PREPARATION OF 2-AMINO-4*H*-PYRAZOLO[1,5-*a*]INDOLE DERIVATIVES BY BOULTON-KATRITZKY REARRANGEMENT[1]

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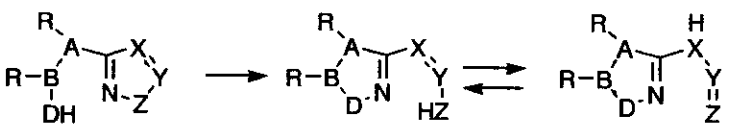
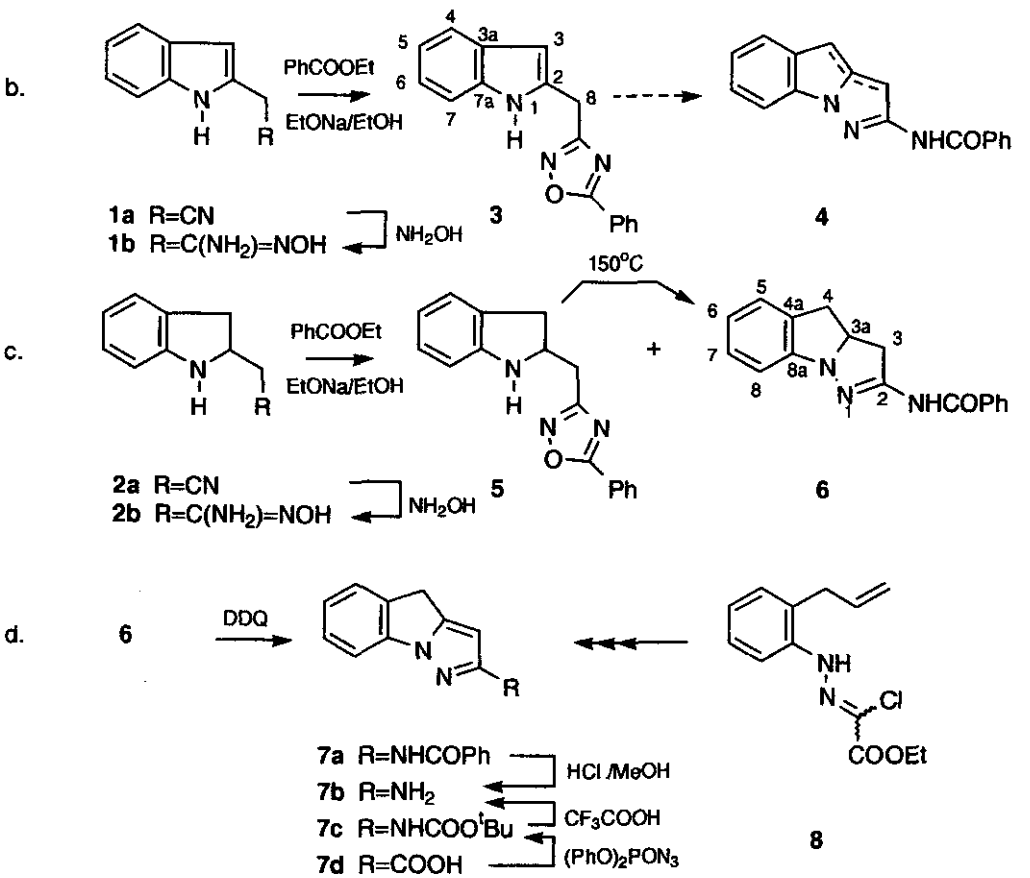
Abstract - 2-Benzoylamino-3,3a-dihydro-4*H*-pyrazolo[1,5-*a*]indole was prepared by extended type-2 Boulton-Katritzky rearrangement and transferred into 2-amino-4*H*-pyrazolo[1,5-*a*]indole.

As an extended form of azole-azole ring transformation,[2] azole-azoline rearrangement was developed and named as the extended type-2 Boulton-Katritzky rearrangement (Eq. a).[3] This reaction was generalized to the preparation of 2-aminopyrazoline derivatives.[3a,4] As one of the methods for the preparation of pyrazolo[1,5-a]indole derivatives,[5] we were interested in this rearrangement and applied it to1,2,4-oxadiazole derivatives such as **3** and **5** for the construction of 4*H*-pyrazolo[1,5-a]indole nucleus having the 2-amino group which allows various functionalization

a. 

at C-2. For the preparation of **3** and **5**, **1a**[6] and **2a**[5b] were derived into the amidoximes (**1b**) and (**2b**) by the reaction with hydroxylamine.[7] Then the indole derivative (**1b**) was subjected to the ester exchange reaction with ethyl benzoate and the subsequent dehydration in dry ethanol

containing sodium ethoxide at refluxing temperature to give 1,2,4-oxadiazole derivative (**3**). When **3** was heated in refluxing *p*-cymene (bp 176-178 °C), the Boulton-Katritzky ring transformation was not induced but **3** was recovered (Eq. b). Then the indoline derivative (**2b**) was subjected to the same reaction (Eq. c). After the reaction of **2b**, the crude product was separated by column chromatography to give two products which possessed the same molecular composition with **2b**. The major product (**5**) had less polarity and showed NH absorption at 3340 cm^{-1} but no carbonyl absorption on the ir spectrum. On the ^{13}C nmr spectrum it had singlet signals at δ 169.2 and 175.6 ppm due to C-3 and C-5 of 1,2,4-oxadiazole ring as observed in **3**. The second product (**6**) eluted out later and had the NH (3420 cm^{-1}) and amide carbonyl (1678 cm^{-1}) absorptions on the ir



spectrum. On the ^{1}H nmr spectrum two ABX type signals were observed at δ 3.08 and 3.33 ppm (J_{AB}=16.1, J_{AX}=7.1 and J_{BX}=9.5Hz) and δ 3.42 and 3.81 ppm (J_{AB}=18.5, J_{AX}=6.1 and J_{BX}=11.0Hz) which are characteristic for 4-H and 3-H of 3,3a-dihydro-4*H*-pyrazolo[1,5-*a*]indole derivatives.[5b,8] Carbons (^{13}C) in benzoylamino group of **6** had almost identical chemical shifts with those of benzamide.[9] The formation of **6** as by-product in this reaction suggested that 1,2,4-oxadiazole derivative (**5**) was derived from **2b** at first, then rearranged into **6**. The high susceptibility of **5** toward ring transformation compared with **3** reminded us that an azole-azoline rearrangement was about twenty times faster than azole-azole ring transformation.[3a] Actually the Boulton-Katritzky rearrangement of **5** proceeded smoothly in refluxing xylene and **6** was obtained as a sole product in 72% yield (52% from **2b**). Since the yield of **5** was not improved more than 52%, benzoyl chloride in acetic acid was used to esterify oxime OH group in order to accelerate the oxadiazole ring formation.[10] But no practical improvement was achieved. The structure of **6** was further proved by the following chemical transformations (Eq. d).

Amide (**6**) was dehydrogenated with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ). The product (**7a**) (94%) had a broad singlet at δ 7.05 which is characteristic for 3-H of 4*H*-pyrazolo[1,5-a]indole derivatives.[5b] Amide (**7a**) was hydrolyzed by refluxing in 2M hydrochloric acid for 11 h and 2-amino-4*H*-pyrazolo[1,5-*a*]indole (**7b**) was obtained as red crystal in 96% yield. Amine (**7b**) was also prepared by the treatment of carbamate (**7c**) with trifluoroacetic acid (98%) which was derived from the acid (**7d**)[5b] by the modified Curtius rearrangement (80%).[11] The skeleton of the acid (**7d**) was formed by the intramolecular 1,3-dipolar cycloaddition of **8**.[8a]

EXPERIMENTAL

Melting points were measured by Yanaco micro mp apparatus and were uncorrected. Perkin-Elmer FT-IR 1720 was used for ir measurement (KBr pellet). ^{1}H Nmr (200 MHz) and ^{13}C nmr (50.1 MHz) were measured with JEOL JNM-FT 200 in $CDCl_3$ containing TMS as an internal standard. Hrms and ms were taken by Hitachi RMU-7MG. Silica gel and dichloromethane containing ethyl acetate were used for chromatographic separation.

Amidoximes (**1b**) *and* (**2b**). - A solution of nitrile (10 mmol), hydroxylamine hydrochloride (1.53 g,

22 mmol) and sodium hydrogen carbonate (1.85 g, 22 mmol) in water (7 ml) and 95% ethanol (50 ml) was refluxed for 25 h. After concentration of the reaction mixture, the residue was dried and dissolved in hot dry ethanol. Insoluble material was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The residual material was either recrystallized from ethyl acetate or chromatographed (neutral alumina, dichloromethane containing 5% methanol). **1b** (59%), mp 122-126 °C. ^{1}H Nmr δ: 3.54(2H, s, 8-H_2), 6.30(1H, s, 3-H), 6.94(1H, dt, J=1.2, 7.3 Hz, 5-H), 7.03(1H, dt, J=1.2, 7.1 Hz, 6-H), 7.27(1H, br d, J=8 Hz, 7-H), 7.43(1H, br d, J=7.3 Hz, 4-H); ^{13}C nmr δ: 31.2(C-8), 101.6(C-3), 111.7(C-7), 120.1(C-5), 120.6(C-4), 122.0(C-6), 130.0(C-3a), 135.0(C-2), 138.1(C-7a), 154.7(C=NOH). **2b** (87%), mp 110-112 °C. Ir cm^{-1}: 3490, 3375, 3340, 3280, 1660; ^{1}H nmr(CD_3OD + D_2O) δ: 2.33(2H, d, J=6.6 Hz, 8-H_2), 2.72(1H, dd, J=7.6, 15.6 Hz, 3-H), 3.09(1H, dd, J=8.6, 15.6 Hz, 3-H), 4.05(1H, m, 2-H), 6.64(1H, d, J=7.6 Hz, 7-H), 6.67(1H, t, J=7.6 Hz, 5-H), 6.97(1H, t, J=7.6 Hz, 6-H), 7.04(1H, d, J=7.3 Hz, 4-H); ^{13}C nmr (CD_3OD + D_2O) δ: 36.2(C-3), 37.8(C-8), 58.5(C-2), 111.1(C-7), 120.2(C-5), 125.6(C-4), 128.2(C-6), 129.8(C-3a), 151.5(C-7a), 155.1(C=NOH); ms m/z: 191(M^+, 8%), 173(4), 130(18), 118(100), 117(50), 91(17), 74(68). Anal. Calcd for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.65; H, 6.77; N, 21.96.

3-(2-*Indolylmethyl*)-5-*phenyl*-1,2,4-*oxadiazole* (**3**) - Amidoxime (**1b**) (0.950 g, 5.0 mmol) and ethyl benzoate (2.264 g, 15.1 mmol) were dissolved in dry ethanol (15 ml) under exclusion of moisture. A solution of 1M sodium ethoxide in ethanol (5 ml) was added and the mixture was refluxed for 15 h. Although the reaction was incomplete, the reaction mixture was worked up. After evaporation of the reaction mixture, water was added into the residue and the solution was extracted with dichloromethane. The extracts were dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure to give the crude product which was chromatographed (dichloromethane-ethyl acetate 95 : 5) to give **3** (0.143 g, 5%), mp 127-129 °C. ^{1}H Nmr δ: 4.29(2H, s, 8-H_2), 6.45(1H, br s, 3-H), 7.06(1H, dt, J=1.2, 7.1 Hz, 5-H), 7.14(1H, dt, J=1.2, 7.1 Hz, 6-H), 7.31(1H, br d, J=7.8 Hz, 7-H), 7.43-7.57(4H, m, 4,3',4',5'-H), 8.10(2H, m, 2',6'-H), 8.62(1H, br s, NH); ^{13}C nmr δ: 25.5(C-8), 101.8(C-3), 110.7(C-7), 119.9(C-5), 120.2(C-4), 121.8(C-6), 123.9(C-1'), 128.1(C-2',6'), 128.3(C-3a), 129.1(C-3',5'), 131.8(C-2), 132.9(C-4'), 136.4(C-7a), 168.3(C-oxadiazole), 176.0(C-oxadiazole).

3-(2-*Indolinylmethyl*)-5-*phenyl*-1,2,4-*oxadiazole* (**5**) *and* 2-*Benzoylamino*-3,3a-*dihydro*-4H-*pyrazolo*[1,5-a]*indole* (**6**). - The similar reaction of **2b** as described for **1b** afforded **5** (35%) and **6** (12%). **5**, mp 79.0-81.0 °C (from ether). Ir cm^{-1}: 3340, 1605, 1560, 1362, 745, 690; ^1H nmr δ: 2.84(1H, dd, J=7.3, 15.6 Hz, 3-H), 3.07(2H, d, J=8.8 Hz, 8-H_2), 3.28(1H, dd, J=8.8, 15.6 Hz, 3-H), 4.33(1H, m, 2-H), 4.46(1H, br s, NH), 6.63(1H, br d, J=7.8 Hz, 7-H), 6.69(1H, t, J=7.3 Hz, 5-H), 7.02(1H, br t, J=7.5 Hz, 6-H), 7.09(1H, br d, J=7.1 Hz, 4-H), 7.46-7.60(3H, m, 3',4',5'-H), 8.12(2H, m, 2',6'-H); ^{13}C nmr δ: 33.1(C-8), 36.2(C-3), 57.2(C-2), 109.3(C-7), 118.7(C-5), 124.1(C-1'), 124.7(C-4), 127.4(C-6), 127.7(C-3a), 128.1(C-2',6'), 129.1(C-3',5'), 132.7(C-4'), 150.3(C-7a), 169.2(C-oxadiazole), 175.6(C-oxadiazole); ms m/z: 277(M^+, 9%), 160(12), 130(6), 118(100), 105(30), 91(10), 77(14). Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.70; H, 5.43; N, 15.16. **6** (41%), mp 184.0-186.0 °C (from benzene). Ir cm^{-1}: 3420, 1678, 1632, 1482, 1378, 1280, 777, 718; ^1H nmr δ: 3.08(1H, dd, J=7.1, 16.1Hz, 4-H), 3.33(1H, dd, J=9.5, 16.1 Hz, 4-H), 3.42(1H, dd, J=6.1, 18.5 Hz, 3-H), 3.81(1H, dd, J=11.0, 18.5 Hz, 3-H), 4.67(1H, m, 3a-H), 7.00(1H, dt, J=1.9, 6.9 Hz, 6-H), 7.08-8.19(3H, m, 5,7,8-H), 7.40-7.58(3H, m, 3',4',5'-H), 7.81(2H, m, 2',6'-H), 8.76(1H, br s, NH); ^{13}C nmr δ: 37.3(C-4), 40.1(C-3), 62.7(C-3a), 117.5(C-8), 124.3(C-6), 125.1(C-5), 127.3(C-2',6'), 127.8(C-7), 128.8(3',5'-H), 130.9(C-4a), 132.6(C-4'), 133.1(C-1'), 150.5(C-8a), 153.0(C-2), 165.2(C=O); ms m/z: 277(M^+, 33%), 172(5), 155(5), 105(100). Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.37; H, 5.35; N, 14.87.

Boulton-Katritzky rearrangement of **5**. - A solution of **5** (339 mg, 1.2 mmol) in xylene (10 ml) was refluxed for 4 h (bath temperature 150 °C). The solvent was removed and the residue was recrystallized from benzene to give **6** (243 mg, 72%). When the reaction temperature was 80 °C, no production of **6** was detected on tlc.

2-*Benzoylamino*-3,3a-*dihydro*-4H-*pyrazolo*[1,5-a]*indole* (**7a**). - A solution of **6** (200 mg, 0.72 mmol), DDQ (246 mg, 1.1 mmol) and dry benzene (20 ml) was stirred at room tempoerature for 1 h. Insoluble material was removed by filtration and the filtrate was evaporated to dryness. The residual material was chromatographed (dichloromethane-methanol 97 : 3) to give **7a** (186 mg, 94%), pale yellow needle, mp 176.0-177.0 °C (from acetonitrile). Ir cm^{-1}: 3220, 3062, 1686, 1670, 1568, 1470,

1340, 996, 694; ^{1}H nmr δ: 3.88(2H, s, 4-H_2), 7.05(1H, br s, 3-H), 7.04-7.22(3H, m, Ar-H), 7.26-7.41(4H, m, Ar-H), 7.88(2H, m, 2',6'-H), 9.65(1H, br s, NH); ^{13}C nmr δ: 28.8(C-4), 93.8(C-3), 109.6(C-8), 123.9(C-6), 125.6(C-5), 127.3(C-2',6'), 127.9(C-7), 128.6(C-3',5'), 131.8(C-4'), 132.5(C-4a), 134.1(C-1'), 140.1(C-3a), 145.5(C-8a), 151.4(C-2), 165.2(C=O); ms m/z: 275(M^+, 22%), 247(10), 141(6), 105(100). Hrms Found: M^+ 275.1048. $C_{17}H_{13}N_3O$ requires 275.1057.

2-*Amino*-3,3a-*dihydro*-4H-*pyrazolo*[1,5-a]*indole* (**7b**). - a) Amide (**7a**) (104 mg, 0.4 mmol) was dissolved in a mixture of 2M hydrochloric acid (12 ml) and methanol (6 ml) and the solution was refluxed for 11 h. After concentration *in vacuo*, the residual solution was basified with soliid sodium carbonate then extracted with dichloromethane. After usual work-up of the extracts, the crude product was recrystallized from benzene to give amine (**7b**) (62 mg, 96%), red crystal, mp 140.0-141.0 °C (decomp.). Ir cm^{-1}: 3361, 3296, 3186, 1562, 1493, 1397, 1368, 746; ^{1}H nmr δ: 3.74(2H, s, 4-H_2), 3.90(2H, br s, NH_2), 5.65(1H, m, 3-H), 7.04(1H, dt, J=1.5, 7.5 Hz, 6-H), 7.26-7.38(3H, m, Ar-H); ^{13}C nmr δ: 28.6(C-4), 89.0(C-3), 108.8(C-8), 122.6(C-6), 125.4(C-5), 127.9(C-7), 131.9(C-4a), 140.9(C-3a), 146.0(C-8a), 158.8(C-2); ms m/z: 171(M+, 100%), 141(23), 129(13), 115(14), 102(10). Hrms Found: M^+ 171. 0780. $C_{10}H_9N_3$ requires 171. 0795. Anal. Calcd for $C_{10}H_9N_3$: 70.16; H, 5.30; N, 24.54. Found: C, 70.32; H, 5.23; N, 24.60. b) A solution of the carbamate (**7c**) (375 mg, 1.4 mmol) dissolved in trifluoroacetic acid (7.5 ml, 97.4 mmol) was stirred under dry nitrogen for 1 h. The solution was diluted with water and basified with solid sodium carbonate. The extraction of basic solution with ethyl acetate gave the product which was purified by column chromatography (dichloromethane-methanol 97 : 3) to give the amine (**7b**) (232 mg, 98%).

2-t-*Butoxycarbonyamino*-3,3a-*dihydro*-4H-*pyrazolo*[1,5-a]*indole* (**7c**). - The carboxylic acid (**7d**)[5b] (500 mg, 2.5 mmol) was dissolved in dry t-butyl alcohol (15 ml) and treated with diphenylphosphoryl azide (0.60 ml, 2.8 mmol) and triethyl amine (0.42 ml, 3.0 mmol) at refluxing temperature in nitrogen atmosphere for 4 h. After evaporating the reaction mixture, the residue was dissolved in ethyl acetate and the solution was washed with 1M sodium carbonate solution and saturated brine successively. The crude product was purified by column chromatography (dichloromethane-ethyl acetate 95 : 5) to give amide (**7c**) (539 mg, 80%), mp 153.5-154.0 °C (from

cyclohexane). Ir cm^{-1}: 3215, 1722, 1578, 1161; ^1H nmr δ: 1.49(9H, s, t-Bu), 3.85(2H, s, 4-H_2), 6.59(1H, br s, 3-H), 7.13(1H, dt, J=1.0, 7.5 Hz, 6-H), 7.34(1H, t, J=8.0 Hz, 7-H), 7.41(1H, d, J=7.8 Hz, 5-H), 7.50(1H, d, J=7.8 Hz, 8-H), 8.08(1H, br s, NH); ^{13}C nmr δ: 28.3(CH_3), 28.7(C-4), 80.7(CMe_3), 92.1(C-3), 109.8(C-8), 123.6(C-6), 125.5(C-5), 127.9(C-7), 132.3(C-4a), 140.4(C-3a), 145.3(C-2), 151.7(C-8a), 152.7(C=O); ms m/z: 271(M^+, 4%), 215(8), 171(100), 143(6), 115(7); Anal. Calcd for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.60; H, 6.34; N, 15.45.

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