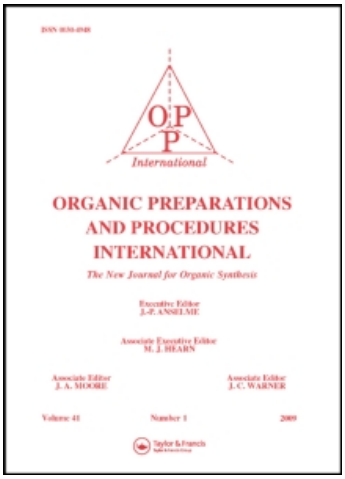

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF FUSED BICYCLO[3.2.2]NONENONES

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To cite this Article Jiang, Xinglong , Prasad, Kapa and Repič, Oljan(2005) 'SYNTHESIS OF FUSED BICYCLO[3.2.2]NONENONES', Organic Preparations and Procedures International, 37: 3, 290 — 293
To link to this Article: DOI: 10.1080/00304940509354963
URL: http://dx.doi.org/10.1080/00304940509354963

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SYNTHESIS OF FUSED BICYCLO[3.2.2]NONENONES

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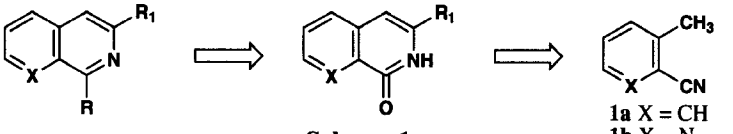
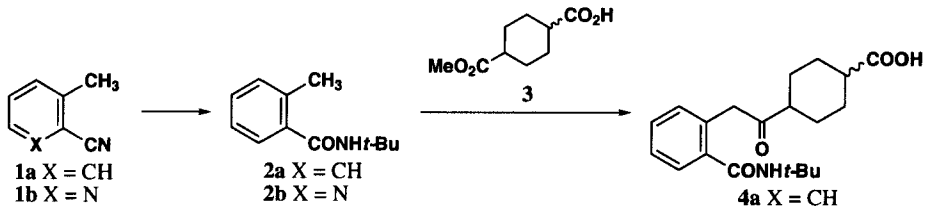
Suitably functionalized heterocyclic compounds are of pharmacological interest. In the process of exploring efficient synthetic routes to 1,3-disubstituted isoquinolines and of the corresponding napthyridine systems (*Scheme 1*), we investigated the functionalization of **1** and **2**, and the results led to an efficient preparation of the title compounds described herein.



1a X = CH
1b X = N

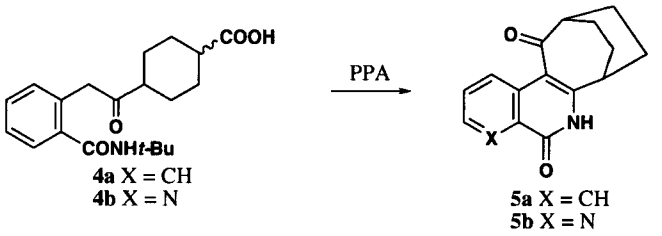
Scheme 1

At the outset, it was felt that the best strategy was to convert the cyano group to the corresponding *t*-butyl amide *via* the Ritter reaction as described by Schumacher *et al.*[1] Reaction of the dianion of **2b**, obtained by treatment with 2.5 equiv. of diisopropylamine/4.54 equiv. of *n*-hexyllithium in THF at –40 to –50°C with **3** at 0°C followed by acidification to pH 5, afforded **4b** in 81% yield as a 85:15 *trans/cis* mixture (*Scheme 2*). The starting *trans:cis* ratio of 40:60 of **3** is immaterial as the final ratio was determined under the highly basic conditions employed for the reaction. Compound **2a** behaved similarly yielding **4a**.



Scheme 2

During an attempt to cyclize these compounds with triflic anhydride (85°C), high melting solids **5a** and **5b** were obtained from **4a** and **4b** in 20 and 30% yield respectively. A change to polyphosphoric acid (PPA) at 140°C afforded these compounds in 70% and 80% yield respectively.[2] Based on MS and ^{1}H NMR, ^{13}C NMR, DEPT135, COSY, HSQC, and HMBC experiments, these compounds were assigned the following fused bicyclic structures.[2]



Efforts to obtain crystals of the free base suitable for single-crystal X-ray study with either **5a** or **5b** were unsuccessful. However, the hydrochloride of **5b** yielded a crystalline solid and a single-crystal X-ray study confirmed the proposed structure **5b**. Further experimentation with **4b** with a *trans/cis* mixture of 1:1 afforded an 80% yield of **5b,** suggesting an equilibration under these conditions with the *cis* form cyclizing to the product. Cyclization of *trans*-4-phenylcyclohexa-necarbox-ylic acid to a benzo[*b*]bicyclo[3.2.2]nonenone using polyphosphoric acid *via* equilibration with *cis*-4-phenylcyclohexanecarboxylic acid was reported earlier in the literature.[3]

Acknowledgment.- We thank Dr. Phillip E. Fanwick of Purdue Chemistry Crystallography Center of Purdue University, West Lafayette, IN for the X-ray measurements.

EXPERIMENTAL SECTION

Mps were determined on an Electrothermal MEL-TEMP 3 digital melting point apparatus and are uncorrected. All reagents and solvents were purchased from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker ARX300 MHz spectrometer in DMSO (d-6). The elemental analyses were performed by Robertson Microlit Labs (Madison, NJ). X-ray measurements for single crystal were performed by Dr. Phillip E. Fanwick at Purdue Chemistry Crystallography Center of Purdue University, West Lafayette (IN). IR spectra were obtained on a Nicolet Magna-IR560 spectrometer.

General Procedure for Compounds 4.- To a solution of 12.6 g (0.12 mole) of diisopropylamine in 190 mL of tetrahydrofuran, cooled to –40 to –50°C was slowly added 64.5 g of *n*-hexyllithium in hexane (34.5% by wt) in 1 L 4-necked flask. The mixture was stirred for 30 min at this temperature. Then a solution of **2b** (9.6 g, 0.05 mole) in tetrahydrofuran (30 mL) while the temperature was maintained at –40 to –50°C. Stirring was continued for another 30 min and the mixture was warmed to 0° to 3°C. Then a solution of **3** (12 g, 0.06 mole) in tetrahydrofuran (30 mL) was added. The mixture was stirred at this temperature for 1.5 h, then cooled to –5 to –2°C and water (125 mL) was added slowly and the temperature was raised to 10-20°C. The two layers were separated and the aqueous layer was extracted with *t*-butyl methyl ether (50 mL). The pH was adjusted by the addition of 6 N HCl (36.5 mL) to the aqueous layer at 10 ± 3°C. The suspension was stirred at 0-5°C for 1 h. The pre-cipitated solid was collected and washed with water (30 g) and dried in the oven at 50°C for 16 h to give 14 g of **4b** (81%), and the product was further purified by recrystallization from EtOAc-hexane (4:6).

4-[[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenyl]acetyl]cyclohexanecarboxylic Acid (4a), colorless solid (85% yield), mp. 178-180°C. ^{1}H NMR (DMSO-d_6): δ 1.35 (s, 9 H), 1.89-1.92 (m, 7 H), 2.13-2.26 (m, 2 H), 2.32-2.44 (m, 1 H), 3.99 (s, 2 H), 7.15 (d, J = 7.14 Hz, 1 H), 7.26 (d, J = 6.42 Hz, 1 H), 7.33 (m , 2 H), 7.73 (br s, 1 H), 12.0 (br s, 1 H); ^{13}C NMR (DMSO-d_6): δ 23.71, 25.96, 26.57, 39.83, 42.83, 46.76, 48.68, 124.34, 125.58, 126.99, 129.40, 131.20, 135.80, 166.78, 174.47, 207.67; IR (KBr): 3290, 2958, 1699, 1621, 1559, 1452, 1365, 1195, 1150, 920, 730 cm^{-1}.

Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.37; H, 7.82; N, 3.80

4-[[2-[[(1,1-Dimethylethyl)amino]carbonyl]3-pyridinyl]acetyl]cyclohexanecarboxylic Acid (4b), colorless solid (81% yield), mp.162-164°C.^{1}H NMR (DMSO-d_6): δ 1.28-1.37 (m, 4 H), 1.32 (s, 9 H), 1.95-1.99 (m, 4 H), 2.00-2.16 (m, 1 H), 2.50-2.52 (m, 1 H), 4.27 (s, 2 H), 7.48 (dd, J = 6.78 Hz, 7.74 Hz, 1 H), 7.65 (d, J = 6.78 Hz, 1 H), 8.03 (brs, 1 H), 8.47 (d, J = 7.74 Hz, 1 H), 12.0 (br s, 1 H); ^{13}C NMR (DMSO-d_6): δ 27.28, 27.90, 28.33, 41.74, 44.78, 48.89, 50.17, 125.42, 131.34, 141.54, 146.32, 148.86, 167.77, 176.98, 209.07; IR (KBr): 3410, 2940, 1699, 1520, 1452, 1364, 1229, 1011, 925, 815, 666 cm^{-1}.

Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.87; H, 7.56; N, 8.09. Found: C, 65.67; H, 7.68; N, 7.96

General Procedure for Compounds 5.- A 100 mL flask was charged with 7.34 mmol of **4** and 30 mL of polyphosphoric acid (PPA). The resulting mixture was heated to 140°C for 2 h, and the

reaction was monitored by HPLC. After **4** had been consumed, the reaction mixture was cooled, quenched by the addition of 70 mL of water, and neutralized with 50% NaOH solution to pH 8. The crude product was collected, washed with water, and was further purified on a silica gel column with 15% methanol in methylene chloride. The desired product was isolated in 70-80% as an off-white solid.

7,8,9,10-Tetrahydro-7,10-ethano-5*H*-cyclohept[*c*]isoquinoline-5,11(6*H*)dione (5a), off-white solid (75% yield), mp. 248-250°C. ^{1}H NMR (DMSO-d_6): δ 1.66-1.96 (m, 8 H), 2.87-2.89 (m, 1 H), 3.28-3.29 (m, 1 H), 7.50 (dd, J = 10 Hz, 10 Hz, 1 H), 7.74 (dd, J = 10 Hz, 10 Hz, 1 H), 8.22 (d, J = 10 Hz, 1 H), 8.87 (d, J = 10 Hz, 1 H), 11.8 (br s, 1 H). ^{13}C NMR (DMSO-d_6): δ 21.0, 21.4, 37.6, 48.4, 110.3, 124.0, 125.1, 126.1, 126.4, 132.9, 135.9, 158.3, 162.1, 204.1; IR (KBr): 2941, 1706, 1645, 1606, 1471, 1370, 1326, 1150, 890, 756, 630 cm^{-1}.

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.95; H, 6.08; N, 5.32

7,8,9,10-Tetrahydro-7,10-ethano-5*H*-cyclohepta[*f*][1,7]naphthyridine-5,11(6*H*)dione (5b), off-white solid (80% yield), mp. >275°C. ^{1}H NMR (DMSO-d_6): δ 1.68-1.98 (m, 8 H), 2.88-2.89 (m, 1 H), 3.32-3.33 (m, 1 H), 7.72 (dd, J = 9.0 Hz, 4.5 Hz, 1 H), 8.76 (dd, J = 4.5 Hz, 1.5 Hz, 1 H), 9.27 (dd, J = 9.0 Hz, 4.5 Hz, 1 H), 12.1 (br s, 1 H). ^{13}C NMR (DMSO-d_6): δ 21.0, 24.1, 37.6, 48.4, 109.2, 127.0, 132.8, 133.5, 139.9, 148.6, 159.2, 160.4, 203.9; IR (KBr): 2939, 1705, 1644, 1587, 1503, 1465, 1398, 1330, 1284, 1254, 880, 823, 683, 634 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.59; H, 5.49; N, 10.95

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2. The hydrochloride of **5b** was prepared by the following procedure: Addition of 6N hydrochloric acid to 1 g of **5b** until solid dissolved. The solution was kept at room temperature for a month. The crystals were collected, washed with isopropyl alcohol and dried in air for 24 h.

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