

A Simple Synthesis of Compounds With the Benz[h]imidazo[1,2-c]quinazoline Ring System

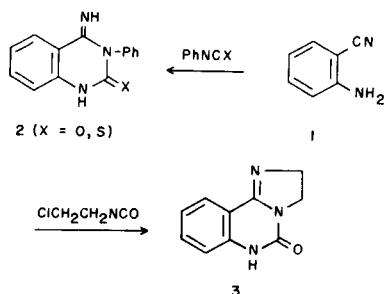
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The ureas obtained from 1-amino-3(or 4)-methyl-2-naphthalenecarbonitrile and 2-chloroethyl isocyanate, or ethyl isocyanatoacetate undergo a double cyclization upon thermal decomposition, or treatment with base to yield compounds with the benz[h]imidazo[1,2-c]quinazoline ring system.

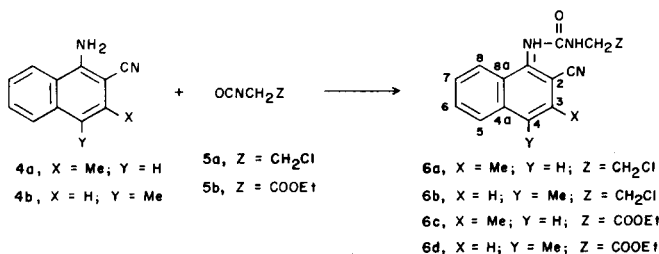
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Aromatic and heteroaromatic 2-aminonitriles undergo readily cyclization reactions which allow convenient preparation of a variety of condensed heterocyclic systems [1]. In particular, the reactions of 2-aminobenzonitrile (**1**) with isocyanates and isothiocyanates yield quinazoline derivatives **2** [2,3], whereas its reactions with reagents containing a leaving group *beta* to an isocyanato group lead conveniently to imidazo[1,2-c]quinazoline derivatives **3** [4,5].



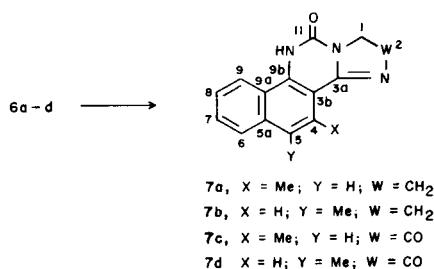
This report describes an extension of the last reaction to a simple and relatively efficient synthesis of compounds with the benz[h]imidazo[1,2-c]quinazoline ring system, which may be considered to possess an 11,13,15-triazasteroidal skeleton. Two representatives of this ring system, 1,2,4,5-tetrahydrobenz[h]imidazo[1,2-c]quinazoline and its 7-methoxy derivative, were prepared earlier in 4-6 steps from the corresponding 2-cyano-1-tetralones and in overall yields of 6-13% [6,7].

Treatment of 1-amino-3-methyl-2-naphthalenecarbonitrile (**4a**), or 1-amino-4-methyl-2-naphthalenecarbonitrile (**4b**) with 2-chloroethyl isocyanate (**5a**), or ethyl isocyanatoacetate (**5b**) yields the expected ureas **6a-d**. These reactions proceed somewhat more slowly and with smaller yields than the corresponding reactions of **1** [4,5], very



likely because of lower nucleophilicity of the amino group in **4a,b**. In connection with this, it has been reported that 1-amino-3-benzyl-2-naphthalenecarbonitrile resists both acylation and diazotization [8].

When they are heated, compounds **6a,b** melt partially and then resolidify, presumably because of their conversion to the hydrochloride salts of the cyclized products **7a,b**, respectively. Indeed, treatment of these solid materials with aqueous ammonia yields the corresponding



free bases **7a,b**, which are also obtained directly when ureas **6a,b** are refluxed with aqueous-ethanolic ammonia. The structures of **7a,b** are supported by their ir, ¹H-nmr, and ¹³C-nmr spectra, as well as by microanalytical data. Upon treatment with base, or thermal decomposition, compounds **6c,d** behave similarly to **6a,b** and yield products **7c,d** respectively. Although we have been unable to obtain correct microanalytical results for the last two compounds (**7c,d**), high resolution, mass spectrometric molecular weight determinations have confirmed their molecular formula.

Thus, tetracyclic compounds **7a-d** possessing an 11,13,15-triazasteroidal skeleton are obtainable from 1-amino-2-naphthalenecarbonitriles and appropriate isocyanates in two steps and overall yields of 40-78%.

EXPERIMENTAL

Melting points were determined in capillaries with a Thomas-Hoover Unimelt apparatus and are uncorrected. Mineral oil mulls were used to record ir spectra on a Perkin-Elmer 337 spectrophotometer. The ¹H and ¹³C-nmr spectra were taken on a Varian FT-80 spectrometer using solutions in hexadeuteriodimethyl sulfoxide (unless otherwise indicated) with

tetramethylsilane as internal standard. The ^{13}C chemical shift assignments were based on the multiplicity (off-resonance decoupled spectra) and Nuclear Overhauser Enhancement of observed signals, calculated values using substituent induced shifts [9], and comparison of spectra of structurally related compounds. The high resolution mass spectra of compounds **7c,d** were recorded at the Midwest Center for Mass Spectrometry, a National Science Foundation Regional Instrumentation Facility (Grant No. CHE 8211164).

Compounds **4a,b** were prepared by cyclization in sulfuric acid of the corresponding ylidenemalononitriles [10], which were obtained by the reaction of malononitrile with 1-phenylpropanone [11] and 2-phenylpropanal following published procedures [12,13].

1-[3-(2-Chloroethyl)ureido]-3-methyl-2-naphthalenecarbonitrile (**6a**). A.

A mixture of aminonitrile **4a** (1.82 g, 0.010 mole) and isocyanate **5a** (1.05 g, 0.010 mole) was heated on a steam bath for 16 hours to yield crude **6a** (2.20 g), which was recrystallized from acetonitrile to give the pure compound (1.54 g, 54%) as colorless crystals, mp 213-215° (partial melting, resolidification).

B.

A mixture of **4a** (0.010 mole), **5a** (0.010 mole), and 5 ml of toluene was heated on a steam bath for 16 hours to form **6a** (2.3 g, 80%, mp 208-210°). Recrystallization from ethyl acetate afforded the pure compound as colorless crystals, mp 214-216° (partial melting, resolidification); ir: 3320, 3260 (N-H), 2210 (C≡N), 1640 (C=O) cm^{-1} ; $^1\text{H-nmr}$: δ 2.55 (s, 3, CH_3), 3.10-3.80 (m, 4, CH_2CH_2), 6.80 (t, 1, NHCH_2), 7.50-8.10 (m, 5, ArH), 8.95 (s, 1, NH); $^{13}\text{C-nmr}$: δ 20.3 (CH_3), 41.7 (NCH_2), 44.1 (CH_2Cl), 116.5 (C≡N), 155.4 (C=O), 140.4 (C-1), 109.6 (C-2), 134.9 (C-3), 126.5 (C-4) [14], 134.8 (C-4a), 128.9 (C-5), 125.7 (C-6) [14], 123.7 (C-7), 127.5 (C-8), 127.8 (C-8a).

Anal. Calcd. for $\text{C}_{15}\text{H}_{14}\text{ClN}_3\text{O}$: C, 62.61; H, 4.90; N, 14.60. Found: C, 62.58; H, 5.08; N, 14.50.

1-[3-(2-Chloroethyl)ureido]-4-methyl-2-naphthalenecarbonitrile (**6b**). A.

When a mixture of aminonitrile **4b** (1.82 g, 0.010 mole) and isocyanate **5a** (1.05 g, 0.010 mole) was heated briefly on a steam bath, an initially formed melt quickly resolidified. This material was allowed to stand at room temperature for 3 days and then was crystallized from methanol to give **6b** (1.66 g, 58%), mp 190-192° (partial melting, resolidification).

B.

A mixture of **4b** (0.010 mole) and **5a** (0.010 mole) was allowed to stand at room temperature for 7 days. The resulting solid material was crushed under anhydrous ethyl ether to yield crude **6b** (2.33 g), recrystallization of which from acetonitrile afforded the pure compound (1.9 g, 66%) as colorless crystals, mp 199-200° (partial melting, resolidification); ir: 3320, 3240 (N-H), 2210 (C≡N), 1640 (C=O) cm^{-1} ; $^1\text{H-nmr}$: δ 2.65 (s, 3, CH_3), 3.30-3.80 (m, 4, CH_2CH_2), 6.8 (t, 1, NHCH_2), 7.56-8.22 (m, 5, ArH), 8.95 (s, 1, NH); $^{13}\text{C-nmr}$: δ 18.4 (CH_3), 41.7 (NCH_2), 44.1 (CH_2Cl), 117.7 (C≡N), 155.6 (C=O), 138.4 (C-1), 107.4 (C-2), 126.4 (C-3), [14], 133.3 (C-4), 134.3 (C-4a), 127.1 (C-5) [14], 124.7 (C-6) [15], 124.4 (C-7) [15], 128.9 (C-8), 129.6 (C-8a).

Anal. Calcd. for $\text{C}_{15}\text{H}_{14}\text{ClN}_3\text{O}$: C, 62.61; H, 4.90; N, 14.60. Found: C, 62.65; H, 5.14; N, 14.40.

1-[3-(Ethoxycarbonylmethyl)ureido]-3-methyl-2-naphthalenecarbonitrile (**6c**). A.

A mixture of aminonitrile **4a** (1.82 g, 0.010 mole) and isocyanate **5b** (1.29 g, 0.010 mole) contained in a closed flask was heated in an oil bath (140-150°) for 0.5 hour. The resulting material was crushed under anhydrous ethyl ether and was recrystallized from acetonitrile to yield **6c** (1.94 g, 62%, mp 223-227°).

B.

A mixture of **4a** (0.010 mole) and **5b** (0.010 mole) was heated on a steam bath for 24 hours to form **6c** (2.53 g, 74%, mp 220-223.5°). The

pure compound was obtained by recrystallization from acetonitrile as colorless crystals, mp 225-227°; ir: 3370, 3250 (N-H), 2220 (C≡N), 1725, 1650 (C=O) cm^{-1} ; $^1\text{H-nmr}$: δ 1.22 (t, 3, CH_2CH_3), 2.60 (s, 3, CH_3), 3.93 (d, 2, NHCH_2), 4.12 (q, 2, CH_2CH_3), 6.86 (t, 1, NHCH_2), 7.0-8.10 (m, 5, ArH), 9.10 (s, 1, NH); $^{13}\text{C-nmr}$: δ 14.0 (CH_2CH_3), 20.3 (CH_3), 41.9 (NCH_2), 60.4 (CH_2CH_3), 116.5 (C≡N), 155.7 (NCON), 170.6 (COO), 140.4 (C-1), 109.8 (C-2), 135.0 (C-3), 126.5 (C-4) [14], 134.9 (C-4a), 129.0 (C-5), 126.0 (C-6) [14], 123.9 (C-7), 127.6 (C-8), 128.0 (C-8a).

Anal. Calcd. for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.52; H, 5.70; N, 13.36.

1-[3-(Ethoxycarbonylmethyl)ureido]-4-methyl-2-naphthalenecarbonitrile (**6d**). A.

A mixture of aminonitrile **4b** (1.82 g, 0.010 mole) and isocyanate **5b** (1.29 g, 0.010 mole) was allowed to stand at room temperature for 3 days and then was crushed under anhydrous ethyl ether to yield **6d** (2.80 g, 90%, mp 218-224°).

B.

When a mixture of **4b** (0.91 g, 5 mmoles) and **5b** (0.65 g, 5 mmoles) was heated briefly on a steam bath, an initially formed melt quickly resolidified. This material was allowed to stand at room temperature for 3 days and then it was crushed under anhydrous ethyl ether to afford **6d** (1.38 g, 89%, mp 221.5-224°). Recrystallization from methanol gave the pure compound as colorless crystals, mp 225-226°; ir: 3340, 3265 (N-H), 2220 (C≡N), 1750, 1640 (C=O) cm^{-1} ; $^1\text{H-nmr}$: δ 1.20 (t, 3, CH_2CH_3), 2.65 (s, 3, CH_3), 3.90 (d, 2, NHCH_2), 4.10 (q, 2, CH_2CH_3), 6.85 (t, 1, NHCH_2), 7.55-8.35 (m, 5, ArH), 9.0 (s, 1, NH); $^{13}\text{C-nmr}$: δ 14.0 (CH_2CH_3), 18.5 (CH_3), 41.9 (NCH_2), 60.4 (CH_2CH_3), 117.7 (C≡N), 155.8 (NCON), 170.6 (COO), 138.4 (C-1), 107.6 (C-2), 126.4 (C-3), 133.7 (C-4), 134.4 (C-4a), 127.2 (C-5), 124.8 (C-6) [14], 124.6 (C-7) [14], 128.9 (C-8), 129.8 (C-8a).

Anal. Calcd. for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_3$: C, 65.58; H, 5.51; N, 13.50. Found: C, 65.67; H, 5.41; N, 13.42.

1,2-Dihydro-4-methylbenz[h]imidazo[1,2-c]quinazolin-11(10H)-one (**7a**). A.

Thermal decomposition (oil bath, 240°) of urea **6a** (1.0 g, 3.5 mmoles) followed by treatment of the resulting solid with aqueous ammonia (1:1, water/concentrated aqueous ammonia) and recrystallization from ethanol gave **7a** (0.22 g, 25%, mp 342-344°).

B.

A mixture of **6a** (0.69 g, 2.4 mmoles), ethanol (10 ml), and concentrated aqueous ammonia (5 ml) was refluxed for 24 hours and then was cooled and diluted with water to yield crude **7a** (0.60 g). The pure compound (0.42 g, 70%) was obtained by recrystallization from ethanol as colorless crystals, mp 342-344°; ir: 1680 (C=O) cm^{-1} ; $^1\text{H-nmr}$: δ 2.92 (s, 3, CH_3), 4.0-5.0 (m, 4, CH_2CH_2), 7.55-8.65 (m, 5, ArH); $^{13}\text{C-nmr}$ (deuteriotrifluoroacetic acid): δ 20.6 (CH_3), 44.1 (C-1), 44.8 (C-2), 148.4 (C-3a), 100.9 (C-3b), 130.1 (C-4), 128.5 (C-5) [14], 137.5 (C-5a), 128.9 (C-6) [14], 133.3 (C-7), 128.7 (C-8) [14], 121.5 (C-9), 119.5 (C-9a), 142.8 (C-9b), 160.2 (C-11).

Anal. Calcd. for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.57; H, 5.43; N, 16.52.

1,2-Dihydro-5-methylbenz[h]imidazo[1,2-c]quinazolin-11(10H)-one (**7b**). A.

Thermal decomposition (oil bath, 200°) of urea **6b** (1.0 g, 3.5 mmoles) followed by treatment of the resulting solid with aqueous ammonia (1:1, water/concentrated aqueous ammonia) and recrystallization from methanol gave **7b** (0.77 g, 73%, mp 276-279°).

B.

A mixture of **6b** (1.0 g, 3.5 mmoles), ethanol (10 ml), and concentrated aqueous ammonia (5 ml) was refluxed for 36 hours and then was cooled and diluted with water to yield **7b** (0.88 g, 100%, mp 275-280°). The pure compound was obtained by recrystallization from methanol as yellow crystals, mp 277.5-279.5°; ir: 1680 (C=O) cm^{-1} ; $^1\text{H-nmr}$ (deuteriotrifluoroacetic acid): δ 2.83 (s, 3, CH_3), 4.20-4.95 (m, 4, CH_2CH_2), 7.60-9.15 (m, 6, ArH, NH); $^{13}\text{C-nmr}$ (deuteriotrifluoroacetic acid): δ 18.0 (CH_3), 44.7

(C-1), 45.2 (C-2), 148.9 (C-3a), 99.7 (C-3b), 117.5 (C-4), 135.7 (C-5), 138.1 (C-5a), 126.0 (C-6), 133.0 (C-7), 129.2 (C-8), 122.4 (C-9), 120.8 (C-9a), 140.3 (C-9b), 160.0 (C-11).

Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.46; H, 5.36; N, 16.49.

4-Methylbenz[h]imidazo[1,2-c]quinazoline-2,11(1*H*,10*H*)-dione (**7c**).

A mixture of urea **6c** (1.0 g, 3 mmoles), ethanol (20 ml), and triethylamine (3 ml) was refluxed for 24 hours to yield crude **7c** (0.61 g). Recrystallization of this material from *N,N*-dimethylformamide gave the pure compound (0.57 g, 67%) as yellow crystals, mp 346-347° dec; ir: 1710, 1675 (C=O) cm^{-1} ; ^{13}C -nmr (deuteriotrifluoroacetic acid): δ 20.5 (CH₃), 169.1 (C-2) [16], 146.7 (C-3a), 101.1 (C-3b), 135.6 (C-4), 129.1 (C-5) [14], 145.4 (C-5a), 129.7 (C-6) [14], 135.7 (C-7), 129.7 (C-8) [14], 122.5 (C-9), 119.3 (C-9a), 139.3 (C-9b), 161.8 (C-11).

Calcd. for M^+ : *m/e* 265.0852. Found: 265.0849.

5-Methylbenz[h]imidazo[1,2-c]quinazoline-2,11(1*H*,10*H*)-dione (**7d**). A.

A mixture of urea **6d** (1.0 g, 3 mmoles), ethanol (15 ml), and triethylamine (1 ml) was refluxed for 3 days to give **7d** (0.72 g, 88%, mp 320-323°).

B.

Thermal decomposition (oil bath, 240°) of **6d** (3 mmoles) gave a crude product, recrystallization of which from ethanol afforded **7d** (0.71 g, 84%) as yellow crystals, mp 322-325°; ir: 1735, 1680 (C=O) cm^{-1} ; ^{13}C -nmr (deuteriotrifluoroacetic acid): δ 17.9 (CH₃), 168.5 (C-2) [16], 145.9 (C-3a), 99.6 (C-3b), 116.9 (C-4), 137.0 (C-5), 144.1 (C-5a), 126.3 (C-6), 135.2 (C-7), 129.8 (C-8), 123.2 (C-9), 120.3 (C-9a), 139.3 (C-9b), 162.4 (C-11).

Calcd. for M^+ : *m/e* 265.0852. Found: 265.0856.

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- [14], [15] For each compound, values with the same superscript may be interchanged.
- [16] The C-1 signal was either very broad, or not detectable, very likely because of deuteration.