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Preparation of 1,5-Methano-2,3,4,5-tetrahydro-1*H*-3-benzazepine via Pd-Catalyzed Cyclization

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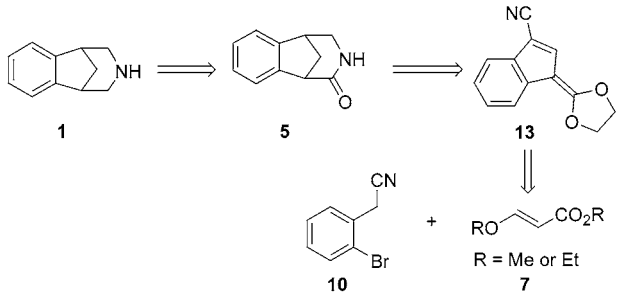
ABSTRACT



A new approach to prepare 1,5-methano-2,3,4,5-tetrahydro-1*H*-3-benzanepine (1) is discussed. This strategy utilized a tandem Michael addition and Pd-catalyzed cyclization to afford cyanobenzofulvene acetal 13. This indene intermediate (13) was subjected to hydrogenolysis to provide an amino ester (12) and was cyclized with base to afford lactam 5. The lactam (5) was reduced with borane to afford the desired benzazepine (1).

Recently, we required a production scale route to 1,5-methano-2,3,4,5-tetrahydro-1*H*-3-benzanepine, **1**, that used commodity chemicals as raw materials and exploited crystalline intermediates. Our previous strategies (Figure 1) used

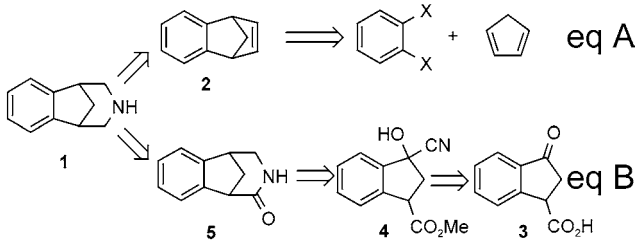


Figure 1. Previous strategies used to prepare benzazepine **1**.

either oxidation of benzonorbornadiene (**2**) followed by reductive amination (eq A)[1] or a cyanohydrin homologation route from 3-carboxyindanone (**3**) (eq B).[2] While the benzonorbornadiene route (eq A) was reliably employed as a first-generation synthesis on scale, it suffered from the use of osmium, a toxic heavy metal, which must be removed from the product. In addition, despite advances in benzyne-mediated protocols for the formation of benzonorbornadiene,[3] cracking of cyclopentadiene dimer and storage of this reactive material proved to be challenging for us on kilogram scale.[4] The clear disadvantage of the carboxyindanone route (eq B) was the need of cyanide to access **4**, a key intermediate.

(1) A modified approach to Mazzochi and Stahly's strategy (Mazzocchi, P. H.; Stahly, B. C. *J. Med. Chem.* **1979**, *22*, 455) was used to prepare **1** that involved osmylation of **2**, $NaIO_4$ cleavage to a dialdehyde, and reductive amination to close the benzazepine ring; see: Brooks, P. R.; Caron, S.; Coe, J. W.; Ng, K. K.; Singer, R. A.; Vasquez, E.; Vetelino, M. G.; Watson, H. H.; Whritenour, D. C.; Wirtz, M. C. *Synthesis*, in press. For a related example, see: Coe, J. *Org. Lett.* **2000**, *2*, 4205.

(2) For details of the cyanohydrin route, see: (a) Coe, J. W.; Brooks, P. R. U.S. Patent 6,605,610, 2003. (b) O'Donnell, C. J.; Singer, R. A.; Brubaker, J. A.; McKinley, J. D. *J. Org. Chem.*, submitted for publication.

(3) Coe, J. W.; Wirtz, M. C.; Bashore, C. G.; Candler, J. *Org. Lett.* **2004**, *6*, 1589.

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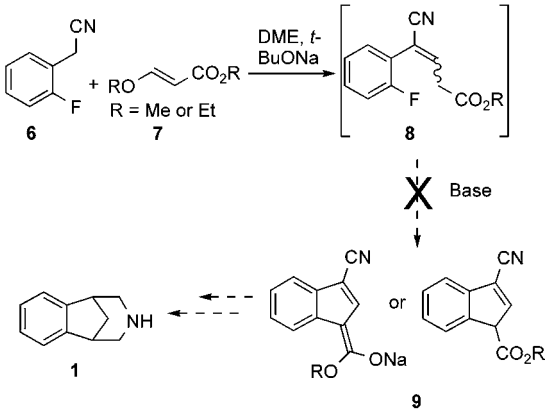
Our attention was turned to nucleophilic aromatic substitution strategies for indane annulation (Scheme 1). Our goal

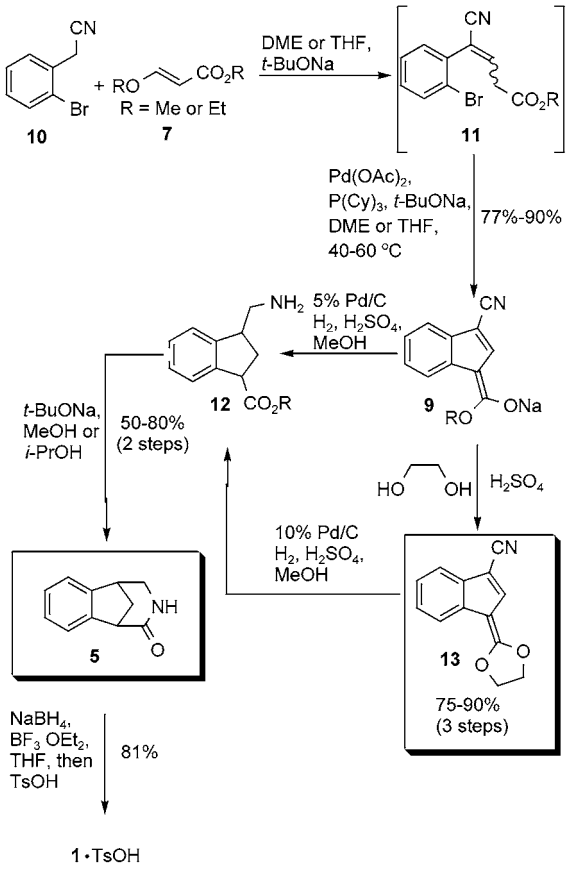
Scheme 1. Unsuccessful SN_{Ar} Strategy To Prepare **1**



was to intercept an intermediate such as **4** or **5** from the cyanohydrin route that we would be able to convert to **1**. While coupling of **6** and **7** proceeded efficiently to provide **8**, all attempts to form **9** failed. We suspect that our inability to close the ring results from poor trajectory for SN_{Ar} attack and from the ability of the allylic anion to delocalize and therefore deactivate the aromatic ring.

In an attempt to remedy the situation, reactions were screened with Pd catalysts using 2-bromophenylacetonitrile (**10**) and acrylates (**7**) (Scheme 2). Our hope was that a Pd-catalyzed reaction pathway would provide a more favorable ring closure. As such, through a judicious choice of the phosphine ligand, the Pd would undergo oxidative addition to the electron rich arene despite the conjugated allylic anion and permit ring closure to the desired indene. Analogous to our SN_{Ar} strategy, 2-bromophenylacetonitrile (**10**) was coupled with acrylate **7** (R = Me) in DME or THF using *t*-BuONa as base to afford **11** as a mixture of olefin isomers (Scheme 2). When heating **11** with *t*-BuONa, catalytic triarylphosphines (such as 0.1 equiv PPh_3, or DPPF) and various Pd sources (0.05 equiv), no reaction occurred. However, when switching to more electron rich dialkylarylphosphines (such as 2- dicyclohexyl-biphenylphosphines),[5] cyclization to indene **9** proceeded efficiently.[6] Ultimately, we found that the coupling and Pd-catalyzed

Scheme 2. Pd-Catalyzed Cyclization Route to **1**



cyclization of **10** and **7** could be conducted in one pot for a tandem process to afford **9**. To improve efficiency, methoxy acrylate (**7**, R = Me) was switched to the ethoxy derivative (**7**, R = Et) to avoid generation of methoxide, which inhibited the Pd catalyst. This switch reduced the Pd catalyst loading from 5−10 mol % Pd to 0.5−2 mol % Pd. We suspect that methanol or methoxide is capable of promoting formation of bridged-dimeric Pd complexes in this system, impeding catalysis.[7] We were also pleased to find that the relatively expensive dialkylbiarylphosphines could be replaced with readily available tri-*tert*-butylphosphine or tricyclohexylphosphine. Tricyclohexylphosphine was typically used since it was a crystalline solid and easy to handle.[8] Isolation of **9** was not as trivial as we had hoped, but we found that the sodium salt of **9** could be isolated despite its poor crystallinity.[9] To address this issue, it was eventually recognized that **9** could be converted to a more crystalline cyanoben-

(4) Cracking of cyclopentadiene dimer required usage of a high-temperature oil bath and a dry ice cooled condenser. While this could be accomplished in conventional glassware, our Pilot Plant could not accommodate this operation.

(5) We found that any dialkylaryl phosphine would provide a catalyst capable of catalyzing the cyclization, including commercially available dicyclohexylphenylphosphine.

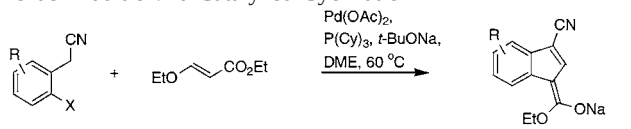
(6) For related applications of Pd-catalyzed arylations α to carbonyls, see: (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108. (b) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000,** *122*, 1360. (c) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am Chem. Soc.* **2003**, *125*, 11818. (d) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382. (e) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (f) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (g) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740.

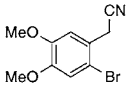
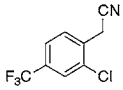
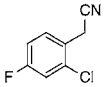
(7) It has been shown that hydroxide bridged-dimeric Pd complexes can form and impede catalysis; see: Hartwig, J. F. *Synlett* **1997**, *4*, 329.

(8) We did observe less efficient reactions with tricyclohexylphosphine which had been exposed to the air, due to oxidation of the phosphine. For best results on scale we used new containers of the phosphine to minimize opportunity for air oxidation prior to use. For improved reliability, we found that dicyclohexylphenylphosphine was less susceptible to air oxidation and provided a more stable catalyst (as did Buchwald dialkylbiarylphosphine ligands).

(9) The sodium salt of **9** was crystallized from acetonitrile and toluene and isolated as a single olefin isomer. The structure was elucidated by single-crystal X-ray diffraction (July 25, 2000). Typically, **9** was isolated as a foamy solid or a dark oil and was challenging to crystallize from solution.

Table 1. Additional Substrates Screened in the Tandem Michael Addition/Pd-Catalyzed Cyclization



entry	substrate	$Pd(OAc)_2$ (mol%)	time (hours)	yield (%)
1		10	22	75
2		5	16	85
3		5	22	67
4		10	16	82
5		10	17	74

zofulvene intermediate (**13**) in situ to facilitate isolation. This was accomplished by adding ethylene glycol and sulfuric acid (as a dehydrating agent) to the reaction mixture. As product **13** formed, it precipitated from solution. After prolonged stirring of the reaction mixture at room temperature (12−48 h), **13** was isolated as a solid by filtration in good yield (75−90%).[10] Attempting to promote the formation of **13** with heat led to inadvertent decarboxylation as a side reaction. Because **13** had much greater crystallinity than **9,** it was preferable to isolate **13** to efficiently purge phosphines and other inhibitors of the subsequent hydrogenation.

Analogous to the cyanohydrin route,[2] **9** or **13** was reduced via Pd-catalyzed hydrogenolysis to **12**. After filtration to remove Pd, **12** was then treated with *t*-BuONa and cyclized to lactam **5** with heating in 50−75% yield.[2] The modest yield for the lactam cyclization was primarily a result of saponification of **12**. Once saponified, the amino acid of **12** was not observed to cyclize to **5** under any reaction conditions examined. In an effort to minimize hydrolysis, the solvent was switched from methanol to 2-propanol so that water could be removed by azeotropic distillation prior to adding the base for lactam cyclization. In practice, distilling off the water with 2-propanol improved the yield (70−80%), but the reaction became more sensitive to the level of water for promoting saponification of **12**.[11] In general, we observed that the more polar solvents slowed the competing rate of ester hydrolysis (ethylene glycol had the slowest rate of saponification, while *n*-butanol promoted more rapid hydrolysis). To convert lactam **5** to the desired benzazepine (**1**), **5** was reduced with borane (generated in situ).[2] Benzazepine **1** was decomplexed from the boron by heating with methanol and HCl, and following aqueous workup, was isolated as the tosylate salt in 81% yield.

For an evaluation of substrate scope of the tandem Michael addition and Pd-catalyzed cyclization, reactions were carried out with readily available 2-halophenylacetonitrile derivatives (Table 1). In general, the reactions were conducted in DME at 60 °C.[12] For the aryl chlorides, typically a loading of 10 mol % Pd was used. Comparable yields were realized for

(10) A typical procedure for conducting the tandem Michael addition/Pd cyclization/ketene acetal formation is as follows: A solution of tricyclohexylphosphine (536 mg, 1.91 mmol) in THF (25 mL) was charged with palladium (II) acetate (287 mg, 1.27 mmol) under nitrogen. After 15−60 minutes the reaction mixture was cooled to 0 °C and charged with *t*-BuONa (31.6 g, 319 mmol). After 5 min, a solution of 2-bromophenylacetonitrile (**10**) (25.0 g, 128 mmol) and *β*-ethoxyacrylic acid ethyl ester (**7**) (18.4 mL, 128 mmol) in THF (75 mL) was added dropwise over 15 min. The reaction was heated to 60 °C. After 2 h 30 min, the reaction mixture was cooled to room temperature and charged with ethylene glycol (200 mL) over 5 min and then charged with sulfuric acid (18.8 M, 36 mL) added dropwise over 15 min. After 15 h the reaction was diluted with water (90 mL) and a solid product was isolated by filtration. The solid was dried under vacuum affording **13** (21.6 g, 102 mmol, 80%) as a light tan solid. The crude material was slurried in 2-propanol (50 mL) for 2 h, filtered and dried under vacuum affording **13** (20.8 g, 98.5 mmol, 77%) as a light tan solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (s, 1H), 7.74 (d, 1H, J = 7.9 Hz), 7.50 (d, 1H, J = 7.1 Hz), 7.22 (m, 2H), 4.97 (t, 2H, J = 7.8 Hz), 4.85 (t, 2H, J = 7.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) 167.4, 136.7, 135.7, 133.1, 124.7, 123.9, 121.1, 119.4, 118.1, 97.8, 92.7, 71.1, 69.9; mp 227−229 °C dec.

(11) For more efficient azeoptropic removal of water, *n*-propanol could be used.

(12) Representative procedure for Pd-catalyzed cyclization, entry 1 of Table 1: A solution of tricyclohexylphosphine (204 mg, 0.720 mmol) in ethylene glycol dimethyl ether (10 mL) under nitrogen was charged with palladium (II) acetate (148 mg, 0.660 mmol). The reaction was stirred at room temperature until the solution was homogeneous (approximately 25 min), cooled to 0 °C, and charged with *t*-BuONa (1.63 g, 16.6 mmol). After 10 min, a solution of 2-chlorophenylacetonitrile (1.00 g, 6.60 mmol) and ethyl 3-trans-ethoxyacrylate (**7**) (953 μL, 6.60 mmol) in ethylene glycol dimethyl ether (10 mL) was added dropwise over 5 min. Upon complete addition, the reaction was warmed to room temperature and then heated to 60 °C for 22 h. The reaction was cooled to room temperature then diluted with methyl *tert*-butyl ether (30 mL) and poured into aqueous potassium dihydrogenphosphate (0.25 M, 40 mL), pH = 7. The aqueous layer was separated then saturated by addition of solid sodium chloride and extracted with ethyl acetate (50 mL). The organic layer was separated and washed with aqueous saturated sodium chloride (2 × 30 mL), dried over sodium sulfate, filtered, and concentrated in vacuo affording 3-(ethoxyhydroxymethylene)-3*H*-indene-1-carbonitrile, sodium salt (**9**), as a foamy orange solid (1.06 g, 5.0 mmol, 75%): mp 150−152 °C; ^{1}H NMR (400 MHz, CD_3CN) δ 8.04 (d, 1H, J = 6.0 Hz), 7.58 (s, 1H), 7.43 (d, 1H, J = 6.0 Hz), 6.98−6.91 (m, 2H), 4.25 (q, 2H, J = 7.2 Hz), 1.35 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, CD_3CN) δ 166.7, 135.5, 132.3, 131.3, 122.8, 120.5, 119.0, 118.4, 117.7, 103.3, 79.2, 58.2, 14.6; IR (ATR, neat) 2176, 1597, 1465, 1257, 1195, 1068, 1029, 754 cm^{-1}. Data for entry 2, Table 1: ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.64 (s, 1H), 7.46 (s, 1H), 6.99 (s, 1H), 4.56 (q, 2H, J = 7.1), 3.86 (s, 6H), 1.38 (t, 3H, J = 7.05); ^{13}C NMR (100 MHz, MeOH-d_4) δ 167.8, 145.0, 144.5, 130.2, 129.4, 126.4, 123.3, 112.5, 104.0, 102.6, 100.7, 79.0, 58.4, 55.6, 14.1; IR (ATR, neat) 3499, 2164, 1629, 1482, 1449, 1282, 1207, 1157, 1124, 1076, 845, 769 cm^{-1}. Data for entry 3, Table 1: mp 152−156 °C.; ^{1}HNMR (400 MHz, CD_3OD) δ 8.31 (s, 1H), 7.70 (s, 1H), 7.49 (d, 1H, J = 7.9 Hz), 7.11 (d, 1H, J = 7.9 Hz), 4.28 (q, 2H, J = 7.1 Hz), 1.39 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 167.6, 137.4, 133.4, 131.0, 126.7 (q, J = 201 Hz), 122.1, 120.5 (q, J = 22.7 Hz), 117.3 (q, J = 3.3 Hz), 117.1, 114.3 (q, J = 2.5 Hz), 104.2, 79.6, 58.7, 14.0; IR (ATR, neat) 2986, 2943, 2180, 1606, 1465, 1326, 1284, 1197, 1156, 1105, 1076, 1027, 900, 853, 814, 778, 753, 708, 645 cm^{-1}. Data for entry 4, Table 1: mp 250−260 °C; ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.63 (dd, 1H, J = 2.5, 11.4 Hz), 7.60 (s, 1H), 7.32 (dd, 1H, J = 5.2, 8.5 Hz), 6.67 (dt, 1H, J = 2.5, 7.1 Hz), 4.26 (q, 2H, J = 7.1 Hz), 1.38 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, MeOH-d_4) 168.1, 159.2, 132.65, 131.92, 122.92, 117.7, 112.5, 106.4, 105.2, 102.8, 79.8, 58.7, 14.1; IR (ATR, neat) 2179, 1602, 1558, 1465, 1250, 1196, 1108, 1061, 1026, 775 cm^{-1}. Data for entry 5, Table 1: ^{1}H NMR (400 MHz, CD_3CN) δ 7.81

all the substrates. Reaction times did vary for the Michael addition/elimination step, since the addition was slower with arenes possessing withdrawing groups.[13]

In summary, we developed an alternative route to **1** using a tandem Michael addition and Pd-catalyzed indene cyclization. To improve the crystallinity of the indene cyclization product and facilitate the workup, a cyanobenzofulvene intermediate (**13**) was formed in situ. In addition, this route offered the crystalline lactam (**5**) as another isolated intermediate. Overall, this strategy offers a novel alternative to preparing substituted indanes and indenes.

Acknowledgment. We thank Mike Vetelino, Bob Handfield, Jim McGarry, and Tim Watson for demonstration of the Pd chemistry route (Scheme 2) on scale. We also thank Jon Bordner and Ivan Samardjiev for carrying out the X-ray crystallography study on **9**.

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(d, 1H, $J = 7.9$ Hz), 7.46 (s, 1H), 6.82 (q, 1H, $J = 2.5$ Hz), 6.52 (dd, 1H, $J = 7.5$, 11.2 Hz), 4.20 (q, 2H, $J = 7.5$ Hz), 1.32 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, d_4-MeOH) 167.8, 156.3, 135.8, 132.8, 123.5, 122.3, 119.3, 116.2, 104.0, 102.8, 75.5, 58.6, 14.0; IR (ATR, neat) 2194, 1628, 1546, 1484, 1462, 1238, 1219, 1095, 1019, 925, 788, 737 cm^{-1}.

(13) Michael additions required several hours at room temperature with substrates possessing withdrawing groups as opposed to minutes with the parent compound. Once the addition between the acrylate and arylacetonitrile was complete, the reactions were typically heated to 60 °C overnight (reaction times are unoptimized).