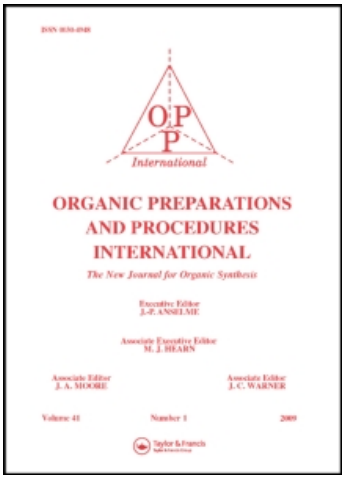

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THE SYNTHESIS OF 3-AMINO-2-DIALKYLAMINOPYRIDINES

A. D. Dunn[a]
[a] Beilstein Institut für Literatur der Organischen Chemie, Frankfurt/Main, GERMANY

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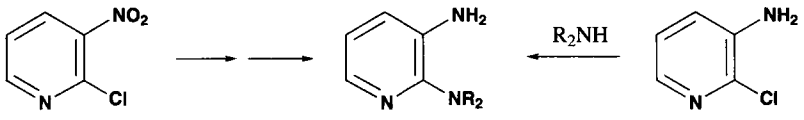
THE SYNTHESIS OF 3-AMINO-2-DIALKYLAMINOPYRIDINES

Submitted by A. D. Dunn
(04/28/98)

Beilstein Institut für Literatur der Organischen Chemie
Carl-Bosch-Haus, Varrentrappstr. 40-42
D60486 Frankfurt/ Main, GERMANY

While compounds of type **3** are readily available from the reaction of amines with 2-halo-3-nitropyridines (1)[1] followed by reduction, the latter compounds (1) are relatively expensive or require considerable time for synthesis and purification. Recently we have found that **3a-c** may be prepared directly from the reaction of secondary cyclic amines with 3-amino-2-chloropyridines (2), which are readily obtained by halogenation of 3-aminopyridines.[2,3] In these reactions, the amine is used in slightly greater than a three-fold excess and acts as reactant, solvent and halogen halide acceptor; this

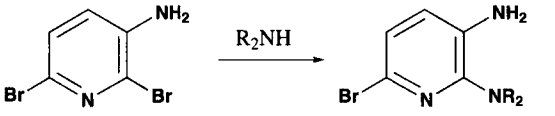
latter use of the amine is possibly unnecessary in some cases since the products from these reactions are strongly basic and may act in this role themselves. Thus when **2** was heated with piperidine, morpholine and N-methylpiperazine the desired diamino derivatives **3a-c** were obtained in 64-73% yield. Compound **3a** (reported as unstable[1]) was converted to its acetyl derivative .



1 **3** **2**

a) $R_2 = (CH_2)_5$ b) $R_2 = O(CH_2CH_2)_2$ c) $R_2 = MeN(CH_2CH_2)_2$

Reaction of the dibromo amine[2] **4** with the same cyclic amines gave exclusively 6-bromo derivatives **5a-c**. No isomeric products arising from displacement of the 6-bromo substituent or disubstituted products could be detected by chromatography (cf. the reaction of **4** with benzyloxy anion[4]). The structures of **5a-c** were readily established by catalytic reduction to **3** and the piperazino derivative **5c** was further characterised as its benzoyl derivative which was isolated directly from the reaction mixture as its hydrochloride. The surprising regiospecificity of the reaction of **4** with amines, (probably due to the relief of steric overcrowding[5] in the transition state), led us to examine the reaction of the 3-amino-2,4,6-tribromopyridine[6] with N-methylpiperazine. Again, only the one product of



4 **5**

a) $R_2 = (CH_2)_5$
b) $R_2 = O(CH_2CH_2)_2$
c) $R_2 = MeN(CH_2CH_2)_2$

substitution at the 2-position could be isolated, although in this instance extensive decomposition precluded any firm conclusions regarding the regiospecificity of this reaction. The structure of this product was unambiguously established by catalytic reduction to **3c**.

EXPERIMENTAL SECTION

All mps were recorded on an Electrothermal Melting Point Apparatus and are uncorrected. Proton NMR spectra were recorded at 90 MHz in $CDCl_3$ solution unless otherwise stated using a Jeol FX 90Q. IR spectra were measured as KBr pellets with a Perkin Elmer 137 and mass spectra at 70 ev on an AEI MS 920S.

Preparation of 3a-c. (a) From 3-Amino-2-chloropyridine (2).- A mixture of **2** (2.00g, 15.56 mmol) and the appropriate amine (3.5 mol equiv.) was heated under gentle reflux for 24 hours (72 hours in the case of piperidine). The reaction mixture was poured into cold 10% aqueous NaOH solution, extracted with ether (x2), dried and the volatiles removed at reduced pressure. The crude products were purified by Kugelrohr distillation and then by recrystallisation from light petroleum (**3b** and **3c**). Compound **3a** (68%) was converted into its acetyl derivative by treatment with acetic anhydride in

pyridine in the usual manner, recrystallised from water containing a little MeOH and obtained as a white solid (64%), mp. 109-110°. ^{1}H NMR: δ 8.55 (dd, H-6), 8.07 (dd and complex, becoming 1H, dd on exchange, H-4 and NH), 7.01 (dd, H-5), 2.95 (d, 2H-2 and 2H-6 piperidine), 2.23 (s, methyl), 1.68 (s, 2H-3, 2H-4 and 2H-5 piperidine). IR: 3225 (NH), 1650 (CO) cm^{-1}. MS (m/z,%): 219 (100).

Anal. Calcd. for $C_{12}H_{17}N_3O$: C, 65.73; H, 7.81; N, 19.16. Found: C, 65.88; H, 7.67; N, 19.23

3b (73%) colorless needles, mp. 127-129°, lit.[1] mp. 127°. ^{1}H NMR (DMSO-d_6): δ 7.56 (dd,H-6), 6.96 (dd, H-4), 6.78 (dd, H-5), 4.83 (broad s, exchangeable NH_2), 3.75 (t, 2H-2 and 2H-6 morpholine), 3.02 (t, 2H-3 and 2H-5 morpholine). IR: 3380, 3220, 3230 cm^{-1} (all NH_2). MS (m/z,%): 179 (71).

Anal. Calcd. for $C_9H_{13}N_3O$: C, 60.32; H, 7.31, N, 23.44. Found: C, 60.28; H, 7.33; N, 23.40

3c (72%) colorless needles darkening on prolonged exposure to air, mp. 110-111° (cf.[7]). ^{1}H NMR: δ 7.80 (dd, H-6), 6.89 (2dd, H-4 and H-5), 3.82 (broad s, exchangeable, NH_2), 3.18 (t, 2H-3 and 2H-5, piperazine), 2.58 (t, 2H-2 and 2H-6 piperazine), 2.36 (s, methyl). IR: 3390, 3280, 3150 cm^{-1} (all NH_2). MS (m/z,%) 192 (13).

Anal. Calcd. for $C_{10}H_{16}N_4$: C, 62.47; H, 8.39; N, 29.14. Found: C, 62.43; H, 8.25; N, 29.26

The dihydrochloride had mp. 229-231° (from EtOH), lit.[8] mp. 234°.

(b) By Reduction of 5a-c. General Procedure.- A mixture of **5a-c** (500 mg), calcium carbonate (1.0g), Pd-C (250 mg, 5%), hydrazine hydrate (98%, 3 mL) and ethanol (60 mL) was heated under reflux with stirring for 2 hours. The mixture was filtered and solvents removed at reduced pressure. The residue was purified by distillation (Kugelrohr) and the product treated as above to yield the acetyl derivative of **3a** (61%), mp. 109°; **3b** (84%), mp. 127-128.5°; **3c** (70%), mp. 109-110°. Mixed melting points with the appropriate compounds in (a) were undepressed.

Preparation of 5a-c. A mixture of **4** (2.0g, 7.94 mmol) was heated under gentle reflux with the appropriate cyclic amine (3.5 mol equiv.) (piperidine 5 hours, morpholine 3 hours and N-methyl-piperazine 1 hour). The reaction mixture was poured into cold 10% NaOH solution, extracted with ether (x2), decolorised with carbon, dried, concentrated and the solid residue recrystallised from an appropriate solvent.

5a (89%), colorless needles, mp. 61-62° (from light petroleum). ^{1}H NMR: δ 6.95 (q, H-4 and H-5), 3.76 (broad s, exchangeable, NH_2), 3.00 (unsym. d, 2H-2 and 2H-6 piperidine), 1.63 (s, 2H-3, 2H-4, 2H-5 piperidine). IR 3420 and 3335 (NH_2) cm^{-1}. MS (m/z,%): 257 (61) and 255 (60).

Anal. Calcd. for $C_{10}H_{14}BrN_3$: C, 46.89; H, 5.51; Br, 31.19; N, 16.40
Found: C, 46.99; H, 5.50; Br, 31.08; N, 16.33.

5b (82%), colorless crystals, mp. 123-125° (from AcOEt and light petroleum). ^{1}H NMR (DMSO-d_6): δ 6.95 (unsym. d, H-4 and H-5), 5.02 (broad s, exchangeable, NH_2), 3.74 (t, 2H-2 and 2H-6 morpholine), 2.95 (t, 2H-3 and 2H-5 morpholine). IR: 3400 and 3325 cm^{-1} (NH_2). MS (m/z,%): 259 (59) and 257 (58).

Anal. Calcd. for $C_9H_{12}BrN_3O$: C, 41.88; H, 4.69; Br, 30.97; N, 16.29
Found: C, 41.86; H, 4.81; Br, 31.06; N, 16.34.

5c (71%), glistening plates, mp. 127-128° (from ether and light petroleum). ^{1}H NMR: δ 6.87 (q, H-4 and H-5), 3.70 (broad s, exchangeable, NH_2), 3.17 (t, 2H-3 and 2H-5 piperazine), 2.55 (t, 2H-2 and 2H-6 piperazine), 2.35 (s, methyl). IR: 3385, 3290 and 3150 (NH_2) cm^{-1}. MS (m/z,%): 272 (55) and 270 (57).

Anal. for $C_{10}H_{15}BrN_4$: C, 44.30; H, 5.58; Br, 29.47; N, 20.66
Found: C, 44.28; H, 5.69; Br, 29.55; N, 20.67

The benzoyl derivative of **5c**, mp. 225-227° (decomp., from aq. EtOH) was obtained in 83% yield by the reaction of **5c** with benzoyl chloride in pyridine solution and isolated as the hydrochloride dihydrate by treatment of the reaction mixture with a little water followed by concentration.

Anal. Calcd. for $C_{17}H_{19}BrN_4O.HCl•2H_2O$: C, 45.60; H, 5.40; Br, 17.87; Cl, 7.92; N, 12.51
Found: C, 45.42; H, 5.56; Br, 17.68; Cl, 8.00; N, 12.73

Reaction of 3-Amino-2,4,6-tribromopyridine with N-Methylpiperazine.- A mixture of 3-amino-2,4,6-tribromopyridine (9.3g, 28.11 mmol) and N-methylpiperazine (ca. 3.7 mol equiv.) was heated under gentle reflux for approximately 45 minutes, when heating was discontinued due to extensive decomposition. The crude product was isolated as described for **5** and recrystallised twice from ether and light petroleum to afford colorless needles of 3-amino-4,6-dibromo-2-(4-methylpiperazin-1-yl)-pyridine in 51% yield, mp. 117.5-118.5°. ^{1}H NMR: δ 7.23 (s, H-5), 4.09 (broad s, exchangeable, NH_2), 3.18 (t, 2H-3 and 2H-5 piperazine), 2.55 (t, 2H-2 and 2H-6 piperazine), 2.35 (s, methyl). IR: 3395, 3300-2400 cm^{-1} (broad) (all NH_2). MS (m/z,%): 352 (23), 350 (47) and 348 (22).

Anal. Calcd. for $C_{10}H_{14}Br_2N_4$: C, 34.31; H, 4.03; Br, 45.65; N, 16.00
Found: C, 34.23; H, 4.00; Br, 45.45; N, 15.89

Catalytic reduction of this compound (700 mg, 2 mmol) as described above gave **3c** (68%), mp. 110-110.5° undepressed on admixture with authentic **3c**.

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the mp. of the hydrochloride, since a sample prepared by the method outlined in this reference had mp., mmp, IR and NMR identical to the samples prepared by us. Its dihydrochloride was also indistinguishable from the dihydrochloride mentioned in this publication.

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TRIMETHYLAMMONIUM CHLOROCHROMATE (TMACC) ADSORBED ON ALUMINA FOR CLEAVAGE OF CARBON-NITROGEN DOUBLE BONDS UNDER NON-AQUEOUS CONDITIONS

Submitted by (04/14/98)

Gui-Sheng Zhang*, De-Hong Yang and Mi-Feng Chen

Department of Chemistry, Henan Normal University
Xinxiang 453002, Henan, P. R. CHINA

Oximes and *p*-nitrophenylhydrazones not only are used for the characterization and purification of carbonyl compounds but also for the protection of carbonyl compounds, as they are generally highly crystalline and stable compounds. The regeneration of carbonyl compounds from their derivatives under mild conditions is an important process in synthetic organic chemistry. The classical methods for the cleavage of oximes to aldehydes and ketones include acid hydrolysis, which is not suitable for acid sensitive compounds.[1] Several oxidative deoximation methods have been developed which have some advantages over the classical hydrolysis method.[2-15] Little attention has been paid to the oxidative cleavage of *p*-nitrophenylhydrazones, and only a few reports are available dealing with the conversion of these derivatives to their corresponding carbonyl compounds.[3a] However, many of these methods do not describe the deoximation of aldoximes[2] or often give low yields[3] or the liberated aldehydes are overoxidized to the carboxylic acid.[4] Moreover, the reagents used are often hazardous or very toxic[3b,4c,5] and expensive.[2b,2c,3b,3h,6] In some case the reagents need to be freshly prepared[2b,2c,3e,3f,7] or the reactions require anaerobic conditions[5b,6a,8] and long reaction times.[3b,4a,4c] We now report that trimethylammonium chlorochromate (Me_3NHCrO_3Cl, TMACC) adsorbed on alumina (TMACC/alumina) is a convenient, non-hazardous and efficient reagent for the oxidative cleavage of carbon-nitrogen double bonds to their parent carbonyl compounds. This reagent is stable and easily prepared by the addition of a weighed amount of alumina to a solution of trimethylammonium chlorochromate in water and rotary evaporation to dryness.

The reaction is performed by stirring of a mixture of the oxidant and oxime or *p*-nitrophenylhydrazone in dichloromethane at a suitable temperature. Our experiments show that oximes