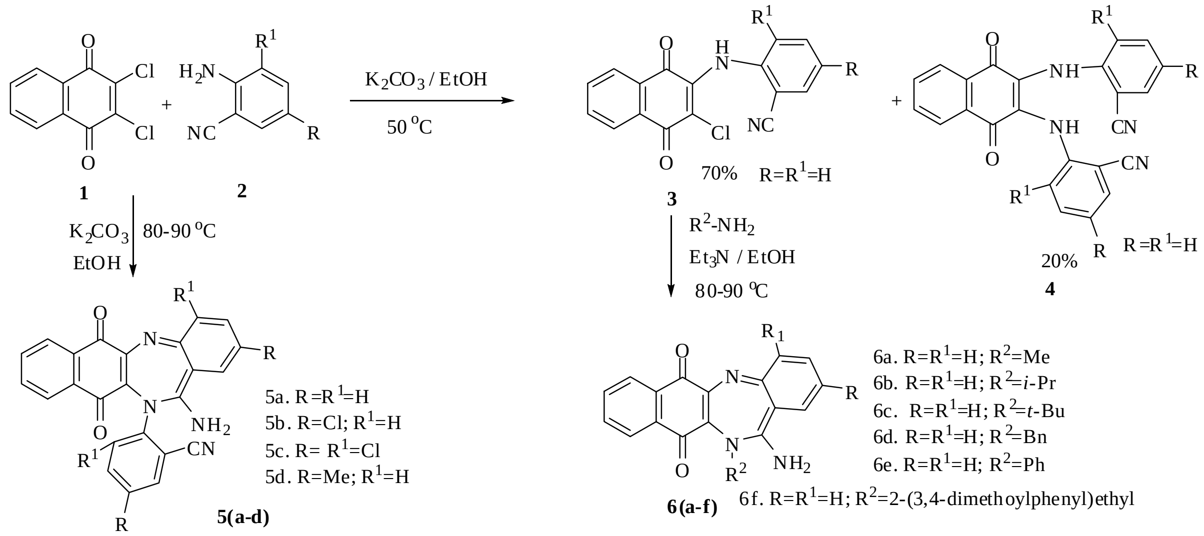
The quinone group forms the basis of biological and pharmacological activity of a number of clinical and experimental drugs that are associated with anticancer, antiviral, antifungal and antibacterial studies.[1-5] The synthesis of quinones condensed with seven-membered heterocycles are rarely reported.[6] However, the synthesis of azepines condensed with naphthoquinone nucleus of Lapachol has been recently described.[7]

In our medicinal chemistry program geared towards synthesis of a seven membered ring with two nitrogen atoms fused to 1,4-naphthoquinone ring, we required a robust approach to a diverse set of title heterocycles **5** and **6**. Herein we report a high-yielding concise synthesis of 12-aryl and alkyl derivatives of 13-amino-12*H*-5,12-diazabenzo[4,5]cyclohepta[1,2-*b*]naphthalene-6,11-diones **5** and **6**.

12-Aryl derivatives of 13-amino-12*H*-5,12-diazabenzo[4,5]cyclohepta[1,2-*b*]naphthalene-6,11-diones **5** were synthesized in one-pot by condensing 2,3-dichloro-1,4-naphthoquinone **1** and monosubstituted 2-aminobenzonitrile derivatives **2** in refluxing ethanol in the presence of potassium carbonate (Scheme 1).

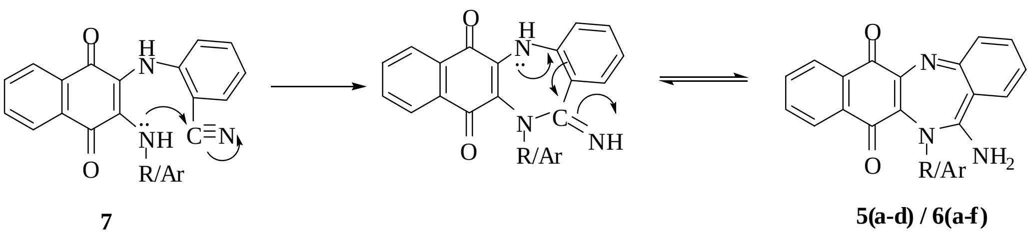
When the reaction was carried out in other bases such as $NaHCO_3$ and DBU, only intermediates 2-[3-(2-cynophenylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]aminobenzonitriles **4** were isolated and **5** were not detected.

In order to synthesize 12-alkyl derivatives of 13-amino-12*H*-5,12-diazabenzo[4,5]cyclohepta[1,2-*b*]-naphthalene-6,11-dione **6**, the reaction of 2,3-dichloro-1,4-naphthoquinone **1** was carried out with monosubstituted 2-aminobenzonitrile derivatives **2** at 50 ^{o}C in ethanol in the presence of potassium carbonate to yield a mixture of monosubstituted 2-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)aminobenzonitriles **3** and disubstituted 2-[3-(2-cynophenylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]aminobenzonitriles **4**. 2-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)aminobenzonitriles **3** on further reaction with alkyl and aryl amines in refluxing ethanol in the presence of Et_3N resulted in the formation of **6** (Scheme 1). A variety of functionalized aliphatic and aromatic amines participated in this reaction to give 1,4-benzodiazepines **6(a-f)** in good to excellent yields.



Scheme1

The formation of 1,4-benzodiazepines **5** and **6** proceeds by intramolecular cyclization of 2,3-diamino-1,4-naphthoquinones **7** and **4** respectively in presence of K_2CO_3/Et_3N. The plausible mechanism of formation of **5** and **6** is depicted in Scheme 2.



Scheme 2

In summary, a general and concise practical method of synthesizing 1,4-benzodiazepines fused with 1,4-naphthoquinone nucleus from 2,3-dichloro-1,4-naphthoquinone has been developed. This method tolerates a variety of alkyl/aryl amines and gives 12,13- disubstituted1,4-benzodiazepines **5** and **6** in good to excellent yields.

Table-1: Physical spectral and micro analytical data of **3-6** [8,9]

Entry	Yield	Mp	Spectra
3	70	233	IR (KBr):554, 680, 734, 836, 879, 1002, 1158, 1229, 1274, 1380, 1478, 1539, 1591, 1679, 2364, 3450, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (bs, 1H, NH), 7.07-8.22 (m, 8H, Ar-H); ^{13}CNMR($CDCl_3$): 99.64, 113.26, 117.12, 118.28, 119.40, 128.82, 130.12, 131.12, 133.80, 134.24, 136.61, 151.72, 152.24, 178.33, 179.12; MS: M^+(M^++1): 309; Anal. Calcd ($C_{17}H_9ClN_2O_2$): C, 66.14; H, 2.94; N, 9.07 Found: C, 65.85; H, 2.70; N, 8.94
4	20	258	IR (KBr): 505, 617, 645, 716, 761, 793, 851, 912, 1016, 1095, 1135, 1241, 1287, 1332, 1383, 1469, 1509, 1598, 1677, 2222, 2366, 3265, 3416 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ +DMSO-D_6): δ 1.25 (bs, 2H, 2NH), 7.02-8.24 (m, 12H, Ar-H); ^{13}CNMR($CDCl_3$): 99.08, 118.52, 119.02, 119.82, 120.85, 126.92, 131.88, 135.42, 134.82, 137.02, 151.22, 181.76; MS: M^+ (M^++1): 391; Anal. Calcd ($C_{24}H_{14}N_4O_2$):C, 73.84; H, 3.61; N, 14.35 Found: C, 74.02; H, 3.82; N, 14.60
5a	85	150	IR (KBr): 491, 531, 602, 670, 719, 757, 858, 984, 1006, 1038, 1071, 1105, 1203, 1252, 1274, 1302, 1350, 1384, 1460, 1507, 1601, 1655, 2363, 2926, 3390, 3451 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (bs, 2H, NH_2), 6.99-8.12 (m, 12H, Ar-H); ^{13}CNMR($CDCl_3$): 68.90, 90.04, 105.04, 116.71, 123.28, 123.51, 126.44, 130.17, 131.79, 132.22, 132.58, 132.65, 133.20, 134.53, 140.80, 142.07, 156.02, 180.21, 182.20; MS: M^+(M^++1): 391; Anal. Calcd ($C_{24}H_{14}N_4O_2$): C, 73.84; H, 3.61; N, 14.35 Found: C, 73.64; H, 3.72; N, 14.52.
5b	81	171-172	IR (KBr): 490, 532, 604, 675, 740, 753, 855, 982, 1008, 1038, 1072, 1106, 1205, 1250, 1276, 1304, 1352, 1388, 1463, 1504, 1607, 1654, 2359, 2930, 3385, 3460 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (bs, 2H, NH_2), 6.95-8.12 (m, 10H, Ar-H); Anal. Calcd ($C_{24}H_{12}Cl_2N_4O_2$): C, 62.76; H, 2.63; N, 12.20 Found: C, 62.90; H, 2.80; N, 12.42.
5c	51	198-199	IR (KBr): 495, 533, 605, 674, 742, 754, 858, 985, 1012, 1042, 1073, 1110, 1208, 1254, 1280, 1305, 1354, 1388, 1466, 1512, 1610, 1655, 2363, 2942, 3392, 3462 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (bs, 2H, NH_2), 6.98-8.15 (m, 8H, Ar-H); Anal. Calcd ($C_{24}H_{10}Cl_4N_4O_2$): C, 54.58; H, 1.99; N, 10.69 Found: C, 54.72; H, 2.20; N, 10.82.
5d	83	158-160	IR (KBr): 490, 530, 608, 670, 720, 758, 859, 985, 1006, 1036, 1072, 1106, 1204, 1252, 1275, 1304, 1352, 1386, 1462, 1509, 1602, 1656, 2362, 2920, 2932, 3392, 3452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (bs, 2H, NH_2), 2.32 (s, 3H, CH_3), 238 (s, 3H, CH_3), 6.90-8.15 (m, 10H, Ar-H); Anal. Calcd ($C_{26}H_{18}N_4O_2$): C, 74.63; H, 4.34; N, 13.39 Found: C, 74.84; H, 4.42; N, 13.52.
6a	90	90	IR (KBr):546, 610,678, 720,816, 869, 965, 1025, 1072, 1124, 1262, 1299, 1337, 1415, 1457, 1520, 1599, 1681, 2942, 3334, 3452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.25 (bs, 2H, NH_2) 3.47 (m, 3H, NCH_3), 6.49-8.15(m, 8H, Ar-H); ^{13}CNMR($CDCl_3$): 35.05, 68.92, 105.22, 116.71, 123.52, 126.54, 131.80, 132.58, 133.22, 134.53, 135.88, 140,38, 156.02, 180.40, 182.02; MS: M^+(M^++1): 304; Anal. Calcd ($C_{18}H_{13}N_3O_2$): C, 71.28; H, 4.32; N, 13.85 Found: C, 71.52; H, 4.50; N, 13.98.
6b	70	158	IR (KBr): 492, 549, 628, 670, 702, 754, 893, 931, 996, 1067, 1121, 1158, 1227, 1252, 1290, 1352, 1460, 1513, 1603, 1672, 2978, 3022, 3224, 3318 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.00 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.25 (bs, 2H, NH_2) 3.55 (m, 1H, isopropyl-H), 6.47-8.11(m, 8H, Ar-H); MS: M^+(M^++1): 332; Anal. Calcd ($C_{20}H_{17}N_3O_2$): C, 72.49; H, 5.13; N, 12.68 Found: C, 72.32; H, 5.02; N, 12.82.
6c	68	136	IR (KBr): 488, 552, 635, 678, 704, 762, 894, 932, 996, 1068, 1125, 1167, 1256, 1292, 1360, 1462, 1514, 1605, 1680, 2854, 2972, 3010, 3264 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.25 (bs, 2H, NH_2) 1.56 (s, 9H, $C(CH_3)_3$), 6.99-8.12(m, 8H, Ar-H); Anal. Calcd ($C_{21}H_{19}N_3O_2$): C, 73.03; H, 5.54; N, 12.17 Found: C, 73.28; H, 5.70; N, 12.38
6d	82	oil	IR (Neat): 495, 607, 701, 753, 971, 1027, 1073, 1162, 1289, 1337, 1454, 1499, 1607, 1670, 2857, 2925, 3050, 3064 3347, 3465 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.25 (bs, 2H, NH_2) 4.21 (s, 2H, NCH_2), 6.60-8.23(m, 13H, Ar-H); Anal. Calcd ($C_{24}H_{17}N_3O_2$): C, 75.97; H, 4.52; N, 11.08 Found: C, 76.22; H, 4.78; N, 11.26.
6e	80	60-62	IR (KBr): 473, 498, 583, 663, 724, 756, 797, 858, 905, 971, 1019, 1041, 1084, 1157, 1202, 1263, 1313, 1385, 1474, 1603, 1675, 2932, 2983, 3072, 3372, 3471 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.25 (bs, 2H, NH_2) 6.72-8.05(m, 13H, Ar-H); Anal. Calcd ($C_{23}H_{15}N_3O_2$): C, 75.60; H, 4.14; N, 11.50 Found: C, 75.82; H, 4.30; N, 11.72.
6f	55	178	IR (KBr):487, 675, 769, 972, 1029, 1081, 1219, 1370, 1461, 1508, 1617, 1657, 2854, 2923, 3370, 3427 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.25 (bs, 2H, NH_2), 2.64 (t, 2H,CH_2), 3.31 (t, 2H, CH_2), 3.79 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3) 6.46-8.09(m, 11H, Ar-H); Anal. Calcd ($C_{27}H_{23}N_3O_4$): C, 71.51; H, 5.11; N, 9.27 Found: C, 71.72; H, 5.32; N, 9.48.

ACKNOWLEDGEMENTS

H. K. M. acknowledges UGC, New Delhi, India for Senior Research Fellowship.

REFERENCES AND NOTES

1. I. Gomez-Monterrey, G. Santelli, P. Campiglia, D. Califano, F. Falasconi, C. Pisano, L. Vesci, T. Lama, P. Grieco, and E. Novellino, *J. Med. Chem.*, 2005, **48**, 1152.
2. H. Seradj, W. Cai, N. O. Erasga, D. V. Chenault, K. A. Knuckles, J. R. Ragains, and M. Behforouz, *Org. Lett.*, 2004, **6**, 473.
3. V. K. Tandon, H. K. Maurya, D. B. Yadav, A. Tripathi, M. Kumar, and P. K. Shukla, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 5883.
4. C. K. Ryu, J. Y. Shim, M. J. Chae, I. H. Choi, J. Y. Han, O. J. Jung, J. Y. Lee, and S. H. Jeong, *Eur. J. Med. Chem.,* 2005, **40**, 438.
5. C. K. Ryu, J. Y. Han, O. J. Jung, S. K. Lee, J. Y. Lee, and S. H. Jeong, *Bioorg. Med. Chem. Lett.,* 2005, **15**, 679.
6. J. A. Valderrama, H. Pessoa-Mohana, and R. Tapia, *J. Heteroycl. Chem.,* 1992, **29**, 1177.
7. C. A. Camara, A. C. Pinto, M. D. Vargas, and J. Zukerman-Schpector, *Tetrahedron*, 2002, **58**, 6135.
8. *General procedure* (**5**): To a solution of 2,3-dichloro-1,4-naphthoquinone **1** (1 g, 4.40 mmol) in abs. EtOH (100 mL), 2-aminobenzonitriles **2** (1.4 g, 8.80 mmol) was added followed by anhydrous K_2CO_3 (871 mg, 8.80 mmol). The reaction mixture was vigorously stirred at 80-90 ^{0}C for 15 h. The reaction mixture was then distilled and dried *in vacuo*. The residue was chromatographed on SiO_2 (0-20% EtOAc in hexane).
9. *General procedure* (**3 and 4**): To a solution of 2,3-dichloro-1,4-napthoquinone **1** (1 g, 4.40 mmol) in abs. EtOH (100 mL), 2-aminobenzonitrile **2** (0.52 g, 4.40 mmol) was added followed by anhydrous K_2CO_3 (435 mg, 4.40 mmol). The reaction mixture was vigorously stirred at 50 ^{o}C for 24 h. The reaction mixture was distilled and dried *in vacuo*. The mixture of **3** and **4** was separated by column chromatography (SiO_2) using EtOAc in hexane (0-35%);
   General Procedure (**6**): To a solution of 2-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)aminobenzonitrile **3** (308 mg, 1 mmol) in abs. EtOH (90 mL), isopropylamine (71 mg, 1.2 mmol) and triethylamine (121 mg, 1.2 mmol) were added. The mixture was stirred first at rt for 0.5 h and then at 80-90 ^{o}C for 10-38 h. The reaction mixture was distilled and dried *in vacuo* and purified by flash column chromatography (SiO_2) using EtOAc in hexane (0-15%).