Aryne-Mediated Arylation of the 3-Benzazepine Scaffold: One-Pot Synthesis of 1-Aryl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepines

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Abstract The coupling of β-amino carbanions derived from 3-benzazepines with in situ generated arynes has been demonstrated as a convenient route for the direct synthesis of a variety of 1-aryl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepines, including the biologically active drug molecule SCH 12679.

Key words arylation, arynes, carbanions, nucleophilic addition, drugs

1-Arylated benzazepines 1 have attracted considerable attention due to their potential pharmaceutical properties (Figure 1).1 Some analogues exhibit strong inhibitory action against norepinephrine, dopamine, and 5-hydroxytryptamine uptake,1a while others act as selective agonists for the putative phosphatidylinositol-linked dopamine receptor.1b Various phenolic 3-benzazepines bearing a 1-aryl substituent are known to act as noncompetitive antagonists of ionotropic N-methyl-D-aspartate1c which is involved in physiological functions like memory and learning,1d,e and some are found to be a potent renal vasodilator.1f 1-Aryl-3-benzazepines are also known to possess analgesic, antihistaminic, anticholinergic, and narcotic properties, which are useful in treating mental disorders like psychoses.1g

Furthermore, SCH 23390 (2a), SKF 83566 (2b), and SKF 103108A (2c) are selective and stereospecific antagonists of dopamine receptors.2 Drug SCH 12679 (1a) is a non-antipsychotic benzazepine involved in neuroleptic antagonism of dyskinetic phenomenon and has a moderate activity in the inhibition of monoamine uptake.1 It is also effective in reducing many forms of aggression including brain stimulated emotional behavior. Another antagonist I-MAB (3) is used as a photoaffinity label for canine, bovine, and porcine neuronal D-1 receptors (Figure 2).4

Many synthetic routes for this class of compounds have been developed and most of these involve the construction of the seven-membered heterocyclic ring as the key step.
Earlier methods utilized the acid-catalyzed (H$_2$SO$_4$,$^{2a}$ HBF$_4$–OMe$_2$,$^{3a}$ H$_2$SO$_4$–TFA,$^{1f}$ and PPA$^{4a}$) intramolecular Friedel–Crafts reaction for this purpose (Scheme 1, eq. 1).

A rearrangement reaction of 1-(α-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinolines under acidic conditions to give the target compounds was also reported (Scheme 1, eq. 2).$^6$ In 1997, Wünsh et al. reported the Michael addition of (2-lithiophenyl)acetaldehyde acetals to β-nitrostyrenes followed by reductive ring closure to afford 1-aryl-3-benzazepines (Scheme 1, eq. 3).$^{1c}$ More recently, Seijas and co-workers reported a new route for arylated benzazepines that involved hydroamination of enol carbamates (Scheme 1, eq. 4).$^7$

Our long-standing research on the generation and reactivity of amino carbanions established that addition of a strong Lewis acid (BF$_3$·OEt$_2$) followed by treatment with sec-butyllithium in tetrahydrofuran at –78 °C generates α-amino carbanion 5, which upon reaction with electrophiles furnishes the α-substituted products 6a.$^8$ In the absence of a Lewis acid, the carbanion formation and reaction with electrophiles occurs at a distant position to afford the β-substituted products 8a or 8b from 4a and 7a respectively.$^9,^{10}$ Recently, we reported our findings involving reactions of amino carbanions 5 and 4a·Li with in situ generated arynes that successfully led to the synthesis of 1-aryl-2-methyl-1,2,3,4-tetrahydroisoquinolines 6b$^{11}$ and 4-aryl-2-methyl-1,2,3,4-tetrahydroisoquinolines 8c (Scheme 2).$^{12}$ We were interested in exploring coupling reactions of the β-lithiated intermediate 7a·Li with in situ generated arynes,$^{13}$ which can lead to a one-step synthesis of 1-aryl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepines.

The unsubstituted 3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (7a)$^{14}$ was first investigated. The β-amino carbanion 5 was generated by the addition of a strong Lewis acid (BF$_3$·OEt$_2$) to 4a followed by treatment with sec-butyllithium in tetrahydrofuran at –78 °C. Upon reaction with electrophiles, the α-substituted products 6a were formed. In the absence of a Lewis acid, the carbanion formation and reaction with electrophiles occurred at a distant position to afford the β-substituted products 8a or 8b from 4a and 7a respectively.

In our research, we explored the coupling reactions of β-lithiated intermediate 7a·Li with in situ generated arynes, which can lead to a one-step synthesis of 1-aryl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepines.

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In our research, we explored the coupling reactions of β-lithiated intermediate 7a·Li with in situ generated arynes, which can lead to a one-step synthesis of 1-aryl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepines.
Banion 7a-Li was generated by treating a solution of 7a (1.55 mmol) in tetrahydrofuran (8 mL) with sec-butyl lithium (1.55 mmol, 1 equiv) at –78 °C. To the deep-red-colored solution thus obtained, a second amount of sec-butyl lithium (1.86 mmol, 1.2 equiv) was added after an interval of one hour followed by chlorobenzene (9a) (1.55 mmol, 1 equiv). The dark-colored reaction mixture was stirred at this temperature for a further 45 minutes after which it was allowed to warm up to room temperature; it was then quenched with 10% hydrochloric acid. Workup and chromatographic separation furnished 3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine (10a) in a very low yield of 13% (Scheme 3). To optimize the yield of 10a, various reaction parameters like solvent and amount of the base or aryl halide were varied (Table 1). Increasing the amount of base (1st and 2nd addition) and aryl halide increased the yield up to 23% (entries 2 and 3). The use of 2.2 equivalents of sec-butyllithium (1st addition) and three equivalents of sec-butyl lithium (2nd addition), three equivalents of aryl halide, and tetrahydrofuran as the solvent gave the best result (entry 4). Further increasing the amount of sec-butyllithium/aryl halide (4 equiv) somewhat depressed the yield (entry 5). The use of solvents like diethyl ether, toluene-diethyl ether (1:1), and tetrahydrofuran-pentane (6:4) gave lower yields (entries 6–8).

Differently substituted aryne precursors were then investigated for C1 arylation of 3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (7a) under the optimized reaction conditions.

Scheme 3 C1 Arylation of 3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (7a)

![Scheme 3](image)

Scheme 4 Synthesis of 10 using variously substituted aryne precursors. Reagents and conditions: 3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (1 equiv), s-BuLi (2.2 equiv, 1st addition), s-BuLi (3 equiv, 2nd addition). 9 (3 equiv), THF (5 mL/mmol); yields are isolated yields and yields in parentheses are calculated on the basis of recovered starting amine.
The reactions proceeded well with all the selected aryne substrates 9a–f to furnish the corresponding products 10a–f in moderate yields (24–32%) (Scheme 4). The regioselectivity exhibited during the nucleophilic addition of lithiated intermediate 7a·Li to the substituted arynes (derived from 9b–f) is in accordance with the aryne-mediated reactions and the methoxy/methylenedioxy substituents in 10b–f appear at the expected positions.16 The highest yield (32%) was obtained for 10c employing 3-chloroanisole (9c) as the aryne precursor while the lowest yield (10b, 24%) was obtained with 4-fluoroanisole (9b).12

In order to further explore the scope and generality of the reaction, the developed strategy was also applied to 7,8-disubstituted benzazepines 7b and 7c. These were reacted with aryne precursors 9a–f under the optimized reaction conditions and C1-arylated benzazepines 1a–l were obtained in moderate yields (Scheme 5). In the process, the

![Scheme 5](image-url)

Scheme 5  C1 Arylation of benzazepines 7b–c. Reagents and conditions: 7b–c (1 equiv), s-BuLi (2.2 equiv, 1st addition), s-BuLi (3 equiv, 2nd addition), 9 (3 equiv), THF (5 mL/mmol); yields are isolated yields and yields in parentheses are calculated on the basis of recovered starting amine.17
drug molecule SCH 12679 was also synthesized in 24% yield (Scheme 5, 1a).

In these reactions, the desired products were obtained in only modest yields (23–32%) and the unreacted starting amine 7a–c was always recovered. Obviously, the benzyne intermediates/7-Li are consumed in some side reactions although the benzyne precursors were used in excess (3 equiv). To address this issue, the reaction of 7a was carried out on a larger scale (1.0 g, 6.8 mmol) with 9a. The expected product 10a was isolated in 30% yield along with the unwanted starting amine 7a (34%) by column chromatography of the basic material obtained after the work up of the reaction mixture. A dimeric compound 11 was also isolated in 6% yield. Its formation may be rationalized in terms of a single-electron transfer (SET) from the anion ortho-anion of chlorobenzene with benzyne, while 12 (380 mg, 10%), 13 (247 mg, 8%), and 14 (140 mg, 3%). The product 12 is formed by the reaction of the ortho-anion of chlorobenzene with benzene, while 13 and 14 are formed by dimerization or trimerization of the benzene intermediate (Figure 3). The formation of these three side products 12, 13, and 14 in the yields mentioned above accounts for the consumption of ~45% of the aryne substrate. Finally, elution of the column with chloroform–methanol (9.5:0.5) afforded another 130 mg of black gummy material that again showed a complex 1H NMR spectrum.

In conclusion, a one-pot strategy for the direct C1 arylation of 3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepines involving nucleophilic addition of β-amino carbanions to arynes has been demonstrated. The method is broadly applicable allowing the variation of substituents on the benzazepine ring as well as on the phenyl group. Although, the yields of the products are modest, its utility in the synthesis of SCH 12679 has been demonstrated.

1H NMR were recorded on Bruker 400 MHz and Jeol AL 300 MHz NMR spectrometers using TMS as internal standard. 13C NMR spectra were recorded on 75 MHz and 100 MHz NMR spectrometers relative to CDCl3 (δ = 77.0). IR spectra were obtained using KBr pellet and film NaCl plate techniques. HRMS data of unknown compounds were recorded on a maxisTM mass spectrometer. Elemental analyses were performed with a Flash 2000 (organic elemental analyzer). Melting points were obtained on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Flash column chromatography was performed using 230–400 mesh silica gel with hexane–EtOAc mixtures.

All lithiation reactions were carried out under a N2 atmosphere. Anhydrous solvents were transferred via a syringe to flame-dried glassware. THF, Et2O, and toluene were dried and distilled from Na/benzophenone. Pentane was purified and dried according to a known procedure. Alkylolithiums were estimated by using 1,10-phenanthroline as an indicator according to a reported procedure. s-BuLi was used as a 2.7 M solution in pentane. The required 3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepines 7 were prepared according to known procedures as discussed in the Supporting Information. Chlorobenzene (9a) is commercially available. Substrates 9d, 9e, and 9f were prepared according to known procedures. Substrate 9b and 9c were prepared by methylation of the corresponding phenols using Me3SO4 and NaOH. All the aryn precursors and starting benzazepines were dried and distilled over CaH2, under reduced pressure, before use.

**Table 1** Optimization of the Reaction Conditions for C1 Arylation of 7a (Scheme 3)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>s-BuLi (equiv)</th>
<th>1st addition</th>
<th>2nd addition</th>
<th>9a (equiv)</th>
<th>Yield% of 10a</th>
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<td>1</td>
<td>13</td>
<td></td>
</tr>
<tr>
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<td>THF</td>
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<td>1.2</td>
<td>1</td>
<td>18</td>
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<tr>
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<td>2</td>
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<tr>
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<td>3</td>
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<tr>
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<td>THF</td>
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<tr>
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<td>3</td>
<td>23</td>
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</tr>
<tr>
<td>8</td>
<td>THF–pentane (6:4)</td>
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<td>3</td>
<td>3</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

*Conditions for C1 carbanion generation; −78 °C, s-BuLi, −78 °C → 0 °C (45 min) → −78 °C. Isolated yield.

**Figure 3** Side products isolated from the reaction of lithiated 7a with 9a
remove non-basic impurities, made alkaline with solid Na2CO3 and extracted with CHCl3 (4 × 10 mL). The organic layer was washed with brine and dried (anhyd Na2SO4). The solvent was evaporated to afford the crude basic product, which was purified by flash chromatography (silica gel, EtOAc-hexane, 8:2) to furnish the 1-aryl-substituted product. Further elution of the column with same solvent afforded the unreacted starting material. The first Et2O layer (25 mL) and the second Et2O washings (2 × 10 mL) were combined, washed with brine, and dried (anhyd Na2SO4). The solvent was evaporated to furnish the crude non-basic material.

3-Methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine (10a)
White crystalline solid; yield: 96 mg (27%); mp 72–74 °C (Lit.7 mp 73–75 °C).
IR (neat): 2973, 2893, 1439, 1275, 1023 cm–1.
1H NMR (400 MHz, CDCl3): δ = 7.19–7.10 (m, 5 H, HAr), 6.97–6.85 (m, 2 H, HAr), 6.81 (t, J = 6.5 Hz, 1 H, HAr), 6.48 (d, J = 7.8 Hz, 1 H, HAr), 4.40 (t, J = 4.8 Hz, 1 H, ArCHPh), 3.12–3.07 (m, 2 H, CH2), 2.92–2.77 (m, 3 H, CH2), 2.65–2.50 (m, 1 H, CH2), 2.42 (s, 3 H, NCH3).
13C NMR (100 MHz, CDCl3): δ = 144.3, 143.3, 141.1, 129.7, 128.8, 128.4, 127.7, 127.6, 127.4, 126.6, 62.7, 57.5, 51.6, 47.7, 37.8.

1-(4-Methoxyphenyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (10b)
White solid; yield: 99 mg (24%); mp 76–78 °C (Lit.7 mp 78–80 °C).
IR (neat): 2953, 2840, 1479, 1236, 1082 cm–1.
1H NMR (400 MHz, CDCl3): δ = 7.04 (d, J = 8.6 Hz, 2 H, HAr), 6.97–6.92 (m, 2 H, HAr), 6.86–6.82 (m, 1 H, HAr), 6.69 (d, J = 8.6 Hz, 2 H, HAr), 6.49 (d, J = 7.8 Hz, 1 H, HAr), 4.35 (t, J = 4.8 Hz, 1 H, ArCHAr), 3.75 (s, 3 H, OCH3), 3.21–3.06 (m, 2 H, CH2), 2.93–2.85 (m, 1 H, CH2), 2.80–2.75 (m, 2 H, CH2), 2.55–2.50 (m, 1 H, CH2), 2.45 (s, 3 H, NCH3).
13C NMR (100 MHz, CDCl3): δ = 157.3, 144.2, 142.3, 141.3, 130.4, 129.4, 128.5, 127.9, 127.3, 122.4, 63.7, 57.2, 55.6, 50.6, 47.7, 36.8.

1-(3-Methoxyphenyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (10c)
Light brown oil; yield: 132 mg (32%).
IR (neat): 2924, 2853, 1479, 1274, 1042 cm–1.
1H NMR (400 MHz, CDCl3): δ = 7.08 (t, J = 7.8 Hz, 1 H, HAr), 6.99–6.93 (m, 2 H, HAr), 6.88–6.84 (m, 1 H, HAr), 6.76 (d, J = 7.5 Hz, 1 H, HAr), 6.71–6.66 (m, 2 H, HAr), 6.53 (d, J = 7.8 Hz, 1 H, HAr), 4.45 (t, J = 4.7 Hz, 1 H, ArCHAr), 3.80 (s, 3 H, OCH3), 3.20–3.00 (m, 2 H, CH2), 2.92–2.76 (m, 3 H, CH2), 2.56–2.51 (m, 1 H, CH2), 2.40 (s, 3 H, NCH3).
13C NMR (100 MHz, CDCl3): δ = 156.8, 146.3, 138.9, 133.9, 130.3, 129.4, 128.1, 127.2, 126.2, 122.2, 115.1, 114.0, 63.0, 58.9, 54.5, 50.3, 48.3, 38.0.
HRMS (ESI): m/z [M + H]+ calc'd for C26H25NO: 368.1868; found: 368.1688.

7,8-Dimethoxy-1-(4-methoxyphenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (1a)
White solid; yield: 80 mg (24%); mp 79–80 °C (Lit.7 mp 80–81 °C).
IR (neat): 2972, 2864, 1520, 1293, 1013 cm–1.
1H NMR (400 MHz, CDCl3): δ = 7.23–7.13 (m, 5 H, HAr), 6.48 (s, 1 H, HAr), 5.97 (s, 1 H, HAr), 4.50 (t, J = 4.8 Hz, 1 H, ArCHPh), 3.86 (s, 3 H, OCH3), 3.65 (s, 3 H, OCH3), 3.22–3.07 (m, 2 H, CH2), 2.99–2.78 (m, 3 H, CH2), 2.64–2.49 (m, 1 H, CH2), 2.39 (s, 3 H, NCH3).
13C NMR (100 MHz, CDCl3): δ = 147.8, 146.3, 143.9, 130.3, 129.4, 128.1, 127.2, 126.2, 113.1, 111.0, 63.9, 57.9, 55.5, 51.3, 47.3, 39.0.

7,8-Dimethoxy-1-(4-methoxyphenyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (1b)
Light tan solid; yield: 97 mg (27%); mp 88–90 °C.
IR (neat): 2964, 2873, 1459, 1274, 1083 cm–1.
8.7-Dimethoxy-1-(3-methoxyphenyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (1c)

Yellow oil; yield: 108 mg (30%).

IR (neat): 2964, 2894, 1540, 1206, 1073 cm⁻¹.

Yellow pasty mass; yield: 92 mg (23%).

13C NMR (100 MHz, CDCl₃): δ = 124.1, 122.0, 114.0, 112.7, 112.2, 112.1, 110.9, 109.3, 62.2, 57.0, 55.6, 54.9, 51.1, 47.0, 37.8.

Anal. Calcd for C₂₀H₂₅NO₃: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.69; H, 7.70; N, 4.37.

8.7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (1d)

Yellow oil; yield: 80 mg (26%).

IR (neat): 2951, 2718, 1497, 1204, 1093 cm⁻¹.

13C NMR (100 MHz, CDCl₃): δ = 145.8, 145.7, 144.0, 131.5, 129.5, 128.3, 127.3, 126.3, 108.4, 107.8, 100.4, 61.2, 57.3, 51.3, 47.3, 37.3.

HRMS (ESI): m/z [M + H]⁺ calcld for C₁₉H₂₂NO₃: 312.1588; found: 312.1592.

8.7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (1e)

White solid; yield: 107 mg (25%); mp 142–144 °C.

IR (neat): 2934, 2831, 1479, 1274, 1039 cm⁻¹.

13C NMR (100 MHz, CDCl₃): δ = 158.9, 145.8, 145.7, 135.9, 131.9, 130.5, 127.4, 113.7, 108.4, 107.8, 100.5, 62.3, 57.1, 55.2, 47.4, 37.1.

Anal. Calcd for C₁₉H₂₂NO₃: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.72; H, 6.71; N, 4.43.

8.7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (1f)

Brown oil; yield: 102 mg (30%).

IR (neat): 2941, 2840, 1489, 1239, 1051 cm⁻¹.

13C NMR (100 MHz, CDCl₃): δ = 159.6, 147.4, 146.6, 130.2, 128.5, 126.2, 122.1, 114.2, 113.0, 111.2, 111.0, 109.2, 100.5, 62.1, 57.1, 55.6, 51.4, 47.4, 37.1.

HRMS (ESI): m/z [M + H]⁺ calcld for C₁₉H₂₅NO₅: 312.1599; found: 312.1591.

8.7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (1g)

Light yellow oil; yield: 80 mg (26%).

IR (neat): 2951, 2718, 1497, 1204, 1093 cm⁻¹.

13C NMR (100 MHz, CDCl₃): δ = 145.8, 145.7, 144.0, 131.5, 129.5, 128.3, 127.3, 126.3, 108.4, 107.8, 100.4, 61.2, 57.3, 51.3, 47.3, 37.3.

HRMS (ESI): m/z [M + H]⁺ calcld for C₁₉H₂₂NO₃: 312.1488; found: 312.1407.

1-(4-Methylphenyl)-3-(methyleneoxy)-2,3,4,5-tetrahydro-1H-3-benzazepine (1h)

Light brown solid; yield: 95 mg (28%); mp 90–92 °C.

IR (neat): 2934, 2831, 1479, 1274, 1039 cm⁻¹.

13C NMR (100 MHz, CDCl₃): δ = 158.9, 145.8, 145.7, 135.9, 131.9, 130.5, 127.4, 113.7, 108.4, 107.8, 100.5, 62.3, 57.1, 55.2, 47.4, 37.1.

Anal. Calcd for C₁₉H₂₂NO₃: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.72; H, 6.71; N, 4.43.
1-(3,4-Dimethoxyphenyl)-3-methyl-7,8-(methyleneoxy)-2,3,4,5-tetrahydro-1H-3-benzazepine (1j)

Light yellow crystalline solid; yield: 81 mg (22%); mp 130–132 °C.

IR (neat): 2954, 2862, 1427, 1235, 1029 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 6.50 (s, 1 H, HAr), 6.87 (d, J = 1.6 Hz, 1 H, H₂OCH₃), 6.52 (s, 1 H, H₂OCH₃), 6.06 (s, 1 H, H₂OCH₃), 5.81 (d, J = 1.4 Hz, 1 H, OCH₂O), 5.79 (d, J = 1.4 Hz, 1 H, OCH₂O), 4.50 (t, J = 1.7 Hz, 1 H, OCH₂O), 3.90 (t, 3 H, CH₃), 3.80 (t, 3 H, CH₃), 3.28–3.03 (m, 2 H, CH₂), 2.98–2.85 (m, 2 H, CH₂), 2.83–2.73 (m, 2 H, CH₂), 2.62–2.50 (m, 1 H, CH₂), 2.42 (s, 3 H, NCH₃).

Anal. Calcd for C₂₀H₂₃NO₄: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.91; H, 6.92; N, 4.35.

13C NMR (100 MHz, CDCl₃):

3-Methyl-7,8-(methyleneoxy)-1-(3,4-(methylenedioxy)phenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (1k)

White crystalline solid; yield: 105 mg (27%); mp 135–137 °C.

IR (neat): 2918, 2869, 1480, 1233, 1032 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.79–7.77 (m, 1 H, HAr), 7.76–7.56 (m, 1 H, HAr), 7.51–7.24 (m, 1 H, HAr). 7.14–7.13 (m, 2 H, HAr). 6.81–6.75 (m, 2 H, HAr). 6.71 (d, J = 1.6 Hz, 1 H, HAr), 6.53 (s, 1 H, HAr), 4.50 (t, J = 1.7 Hz, 1 H, OCH₂O), 3.90 (t, 3 H, CH₃), 3.80 (t, 3 H, CH₃), 3.28–3.03 (m, 2 H, CH₂), 2.98–2.85 (m, 2 H, CH₂), 2.83–2.73 (m, 2 H, CH₂), 2.62–2.50 (m, 1 H, CH₂), 2.44 (s, 3 H, NCH₃).

Anal. Calcd for C₁₉H₁₉NO₄: C, 70.14; H, 5.89; N, 4.31. Found: C, 68.09; H, 6.92; N, 4.35.

3-Methyl-7,8-(methyleneoxy)-1-(3,4-(methyleneoxy)phenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (1l)

Yellow crystalline solid; yield: 380 mg (10%); mp 160–162 °C.

IR (neat): 2931, 2848, 1470, 1247, 1074 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.78–7.76 (m, 1 H, HAr), 7.76–7.55 (m, 1 H, HAr), 7.51–7.24 (m, 1 H, HAr), 4.50 (t, J = 1.7 Hz, 1 H, OCH₂O), 3.90 (t, 3 H, CH₃), 3.80 (t, 3 H, CH₃), 3.28–3.03 (m, 2 H, CH₂), 2.98–2.85 (m, 2 H, CH₂), 2.83–2.73 (m, 2 H, CH₂), 2.62–2.45 (m, 1 H, CH₂), 2.40 (s, 3 H, NCH₃).

Anal. Calcd for C₁₉H₁₉NO₄: C, 70.91; H, 6.92; N, 4.48.

3-Methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine (10a)

To a flame-dried, 2-necked, round-bottomed flask, equipped with a magnetic stirrer bar, septum cap, and a bubbler, was added 3 moles of 3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (7a, 1.0 g, 6.8 mmol, 1 equiv) in anhyd THF (30 mL) under an inert N₂ atmosphere. The solution was stirred at 78 °C and 2.61 M s-BuLi in pentane (60 mL, 15.0 mmol, 2.2 equiv) was added. A deep red color, which was indicative of benzylic carbanion formation, appeared immediately. The solution was stirred at this temperature for 1 h. The reaction was quenched with 10% HCl (40 mL). Workup as discussed in the general lithiation/arylation procedure afforded the crude basic (1.6 g) and non-basic material (0.91 g). The column chromatographic separation of basic portion as earlier afforded 3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine (10a) (440 mg, 30%) as a white crystalline solid. Further elution furnished 3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (7a, 340 mg, 34%) as a colorless oil and the dimeric compound 11 (106 mg, 6%) as a yellow oil.

Paper
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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380453.

References


(13) Treatment of aryl chlorides or fluorides with alkyllithium at low temperature was used for arylene generation as these conditions are compatible with generation and reactions of amino carbamions, see refs. 11 and 12.


(15) All new products were characterized by 1H and 13C NMR, IR spectroscopy, HRMS, and CHN analysis.


(17) (a) This experiment on a larger scale was carried out on the suggestion of a reviewer. (b) The formation of similar side products in the reaction of lithiated 2-methyl-1,2,3,4-tetrahydrosquoline moiety with benzyne was noted in our earlier publication11 as well.


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