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Synthesis of Novel Tetrahydrobenzazepinones

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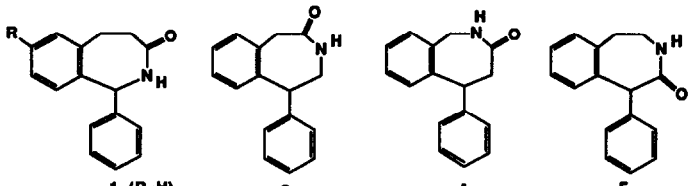
Abstract: *The synthesis of novel tetrahydrobenzazepinones 1, 2, and 3 is described, as well as an improved synthesis of 4. The palladium catalyzed arylation approach to 1, 2, and 4 allows facile entry to benzazepinones lacking electron donating substituents on the benzo ring.*

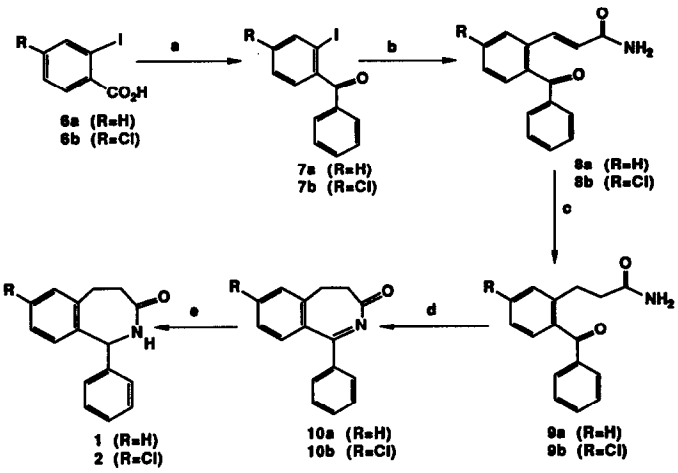
Considerable recent interest has been generated in substituted phenyl benzazepines as medicinal agents for the treatment of psychosis, ischemic CNS injury, and as specific ligands for serotonin and dopamine receptor subtypes.[1-3] We have also had an interest in substituted benzazepines, and required multigram quantities of isomeric benzazepinones **1-5** as intermediates. A literature search revealed that only lactams **4** and **5** are known.[4,5] We wish to



report here the first syntheses of systems **1-3** and an improved synthesis of lactam **4**.

Scheme 1 details the preparation of systems **1** and **2**. Conventional Pd(0) catalyzed arylations of iodobenzophenones **7** with acrylamide gave only trace amounts of **8**. The recently reported methodology for introduction of an acrylamide moiety, however, furnished the cinnamamides in good yield.[6,7] Hydrogenation of **8** in 1,4-dioxane avoided the concommitant ketone reduction observed in ethanol solvent to provide key ketoamides **9** in high yield. Reductive cyclization led to crude dihydrobenzazepinones **10**, which were carried on directly to the targets *via* routine catalytic hydrogenation.[8]

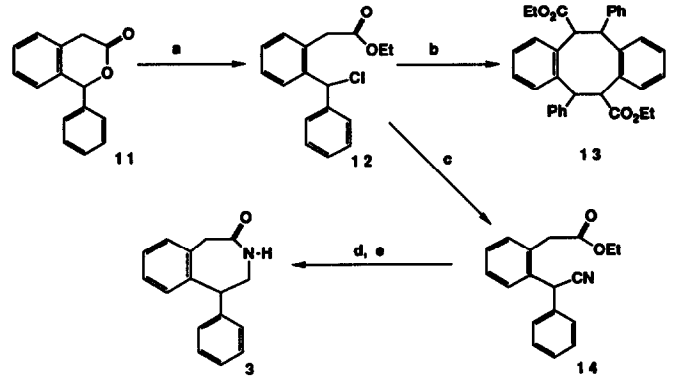
The synthesis of the novel lactam **3** is shown in Scheme 2. Lactone **11** was first reacted with ethanolic HCl to give **12** in high yield.[9] Treatment of **12** with NaCN in acetone, however, led not to desired species **14**, but to dimer **13**, assigned on the basis of MS and ^{13}C/DEPT data. Introduction of the cyano group under non-nucleophilic conditions was thus employed, providing



a) PCl_5, C_6H_6, $AlCl_3$, 1,2-dichlororoethane, 91%(7a); 82%(7b) b) acrylamide, 5 mol % $Pd(OAc)_2$, NaOAc, DMF, H_2O, 16h 125°, 81%(8a); 84%(8b) c) H_2, 10% Pd/C, 1,4-dioxane, 88%(9a); 89%(9b) d) p-TSA, $PhCH_3$, -H_2O 48h e) H_2, 10% Pd/C, EtOH, 50%(1 from 9a); 43%(2 from 9b)

Scheme 1

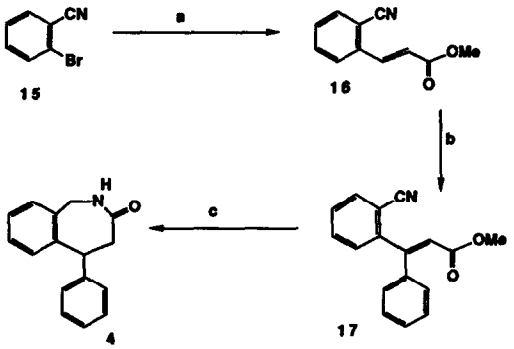
cyanoester **14** in high yield.[10] This species was then reduced to the crude aminoester with $NaBH_4/CF_3CO_2H$ and thermally cyclized to target lactam **3** in modest yield.[11,12]



a) anhyd. ethanolic HCl, 25°, 99% b) NaCN, acetone reflux, 90% c) TMSCN, cat. $SnCl_4$, CH_2Cl_2, 30 min., 91% d) 10eq. $NaBH_4/CF_3CO_2H$, 5h 25° e) $PhCH_3$ 8h reflux, then chrom. (SiO_2, EtOAc), 35% from 14

Scheme 2

A convenient synthesis of lactam **4** with a greater overall yield than the original procedure was developed, as shown in Scheme 3.[4] A single step conversion of nitrile **15** to **17** was generally unsuccessful using a wide variety of Pd(0) catalyzed arylation protocols, and the use of 2-iodobenzonitrile did not enhance yields.[13] Two successive arylations were thus employed,



a) methyl acrylate, 3 mol % $Pd(OAc)_2$, $NaHCO_3$, $(n\text{-}Bu)_4NCl$, DMF, 24h 90°, 97%
b) PhI, 1 mol % $Pd(OAc)_2$, TEA, CH_3CN, 48h 100° bomb, 67% c) H_2, 10% Pd/C, PtO_2, 5:1 EtOH:$(iPr)_2NH$ 50°, vent, then 2h 68°, 75%

Scheme 3

using first 2-bromobenzonitrile and second iodobenzene, furnishing phenylcinnamate **17** in 65% overall yield. Reductive cyclization in (5:1 ethanol:$(iPr)_2NH$) led to target lactam **4** in good yield, avoiding the arene reduction observed in ethanol solvent.

In summary, the preparation of several novel tetrahydrobenzazepinones has been described. The clear advantage of Pd(0) assisted C-C bond formation shown for systems **1**, **2**, and **4** is the accelerated rate of oxidative addition with electron deficient arylhalides.[14] This allows the facile formation of new ring systems which are inaccessible *via* classical electrophilic aromatic substitution methodologies.

REFERENCES AND FOOTNOTES

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4. Croisier, D.; Rodriquez, L.; U.S.Pat. 4,080,449 , **1978**. Physical data for lactam **4**: solid, m.p. 180-181°(Lit. 181-182°); **^{1}H NMR** (300 MHz, C_6D_6)δ: 7.10-6.94 (m, 4H), 6.85-6.79 (m, 4H), 6.68-6.59 (m, 2H), 4.20 (dd, J=9.8, 4.7 Hz, 1H), 3.85 (dd, J=16.0, 6.1 Hz, 1H), 3.60 (dd, J=16.0, 5.2 Hz, 1H), 2.82 (dd, J=14.3, 9.9 Hz, 1H), 2.75 (dd, J=14.3, 4.7 Hz, 1H). **^{13}C NMR**

(75.5 MHz, $CDCl_3$)δ: 174.87(s), 145.05(s), 140.86(s), 135.79(s), 131.73(d), 128.65(d), 128.11(d), 128.04(d), 126.66(d), 126.47(d), 46.28(t), 44.83(d), 41.50(t). **IR** (KBr) cm^{-1}: 3207, 3078, 2935, 2886, 1677, 1488, 1415, 1404, 775, 756, 705. **MS** (CH_4 CI, 70eV) m/e: 238(MH^+), 192, 179, 178, 117. **Calc'd** for $C_{16}H_{15}NO$: 80.98%C, 6.37%H, 5.90%N; Found: 81.06%C, 6.30%H, 5.84%N.

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8. Physical data for lactam **1**: solid, m.p. 166-167°. **^{1}H NMR** (300 MHz, $CDCl_3$)δ: 7.54-7.05 (m, 9H), 5.59 (d, J=6.2Hz, 1H), 2.68-2.55 (m, 4H). **^{13}C NMR** (75.5 MHz, $CDCl_3$)δ: 175.39(s), 141.72(s), 139.65(s), 138.82(s), 129.83(d) 129.37(d), 128.68(d), 128.43(d), 127.47(d), 126.57(d), 126.46(d), 59.93(d), 35.30(t), 28.24(t). **IR** (KBr)cm^{-1}: 3278, 3053, 2938, 1646, 1490, 1428, 1404, 1337, 759, 737, 698. **MS** (CH_4 CI, 70eV)m/e: 238(MH^+), 192, 178, 160, 117, 106. **Calc'd** for $C_{16}H_{15}NO$: 80.98%C, 6.37%H, 5.90%N; Found: 80.85%C, 6.36%H, 5.80%N. Physical data for lactam **2**: solid, m.p. 204-205°. **^{1}H NMR** (300 MHz, $CDCl_3$)δ: 7.40-7.15 (m, 7H), 6.93 (d, J=8.1 Hz, 1H), 6.73 (d, J=4.9Hz, 1H), 2.84 (m, 2H), 2.67 (m, 2H). **^{13}C NMR** (75.5 MHz, $CDCl_3$)δ: 174.56(s), 141.46(s), 140.97(s), 137.43(s), 134.26(s), 130.51(d), 129.75(d), 128.87(d), 127.83(d), 126.57(d), 126.46(d), 59.26(d), 34.96(t), 28.15(t). **IR** (KBr)cm^{-1}: 3188, 3052, 1666, 1597, 1404, 874, 727. **MS** (CH_4 CI, 70eV)m/e: 272(MH^+), 271, 194, 151. **Calc'd** for $C_{16}H_{14}ClNO$: 70.72%C, 5.19%H, 5.15%N; Found: 70.69%C, 5.13%H, 4.93%N.
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12. Physical data for lactam **3**: solid, m.p. 154-155°. **^{1}H NMR** (300 MHz, $CDCl_3$)δ: 7.31-6.95 (m, 8H), 6.91 (d, J=7.0 Hz, 1H), 6.72 (t, J=5.1 Hz, 1H), 4.38 (dd, J=8.2, 4.3Hz, 1H), 4.04 (d, J=14.7 Hz, 1H), 3.80 (d, J=14.9 Hz, 1H), 3.76 (ddd, J=15.4, 6.6, 4.5 Hz, 1H), 3.62 (ddd, J=15.0, 8.3, 6.2 Hz, 1H). **^{13}C NMR** (75.5 MHz, $CDCl_3$)δ: 174.94(s), 144.00(s), 139.18(s), 132.56(d), 131.19(s), 128.77(d), 128.61(d), 127.30(d), 126.90(d), 126.80(d), 126.73(d), 50.11(d), 46.98(t), 42.64(t). **IR** (KBr)cm^{-1}: 3211, 3085, 1669, 1475, 1402, 1353, 1154, 1123, 770, 747, 697, 590, 490. **MS** (CH_4 CI, 70eV)m/e: 238(MH^+), 208, 180, 165, 120, 115. **Calc'd** for $C_{16}H_{15}NO$: 80.98%C, 6.37%H, 5.90%N. Found: 80.59%C, 6.30%H, 5.69%N.
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