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2-AMINOCARBAZOLE SYNTHESIS

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Aminocarbazoles are useful intermediates for syntheses of various dyes and pigments, stabilizers for polymers, pesticides, photographic materials and diagnostic reagents in cytochemical studies. The derivatives of 3-aminocarbazole have been investigated and the preparation of 1-aminocarbazole and its application for pharmaceuticals and dyestuffs was reported about 50 years ago. The chemical properties of 2-aminocarbazole and its derivatives are not well known owing to the lack of an effective method of its preparation.

2-Nitro- and 4-nitro-3-acetylaminocarbazoles were obtained simultaneously by nitration of a mixture of the diacetyl and triacetyl derivatives of 3-aminocarbazole. The compounds were isolated by fractional crystallisation in poor yields.[1] Both isomers after hydrolysis and deamination gave 2-nitro- and 4-nitrocarbazole respectively.[2,3] This mixture of nitrocarbazoles was also obtained in Borshe's carbazole synthesis. Cyclisation of cyclohexanone 3-nitrophenylhydrazone yielded a mixture of equimolar amounts of 5-nitro- and 7-nitro-1,2,3,4-tetrahydrocarbazole. After dehydrogenation with chloranil, the nitrocarbazoles were separated chromatographically.[4,5] 2-Nitrocarbazole can be obtained from 2-nitrodiphenyl in overall yield of 50–60%.[6] Hydrogenation of 2-nitrocarbazole on Adams catalyst gave poor yields of an unstable product melting with decomposition at 238–9°.[2] Better results were obtained using stannous chloride as the reducing agent.[7] The most convenient method of 2-aminocarbazole preparation involves arylation of 2-(1-morpholinyl)-cyclohexene to 2-(2,4-dinitrophenyl)-cyclohexanone which can be easily converted to 7-amino-1,2,3,4-tetrahydrocarbazole through catalytic hydrogenation. Aromatisation of its acetyl derivative yields 2-aminocarbazole.[9,10]

Electrophilic reagents attack position 3 and to a lesser extent position 1 in carbazole and its 9-substituted derivatives, with the exception of 9-acylcarbazoles which form 2,9-diacyl derivatives when acylated.[11,12] It was presumed that 2-acetylcarbazole could be used as the best intermediate in 2-aminocarbazole synthesis. The Beckmann rearrangement is the key step in the following reaction sequence:

Acylation of carbazole gave 9-acetylcarbazole in 37–90% yield if the product was isolated chromatographically.[13,14] We found that if the reaction was performed using a threefold quantity of acetic anhydride and a minute amount of boron fluoride as the catalyst, 9-acetylcarbazole was isolated more readily as pink crystals. The Friedel–Grafts reaction was carried out as described.[11,12] The optimum amount of the catalyst is 4.5 moles of aluminum chloride per mole of 9-acetylcarbazole. 2,9-Diacetylcarbazole can be isolated in a pure state if the reaction mixture is intensely cooled during decomposition of its complex. The crude product readily hydrolyses in an alkaline alcoholic solution yielding 2-acetylcarbazole.

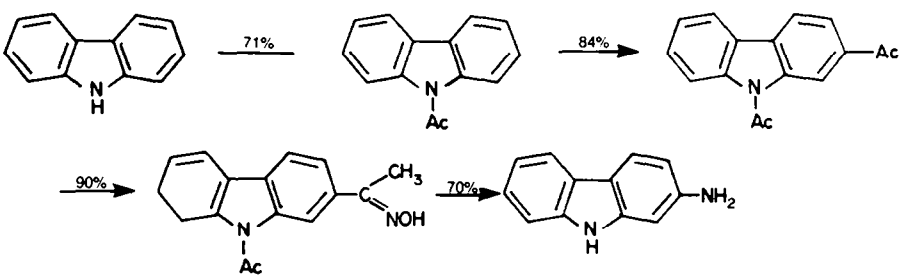
The most convenient way of 2-acetyl- and 2,9-diacetylcarbazole oximation involves heating their pyridine solutions with hydroxylamine hydrochloride. The oximes were isolated by pouring the solutions into cool, diluted hydrochloric acid and used without crystallisation.

2-Aminocarbazole was obtained from 2,9-diacetylcarbazole oxime via the Beckmann rearrangement followed by hydrolysis of the corresponding amide which was not isolated. The rearrangement was performed either in a boiling trifluoroacetic acid solution or in a melt of the substrate and the boron trifluoride–acetic acid liquid complex. Reaction mixtures were then diluted with water and refluxed until hydrolysis was completed. 2-Acetylcarbazole can be also used as the substrate but the total yield of 2-aminocarbazole is lower.

2-Acetylaminocarbazole and its 9-acetyl derivative can be easily prepared crom the corresponding oximes under influence of phosphorus pentachloride. The oxime acetic esters are resistant to phosphorus pentachloride but boron trifluoride in acetic acid solutions causes their rearrangement. Multicomponent mixtures are produced when the oximes are refluxed in "Beckmann mixture" irrespective of its composition. Probably esterification of the oximes retards their rearrangement and some side reactions occur.

EXPERIMENTAL

9-Acetylcarbazole. In 150 ml Ac_2O 50.14 g (0.30 M) carbazole



was suspeneded. BF_3Et_2O (10 μl) was added and the mixture refluxed for 25 min. From the cooled, dark brown soln 40.25 g of the crude product was isolated, m.p. 66–71°. The filtrate was concentrated to the volume of 80 ml and cooled to −20°. The second crop of the product (13.10 g, m.p. 65–9°) was filtered off and combined with the first; the total yield 85%. The crude product was dried in vacuum over KOH and crystallised twice from 900 ml *n*-heptane boiling with charcoal. Pure 9-acetylcarbazole (44.70 g—71%) was obtained as colourless needles m.p. 72–4°, lit. m.p. 68–9°.[14] Found: C, 80.21; H, 5.21. Calc. for $C_{14}H_{11}NO$: C, 80.36; H, 5.30%. IR (KBr): 730, 760 (aromatic protons wagging), 1040, 1125, 1160, 1245 (in-plane H-bending), 1680 (CO band in N,N-disubstituted amides). MS, *m/e*: 211 (0.8), 210 (7.3), 209 (45.0, M^+), 168 (25.2), 167 (100.0), 166 (20.5), 140 (10.3), 139 (12.0), 43 (16.5). NMR (Me_2CO-d_6): 2.10, d $J_0 = 7.0$ Hz of doublets $J_m = 2.5$ Hz, 2H (4,5-aromatic protons); 2.30, d $J_0 = 7.0$ Hz of doublets $J_m = 2.5$ Hz, 2H (1,8-protons); 2.77–3.12, m, 4H (remaining aromatic protons); 7.51, s, 3H (protons of acetyl group).

2,9-*Diacetylcarbazole.* 9-Acetylcarbazole (41.85 g—0.20 M) and anhyd $AlCl_3$ (120 g—0.9 M) were dissolved in 1l CS_2. Acetyl chloride (2.85 ml—0.40 M) was added and the mixture stirred under reflux for 2 hr. HCl (6N, 1000 ml) was added to a cooled on dry ice bath and intensely stirred reaction mixture. It was allowed to warm to room temp, CH_2Cl_2 (600 ml) was added in small portions until the ppt dissolved. The organic layer was separated, dried with Na_2SO_4 and stirred with charcoal. The soln was filtered, evaporated to dryness, and the residue crystallised from benzene–heptane 1:1 mixture. After recrystallisation colourless needles of 2,9-diacetylcarbazole (m.p. 107–9°) were obtained in 84% yield, (42.30 g; lit. m.p. 105–6°[15]). Found: C, 76.71; H, 5.11. Calc. for $C_{16}H_{13}NO_2$: C, 76.46; H, 5.21%. IR (KBr): 730, 760, 825, 900 (aromatic C–H deform.), 1375, 1425 (aliphatic C–H deform.), 1310 (amide band), 1690 (CO stretching), 2950, 3000, 3080 (C–H stretch.) MS, *m/e*: 252 (8.6), 251 (44.6, M^+), 210 (12.9), 209 (74.1), 195 (14.7), 194 (100.0), 167 (25.6), 166 (45.2), 139 (24.5), 43 (42.9). NMR ($CDCl_3$): 1.35, d $J_m = 2.0$ Hz, 1H (1-proton); 2.03, d $J_0 = 7.3$ Hz of doublets $J_m = 2.0$ Hz, 1H (3-proton); 2.11–2.22, m, 3H (4,5,8-protons); 2.57, sextet overlapped, $J_0 = 7.1$ Hz, $J_0' = 6.0$ Hz, $J_m = 1.9$ Hz, 1H and 2.74, sextet overlapped $J_0 = J_0' = 6.0$ Hz, $J = 2.2$ Hz, 1H (6- and 7-proton); 7.28, s, 3H (9-acetyl group); 7.44, s, 3H (2-acetyl group).

2-*Acetylcarbazole.* To a soln of 25.13 g (0.10 M) 2,9-diacetylcarbazole in 600 ml boiling MeOH, KOH (0.60 g—0.1 M) as 20% aqueous soln was slowly added. The suspension was allowed to cool and the crude product (18.40 g—88%) was filtered off and dried; m.p. 232–236°. After crystallisation from 1700 ml toluene 17.27 g (82%) 2-acetylcarbazole was obtained as lemon yellow needles m.p. 234–6° (lit. m.p. 230–1°[16]). Found: C, 80.40; H, 5.42. Calc. for $C_{14}H_{11}NO$: C, 80.35; H, 5.3%. IR (KBr): 735, 760, 830, 870 (out of plane hydrogen wagging), 1360, 1430 (Me group deformations), 1670 (CO band), 3080 (N–H stretch). MS, *m/e*: 211 (1.5), 210 (11.8), 209 (69.9, M^+), 195 (15.1), 194 (100.0), 166 (57.2), 165 (10.7), 140 (10.8), 139 (28.6). NMR (DMSO-d_6): 1.71–1.80, m, 3H (1,3,4-protons); 2.12–2.87, m, 4H (remaining aromatic protons); 7.90, s, 3H (acetyl group).

2-*Acetylcarbazole oxime.* A soln of 2-acetylcarbazole (20.92 g—0.10 M) and hydroxylamine hydrochloride (10.42—0.15 M) in 100 ml pyridine was stirred on a boiling water bath for 20 min. The cooled mixture was poured onto crushed ice with 70 ml conc HCl. The ppt was collected by filtration, washed with a large amount of water and dried in vacuum over KOH. Crystallisation from 2 l of abs EtOH gave 20.86 g (93%) of the product melting at 268–72°. After recrystallisation pure 2-acetylcarbazole oxime (17.95 g—80%) was obtained as silver plates m.p. 274–6°. Found: C, 74.83; H, 5.45. Calc. for $C_{14}H_{12}N_2O$: C, 74.97; H, 5.39%. IR (KBr): 740, 765, 830, 875 (arom. C–H deformations), 960, 1635 (N–O and C=N stretch), 3240 (N–H stretch), 3420 (O–H stretching vibrations). MS, *m/e*: 225 (16.7), 224 (100.0, M^+), 208 (19.9), 207 (17.8), 193 (21.8), 192 (22.0), 191 (10.2), 183 (12.7), 167 (43.2), 166 (56.2), 154 (10.6), 139 (25.4). NMR (DMSO-d_6): 1.86–2.17, m, 3H and 2.41–2.95, m, 4H (aromatic protons); 7.73, s, 3H (acetyl group).

2,9-*Diacetylcarbazole oxime.* The reaction was performed as described above. The crude product, m.p. 177–82° was crystallised from ethylene chloride. 2,9-Diacetylcarbazole oxime was obtained in 90% yield (24.00 g) as white needles melting at 180–2° with decom. Found: C, 72.30; H, 5.41. Calc. for $C_{16}H_{14}N_2O$: C, 72.16; H, 5.30%. IR (KBr): 730, 750, 820, 870 (arom. C–H deformation), 940 (N–O stretch), 1670 (azomethine band), 1690 (CO band), 3310 (O–H stretching vibration). MS, *m/e*: 267 (14.8), 266 (70.7, M^+), 265 (11.4), 250 (39.2), 225 (19.0), 224 (84.9), 209 (19.3), 208 (100.0), 207 (38.6), 194 (18.7), 193 (86.6), 192 (49.0), 167 (67.9), 140 (23.3), 139 (50.0). NMR (DMSO-d_6): −1.35, s, 1H (hydroxylic proton); 1.42, d $J_m = 1.0$ Hz, 1H (1-proton); 1.75–2.05, m, 3H and 2.24–2.60, m, 4H (remaining aromatic protons); 7.14, s, 3H (Me group next to the azomethine bond); 7.72, s, 3H (acetyl group).

2-*Acetylcarbazole oxime acetic ester.* 2-Acetylcarbazole oxime (6.73 g—0.03 M) was refluxed in 80 ml Ac_2O for 1.5 hr. The anhydride was evaporated under reduced pressure and the residue crystallised twice from 60 ml toluene. Pure ester was obtained in 75% yield (6.00 g) as creamy needles m.p. 165–6°. Found: C, 72.16; H, 5.31. Calc. for $C_{16}H_{14}N_2O$: C, 72.16; H, 5.30%. IR (KBr): 735, 755, 815, 870 (aromatic C–H def.), 950, 1615 (oxime group vibrations), 1215, 1750 (ester group stretching), 3290 (N–H stretch). MS, *m/e*: 267 (18.4), 266 (93.9, M^+), 265 (14.1), 225 (17.2), 224 (100.0), 223 (20.2), 208 (77.3), 194 (19.6), 193 (84.0), 192 (50.9), 167 (44.8), 166 (88.3), 139 (47.9), 43 (88.3). NMR (CD_3NO_2): 1.98, broad doublet $J_0 = 8.1$ Hz, 2H (3,4-protons); 2.19, d $J_m = 1.5$ Hz of doublets $J_0 = 0.7$ Hz, 1H (1-proton); 2.41–2.96, m, 4H (remaining aromatic protons); 7.63; s, 3H (acetyl group); 7.81, s and 7.84, s, 3H (methyl group next to the azomethine bond, syn and anti).

2,9-*Diacetylcarbazole oxime acetic ester.* Conc HCl (0.86 ml—0.01 M) was added to 50 ml Ac_2O and the soln warmed to 40–50°. 9-Acetylcarbazole oxime acetic ester (2.66—0.01 M) was added and the mixture refluxed for 1 hr. Ac_2O was evaporated under reduced pressure. The crude product was crystallised twice from toluene boiling with charcoal. 2,9-Diacetylcarbazole oxime acetic ester (2.03 g—65%) was obtained as colourless needles, m.p. 146–7°. Found: C, 70.22; H, 5.30. Calc. for $C_{16}H_{14}N_2O$: C, 70.11; H, 5.23%. IR (KBr): 730, 760, 830, 890 (aromatic C–H deform.), 945, 1620 (oxime group), 1210, 1775 (ester group stretchings), 1710 (amide band), 2940, 2990, 3020, 3060 (C–H stretch). MS, *m/e*: 309 (7.2), 308 (36.6, M^+), 266 (36.0), 250 (27.0), 224 (64.2), 208 (64.8), 193 (57.0), 166 (49.0), 154 (10.6), 139 (28.3), 43 (100.0). NMR ($CDCl_3$): 1.46, d $J_m = 1.4$ Hz, 1H (1-proton); 1.96–2.27, m, 4H and 2.35–2.81, m, 2H (remaining aromatic protons); 7.26, s, 3H (N-acetyl group); 7.64, s, 3H (O-acetyl group); 7.79, s, 3H (Me group).

2-*Acetylaminocarbazole.* A soln of 2.24 g (0.01 M) 2-acetylcarbazole oxime and 3.08 g (0.01 M) PCl_5 in 50 ml THF was left for 1 hr in the room temp. The mixture was poured on to 300 ml ice and the ppt was dissolved in 100 ml hot toluene, boiled with charcoal and filtered. The filtrate was pured into 200 ml cold petroleum ether. 2-Acetylaminocarbazole (1.14 g—51%) was isolated as amorphous powder melting 238–40° (lit. m. . 243°[10]).

2-Acetylamino-9-acetylcarbazole (2.66 g—0.01 M) was dissolved in 40 ml hot 2% methanolic KOH soln. The mixture was boiled for 5 min, cooled and neutralised with dil HCl. The solvent was evaporated and the residue dissolved in 25 ml THF filtered and diluted with 40 ml ethyl ether. From the cooled soln 1.74 g (yield 77%) 2-acetylaminocarbazole, m.p. 241–2° was obtained. Found: C, 75.04; H, 5.62. Calc. for $C_{14}H_{12}N_2O$: C, 74.97; H, 5.39%. IR (KBr): 730, 750, 820, 865 (aromatic C–H deform.), 1535, 1670 (amide band in secondary amides), 2940, 3080 (C–H stretch), 3340 (amide N–H stretch), 3415 (pyrrole N–H stretch). NMR (DMSO-d_6): −1.22, s, 1H (N–H pyrrole ring); −0.12, s, 1H (amide N–H); 1.93–2.08, m, 3H and 2.49–2.97, m, 4H (aromatic protons); 7.87, s, 3H (acetyl group).

2-*Acetylamino-9-acetylcarbazole.* 2,9-Diacetylcarbazole oxime acetic ester (3.08 g—0.01 M) and BF_3–acetic acid liquid complex (4.0 ml—0.024 M) were heated for 5 min on a boiling water bath. AcOH (10 ml) was added to the brown melt and the mixture left for 1 hr in the room temp. The product was precipitated with ice cooled 2% ammonium hydroxide. It was collected by filtration and dried in vacuum; 2.55 g crude 2-acetylamino-9-acetylcar-

bazole was obtained; m.p. 216–224°. After two crystallisations from EtoH the pure product (1.60 g—60%) was obtained as colourless prisms m.p. 230–1°.

To a stirred soln of 3.08 g (0.01 M) PCl_5 in 30 ml THF 2.66 g (0.01 M) 2,9-diacetylcarbazole oxime in 20 ml of THF was added. A yellow ppt was formed. The mixture was left for 1 hr in the room temp and then poured onto ice. The ppt was washed with water and dried. After crystallisation from 200 ml EtOH 2.40 g (90%) 2-acetylamino-9-acetylcarbazole was obtained; m.p. 230–1°. Recrystallisation from 25 ml pyridine gave a product melting at 232–3°. Found: 72.33; H, 5.73. Calc. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30%. IR (KBr): 730, 760, 830, 870 (aromatic C–H deform.), 1430, 1705 (tertiary amide bands), 1600, 1665 (secondary amide bands), 3150, 3300, 3460 (N–H stretching vibrations). MS, *m/e*: 267 (9.0), 266 (42.5 M^+), 224 (50.0), 182 (100.0), 167 (2.0), 166 (2.7), 154 (28.0), 140 (2.6), 127 (13.0), 43 (34.0). NMR ($CDCl_3$): −0.30, s, 1H (amide proton); 1.16, m, 1H and 1.65–1.81, m, 1H and 2.03–2.18, m, 3H and 2.60–2.74, m, 2H (aromatic protons): 7.33, s, 3H (9-acetyl group); 7.83, s, 3H (N-acetyl group).

2-Aminocarbazole. To a boiling soln of 2.66 g (0.01 M) 2-acetylamino-9-acetylcarbazole in 50 ml 80% AcOH 5 ml conc HCl was added. The mixture was refluxed for 2.5 hr and poured into 250 ml cold 10% ammonium hydroxide. The ppt was washed with water and dried in vacuum. After two crystallisations from 100 ml toluene 1.42 g (78%) 2-aminocarbazole was obtained as colourless, transparent plates m.p. 245–7° (lit. m.p. 238–9°[2]).

In 50 ml trifluoracetic acid 13.21 g (0.05 M) 2,9-diacetylcarbazole oxime was dissolved. The soln was refluxed for 20 min, cooled and diluted with 50 ml water. Refluxing was continued for 3 hr until the ppt dissolved. The soln was poured into a mixture of 150 ml conc ammonia and 300 ml ice. The crude product was purified as described above; 6.38 g (70%) of 2-aminocarbazole was obtained; m.p. 245–7°. Found: C, 79.19; H, 5.50. Calc. for $C_{12}H_{10}N_2$: C, 79.09; H, 5.35%. IR (KBr): 730, 770, 820, 850 (arom. C–H deform.), 1320 (C–NH_2 stretch), 1620 (NH_2 deform.), 3320, 3400 (N–H stretch). MS, *m/e*: 184 (1.1), 183 (15.0), 182 (100.0, M^+), 181 (27.5), 154 (13.7), 127 (7.7). NMR (Me_2CO-d_6): 0.15, s, broad, 1H (proton on pyrrole nitrogen); 2.19–2.40, m, 2H and 2.68–3.17, m, 3H (4,5,6,7,8-protons on carbazole rings); 3.36, d $J_m = 2.0$ Hz of doublets $J_p = 0.7$ Hz, 1H (1-proton); 3.51, d $J_o = 8.3$ Hz of doublets $J_m = 2.0$ Hz, 1H (3-proton); 5.25–5.85, broad band (protons on amine group).

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