A Convenient Preparation of 3-Methyl-3,4-dihydro-2(1*H*)-quinazolinone

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3-Methyl-3,4-dihydro-2(1*H*)-quinazolinone (**5**) can be prepared in good yield and quality from *o*-nitrobenzyl chloride (**1**). The three-step sequence requires no purification of intermediates or final product.

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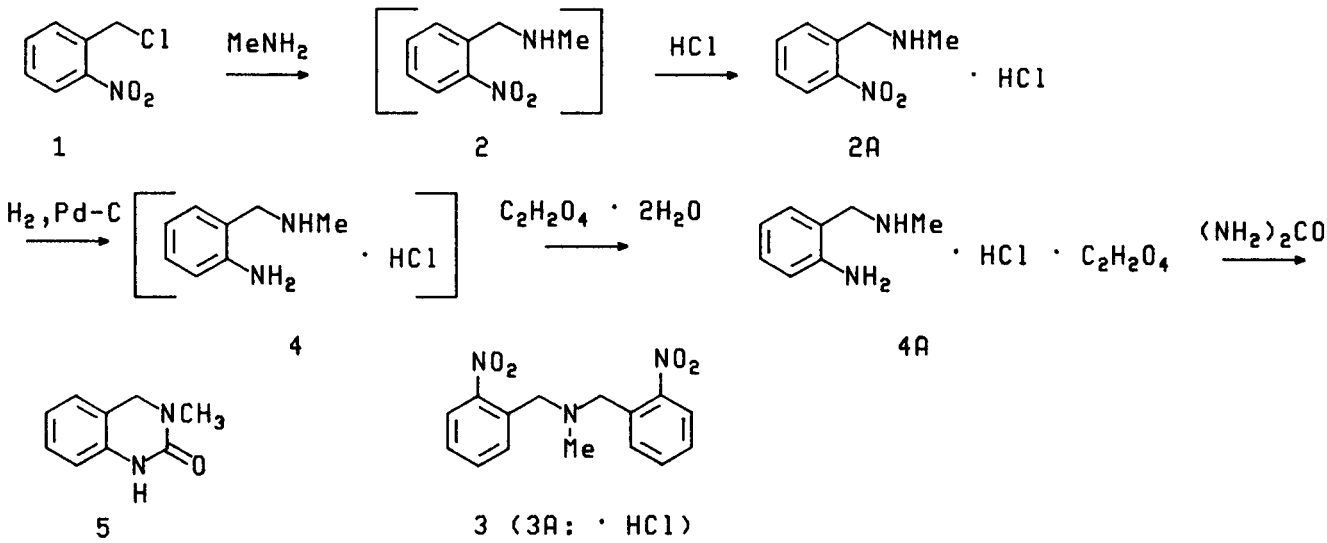
In connection with our cardiotonic program, we required large amounts of 3-methyl-3,4-dihydro-2(1*H*)-quinazolinone (**5**). The literature provides two routes to **5** [1,2]. One suffers from the use of an exotic quinazolidinol starting material [1]. The other poses potential difficulties in scale-up, most notably a diborane reduction and a high temperature fusion, and proved to be erratic in our hands [2]. In this paper we report a reliable and efficient route to **5** which is well-suited to large-scale preparations.

The preferred route to **5** is shown in Scheme I. Alkylation of *o*-nitrobenzyl chloride (**1**) with methylamine (40% aqueous solution) in methanol gives amine **2** [3,4] in 90% yield, contaminated with dialkylation product **3**. Isolation as the hydrochloride **2A** offers a convenient precipitation method. Even a large excess of methylamine doesn't eliminate overalkylation, the isolated hydrochloride **2A** being a 6.3:1 ratio of **2A** to **3A** as determined by hplc. Although **3A** is removable by recrystallization, a convenient means of purification was discovered at the next step and, hence, purification can be delayed.

Hydrogenation of impure **2A** in acetic acid gives diamine salt **4** [2,4], which can be isolated directly from the reaction mixture in 72% yield by crystallization of the oxalate hydrochloride mixed salt **4A**. This isolation technique is especially attractive for several reasons. Not only is oxalic acid selective at precipitating **4A** from solution (and not the triamine obtained by reduction of **3A**) but it also allows elimination of purification of the free base by vacuum distillation, which is difficult on a large scale. Furthermore, **4A** can be used directly in the final step to afford **5** by treatment of **4A** with urea in refluxing water. A homogeneous solution initially, **5** crystallizes out of solution as it is formed and can be simply filtered and dried at reaction's end to afford the desired product in 58% yield. The quality of product thus obtained is excellent and suitable, as we have demonstrated in our laboratories, for further elaboration.

The procedure detailed herein offers a desirable alternative to the current literature routes [1,2] to **5**. In addition to being high yielding, this pathway is especially convenient for large-scale work by providing **5** of high quality without purification of intermediates or final product.

Scheme I



EXPERIMENTAL

Melting points were taken in capillary tubes with a Thomas Hoover melting point apparatus and are uncorrected. Thin layer chromatography was done using E. Merck Silica gel 60 F_{254} pre-coated plates (5 cm by 10 cm, layer thickness 0.25 mm), eluting with ethyl acetate:methanol::85:15 (v/v). Analytical hplc was obtained on a Varian Model 5000 liquid chromatograph using a Micro-Pak MCH-10 column (30 cm by 4 mm). Elution was with 1.5% trifluoroacetic acid in water:methanol::40:60 (v/v) at 2.0 milliliters per minute. Data were processed using a Varian CDS 111L system and recorded using a Varian model 9176 recorder. Infrared spectra were obtained using a Perkin-Elmer Model 299B infrared spectrophotometer. Nuclear magnetic resonance spectra were recorded with a Varian VXR 200 spectrometer (^{1}H: 200 MHz; ^{13}C: 50 MHz) using tetramethylsilane as an internal standard. The proton signals are designated as s = singlet, d = doublet, m = multiplet. Mass spectra were determined on a VG 7070SE spectrometer. The ei spectra were obtained at 70 eV. The fab spectra were obtained using xenon gas bombardment.

2-Nitro-*N*-methylbenzylamine Hydrochloride (**2A**).

With ice bath cooling, a solution of 100.0 g (0.583 mole) of 2-nitrobenzyl chloride [5] in 400 ml of methanol was added in a steady stream over 10 minutes to a solution of 226.0 g (2.91 moles) of 40% methylamine in water [5] in 200 ml of methanol. The reaction mixture was then refluxed for 45 minutes. Tlc analysis showed the reaction to be complete. After cooling, the reaction mixture was concentrated under reduced pressure and the residue partitioned twice between 400 ml of 10% sodium hydroxide (w/w) and ethyl acetate (200 ml and 100 ml). The combined ethyl acetate solution was washed with 400 ml of brine, dried over anhydrous sodium sulfate (90 g) and filtered with 100 ml ethyl acetate wash of the filter cake. With ice bath cooling, the filtrate was poured into 200 ml of ethyl acetate previously saturated with hydrogen chloride gas. Heptane (600 ml) was then added in a steady stream over 10 minutes and the solid that formed was collected, washed with two 125 ml portions of heptane and dried *in vacuo* to constant weight. There was thus obtained 106.2 g (90%) of crude 2-nitro-*N*-methylbenzylamine hydrochloride (**2A**) of suitable purity for the next step, mp 163-171°; hplc: retention time 1.9 minutes with **3A**, retention time 3.9 minutes in a ratio of 6.3:1 (area percent); ir (potassium bromide): 1520 and 1335 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 9.83 (br s, 2H, NH), 8.20 (d, 1H, $J_{CH\text{-}CH}$ = 7.4 Hz, CH-C-NO_2), 7.83 (m, 3H, ArH), 4.43 (s, 2H, $ArCH_2$) and 2.63 ppm (s, 3H, NCH_3); ^{13}C nmr (DMSO-d_6): δ 148.2, 134.2, 132.9, 130.5, 127.2, 125.1, 48.2 and 32.5 ppm. An analytical sample was prepared by recrystallization from methanol:ethyl acetate, mp 175-176° (lit [4] mp 185-187° dec; ms: (fab) m/e 167 (M^+ + 1 of free base).

Anal. Calcd. for $C_8H_{11}ClN_2O_2$: C, 47.42; H, 5.47; N, 13.82. Found: C, 47.62; H, 5.62; N, 13.61.

Concentration of the mother liquors gave crude **3A**. An analytical sample was prepared by recrystallization, with hot filtration of insolubles, from 2-propanol:methanol:water, mp 199-202°; ir (potassium bromide): 1610, 1575, 1525 and 1340 cm^{-1}; ^{1}H nmr (perdeuteriomethanol): δ 8.35 (d, 2H, $J_{CH\text{-}CH}$ = 7.0 Hz, CH-C-NO_2), 7.86 (m, 6H, ArH), and 3.00 ppm (s, 3H, NCH_3) [6]; ^{13}C nmr (perdeuteriomethanol): δ 136.9, 136.0, 133.4, 127.3, 59.6 and 42.1 ppm [7]; ms: (ei) m/e 301 (M^+ of free base).

Anal. Calcd. for $C_{15}H_{16}ClN_3O_4$: C, 53.34; H, 4.77; N, 12.44; Cl, 10.50. Found: C, 52.91; H, 4.75; N, 12.41; Cl, 9.96.

2-Amino-*N*-methylbenzylamine Oxalate Hydrochloride (**4A**).

2-Nitro-*N*-methylbenzylamine hydrochloride (**2A**, 100.0 g, 0.493 mole) was reduced catalytically in two equal batches of 50.0 g (0.247 mole), using 1.2 g of 10% Pd-C [5] in 200 ml of acetic acid in each case. Reduction was complete, at 30 psi, in one hour. The batches were each filtered through a Celite bed and the spent catalyst washed with 10 ml of acetic acid. The filtrates were combined and treated with a solution of 62.2 g (0.493 mole) of oxalic acid dihydrate [5] in 200 ml of methanol. Toluene (600 ml) is then added dropwise over 25 minutes. Crystallization of product commences about halfway through this addition and proceeds as toluene is added. After cooling in an ice bath for 30 minutes, the product was collected, washed with 250 ml of toluene and 250 ml of heptane and dried *in vacuo* to constant weight to yield 92.7 g (72%) of 2-amino-*N*-methylbenzylamine oxalate hydrochloride (**4A**), mp 153-154° dec; hplc: retention times of 1.4 minutes (oxalic acid) and 1.6 minutes (2-amino-*N*-methylbenzylamine); ir (potassium bromide): 2800 and 705 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 9.42 (br s, 6H, NH and OH), 7.16 (m, 4H, ArH), 4.23 (s, 2H, $ArCH_2$) and 2.72 ppm (s, 3H, NCH_3); ^{13}C nmr (DMSO-d_6): δ 161.5, 145.8, 132.2, 130.1, 117.7, 116.8, 116.4, 47.5 and 32.2 ppm; ms: (ei) m/e 136 (M^+ of free base).

Anal. Calcd. for $C_{10}H_{15}ClN_2O_4$: C, 45.72; H, 5.76; N, 10.66; Cl, 13.50. Found: C, 45.67; H, 5.68; N, 10.62; Cl, 13.41.

3-Methyl-3,4-dihydro-2(1*H*)-quinazolinone (**5**).

A solution of 90.0 g (0.398 mole) of 2-amino-*N*-methylbenzylamine oxalate hydrochloride (**4A**) and 27.0 g (0.449 mole) of urea [5] in 450 ml of water was refluxed for 6.5 hours. Precipitation of product begins after 3 hours at reflux. Additional urea (12.6 g, 0.210 mole) is then added and the reaction mixture refluxed for 16.5 hours. The reaction mixture was cooled to 15° in an ice bath and the product was filtered, washed three times with 100 ml of water and dried *in vacuo* at 60° to constant weight to yield 32.1 g (58%) of 3-methyl-3,4-dihydro-2(1*H*)-quinazolinone (**5**), mp 194-202°; hplc: retention time of 4.2 minutes; ir (potassium bromide): 1665 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 9.18 (s, 1H, NH), 6.93 (m, 4H, ArH), 4.36 (s, 2H, CH_2) and 2.83 ppm (s, 3H, NCH_3); ^{13}C nmr (DMSO-d_6): δ 153.7, 137.7, 127.6, 127.2, 125.8, 120.8, 117.7, 113.1, 49.9 and 33.9 ppm. An analytical sample was prepared by recrystallization, with hot filtration of insolubles, from toluene, mp 198-202° (lit [2] mp 198-202°); ms: (ei) m/e 162 (M^+).

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 67.03; H, 6.53; N, 17.06.

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[6] The methylene protons are enveloped by the exchangeable proton peak at 4.9 ppm.

[7] The quaternary carbons are insufficiently relaxed to register signals.