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A Practical Synthesis of Regioisomeric 6- and 7-Methoxytetrahydro-3-benzazepines

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Abstract:

A concise and versatile synthetic route for 6- and 7-methoxy tetrahydro-3-benzazepines is described. The key feature of the synthesis is a one-pot acylation/cyclization/elimination sequence to construct either of the isomeric dihydrobenzazepine ring systems from the same starting material. The route is high yielding and chromatography-free.

Introduction

Drugs comprising tetrahydrobenzazepine derivatives have been thoroughly investigated for their pharmacological and biological effects (Figure 1). Fenoldopam mesylate, for example, is the first selective dopamine D_1 receptor agonist approved for severe hypertension.[1] Many drug candidates bearing the same structural motif are also currently under development in a range of therapeutic areas (Figure 1). For instance, a number of tetrahydrobenzazepine derivatives are potent modulators of dopamine D_3 receptors, potentially useful for treatment of central nervous system disorders such as schizophrenia, depression, and substance abuse.[2] Much attention has also been focused on developing selective $5HT_{2C}$ agonists for the treatment of obesity, obsessive-compulsive disorder, sexual dysfunction, glaucoma, and Alzheimer disease.[3] The same structural motif is also found in nonselective opioid receptor antagonists[4] as well as novel antibacterial agents.[5] In connection with one of our drug discovery programs, we were interested in developing a regioselective and scalable synthesis of both 6- and 7-alkoxytetrahydro-3-benzazepine core structures **1a** and **2a** (Figure 2). In the literature, there are four common synthetic strategies to assemble the tetrahydrobenzazepine ring (Scheme 1): (a) Lewis acid-promoted Friedel−Crafts cyclization of acetals **3** followed by reduction of the olefin and carbonyl groups;[4,6] (b) intramolecular Friedel−Crafts acylation of an acid chloride **4** followed by reduction of the carbonyl group;[7] (c) intramolecular Friedel−Crafts alkylation of an alkyl halide **5**;[3b] (d) Ni-catalyzed high-pressure and high-temperature hydrogenation of *o*-phenylene diacetonitriles **6** in the presence of ammonia.[2c] The first three strategies share a similar bond disconnection probably because of the easy access to the starting materials. An example of compound **1** was prepared via route **a** through the intermediate acetal **3** in six steps (Scheme 2).[4] Regioselective synthesis of isomer **2**, however, has not been reported.

We envisioned a more redox-efficient cyclization strategy[8] through amine intermediate **8** which would minimize oxidation state manipulation and protecting group exchange, thus significantly shortening the overall sequence (Scheme 3). Herein, we report the successful implementation of this strategy for the regioselective synthesis of both isomers **1** and **2** through common precursor **8**, which was readily prepared from commercially available starting materials. The key step is a one-pot transformation that includes *N*-protection, Friedel−Crafts cyclization, and elimination. We believe that this sequence would be applicable to the syntheses of related tetrahydro-3-benzazepine compounds.

Results and Discussion

Commercially available 2-(3-methoxyphenyl)ethylamine (**7**) was chosen as the starting material because the electron-donating alkoxy group should activate the ortho and para positions for the Friedel−Crafts cyclization, thus potentially providing both regioisomers of interest. To test this idea, the requisite precursor

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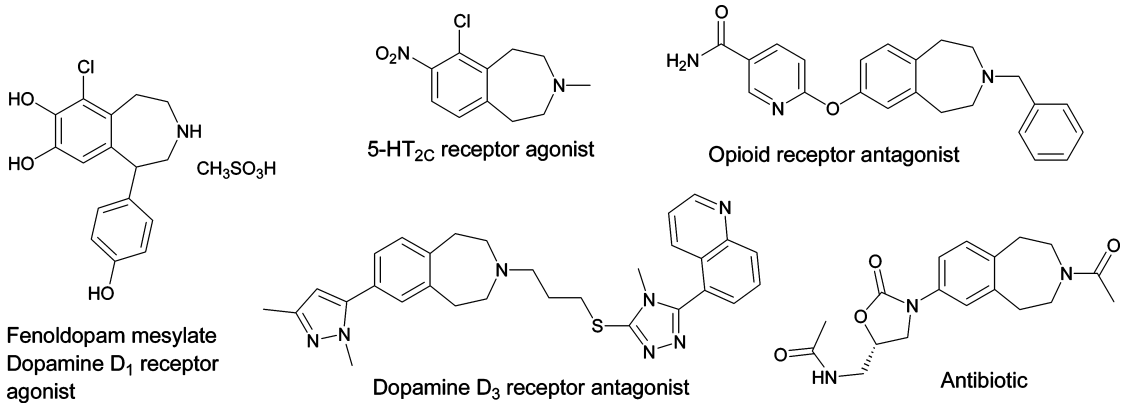

Figure 1. **Drug candidates with tetrahydrobenzazepine motif.**

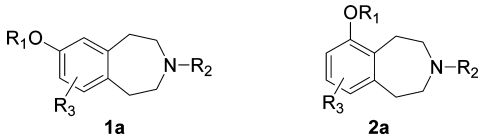

Figure 2. **Regioisomeric tetrahydro-3-benzazepines of interest.**

8 was first prepared by reductive amination of compound **7** with dimethoxyacetaldehyde in quantitative crude yield (Scheme 4). With acetal **8** in hand, the Friedel−Crafts cyclization step was investigated utilizing both Brønsted ($AlCl_3$, $BF_3 \cdot Et_2O$) and Lewis acids (H_2SO_4, 6 N HCl, TFA). Unfortunately, none of these conditions provided either the desired dihydro-3-benzazepine **9** or **10** (Scheme 5). We reasoned that the difficulty of the cyclization reaction stemmed from the coordination of the acids with the secondary amine, which inductively hindered the necessary formation of the neighboring carbocation for the Friedel−Crafts cyclization to occur. Similar cyclization reactions are also reported to occur in poor yield.[3a,6,9] To address this problem, we intended to install a trifluoroacetyl protecting group on the nitrogen atom using trifluoroacetic anhydride (TFAA). To our pleasant surprise, when compound **8** was treated with TFAA in CH_2Cl_2 at room temperature, not only did *N*-protection occur, but also the subsequent Friedel−Crafts cyclization and methanol elimination took place to afford compound **11** in excellent yield. Presumably, the cyclization and elimination steps were mediated by the trifluoroacetic acid generated in the *N*-protection step. Interestingly, the cyclization step occurred exclusively at the para position relative to the methoxy group. None of the ortho isomer was isolated. Crude compound **11** was then hydrogenated in EtOAc over Pd/C as catalyst to provide crude product **1** (Scheme 6). It is worth noting that all the intermediates were telescoped after simple workup to the next step without chromatographic purification. Trituration with 1:1 *tert*-butylmethyl ether/hexanes of the crude product afforded pure compound **1** in 70% overall yield over three steps.[10]

Encouraged by these results, we turned our attention to the regioselective synthesis of isomer **2**. To avoid the regioselectivity issues with the Friedel−Crafts cyclization step, one solution was to pursue intermediate **12** (Scheme 7, route e). However, it soon became clear to us that the intramolecular Friedel−Crafts cyclization of **12** was extremely difficult. The desired product was not observed at all in the presence of strong acid promoters (HCl, $BF_3 \cdot Et_2O$, TFA, or TfOH), and starting material **12** eventually decomposed upon prolonged heating. This was not a total surprise since the meta position was deactivated by the methoxy substituent via inductive effect. We then pursued an alternative intermediate **14** (Scheme 7, route f). With the knowledge that the Friedel−Crafts cyclization of **8** preferentially took place at the para position, we decided to block the para position with bromine to force the ortho cyclization. Precursor **14** was synthesized in two steps from the same starting material **7** as before (Scheme 8). Bromination of amine **7** with Br_2 in AcOH occurred exclusively at the 4-position to give **13,** which crystallized out as the HBr salt in good yield and high purity upon trituration with *tert*-butylmethyl ether. In the next step, reductive amination of dimethoxyacetaldehyde with amine **13** gave amino acetal **14** in 97% yield. Compound **14** was isolated after extractive aqueous workup, and no further purification was needed. With precursor **14** in hand, the key cyclization step was investigated. Unfortunately, under the reaction conditions developed previously for acetal **8** (TFAA, CH_2Cl_2, rt), only *N*-trifluoroacetylation was observed. The lower reactivity of acetal **14** relative to that of **8** was somewhat expected because the ortho position (relative to the methoxy group) was much less reactive than the para position as demonstrated by the excellent regioselectivity in the cyclization of **8**. In addition, the bromide substituent also deactivated **14** towards the cyclization reaction.[11] This problem was readily addressed by performing the reaction in TFA as the solvent at slightly elevated temperature (40 °C). Under these conditions, the one-pot acylation, cyclization, and elimination again occurred cleanly to provide crude **15** after a simple extractive workup (Scheme 9). Subsequent hydrogenation in EtOH/EtOAc reduced enamide **15** with concomitant removal of the bromine blocking group in a single step to afford compound **2** in good overall yield. Thus, the regioselective synthesis of both **1** and **2** was accomplished via a similar sequence from the same starting material **7**.

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(10) The *N*-trifluoroacetyl protecting group can be easily removed in high yields. The use of other amide-type N-protecting groups has not been tested.

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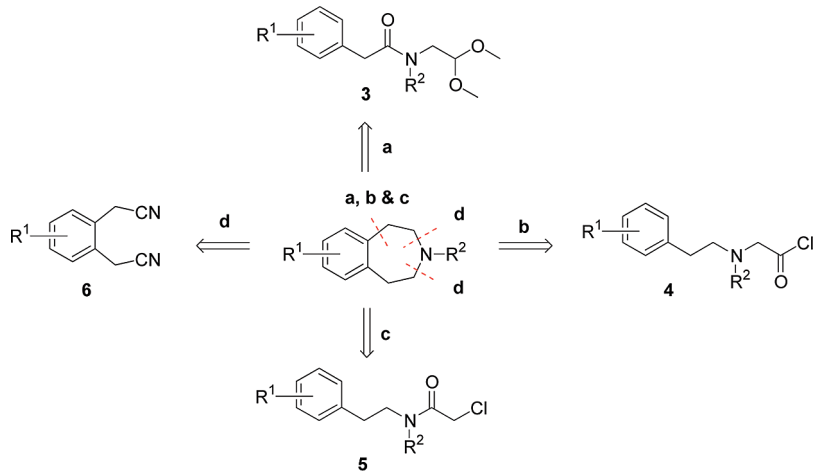
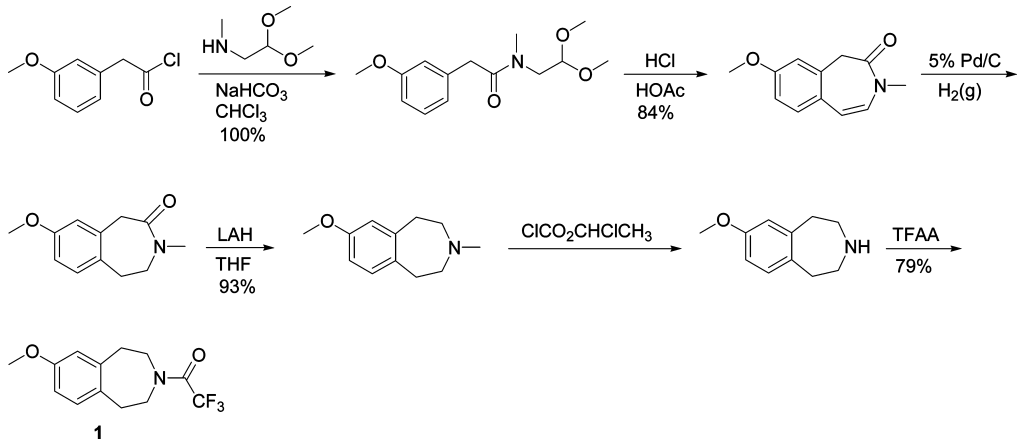
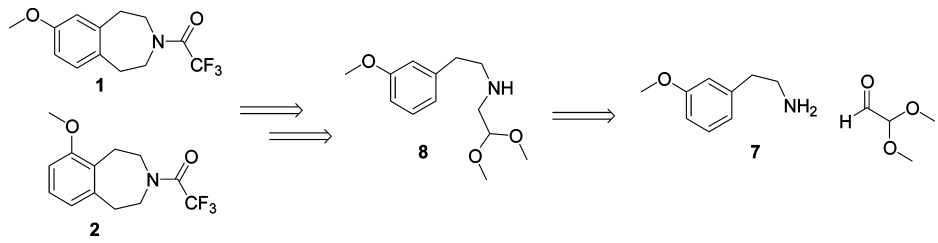
Scheme 1. **Four common synthetic strategies to construct tetrahydro-3-benzazepine ring**



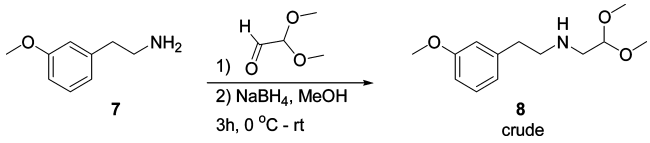
Scheme 2. **Six-step literature approach to 6-methoxytetrahydro-3-benzazepine[4]**



Scheme 3. **Strategy for the regioisomeric synthesis of 1 and 2**



Scheme 4. **Reductive amination step**



In the above synthesis, the bromide was employed as a 'protecting group' for the more reactive para position and was removed in the last step. However, aryl bromide functionality would open up many new opportunities for further derivatizations and structure−activity relationship (SAR) studies. To preserve the bromide group, an alternative reduction method was needed. It is known that enamides can be reduced with silanes, usually in strongly acidic solvents such as TFA.[12] Since the acylation/cyclization of **14** was already carried out in TFA, there was the possibility of a one-pot transformation. Indeed, when the reaction sequence was performed in a one-pot manner by adding Et_3SiH to the reaction mixture containing **15** at 60 °C, compound **16** was formed cleanly (Scheme 10). Thus, four transformations, N-acylation, cyclization, enamine formation, and reduction, are all accomplished in a simple one-pot reaction, and the formation of intermediates at each stage can be monitored by HPLC. The isolation of compound **16** was somewhat challenging because of the presence of TFA and Et_3SiOH, the byproduct from the Et_3SiH reduction step. After some optimization, we found that TFA was effectively removed by dissolving the reaction mixture in toluene and washing successively with water and saturated $NaHCO_3$ solution. The toluene layer was concentrated and then triturated with hexanes to remove the Et_3SiOH byproduct. Using this procedure, benzazepine **16** crystallized out of the solution in good yield

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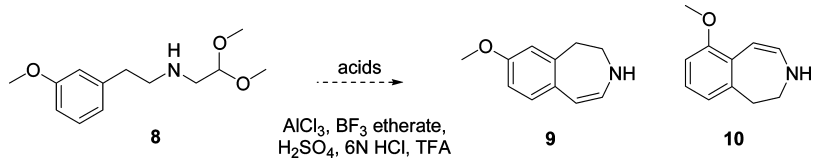
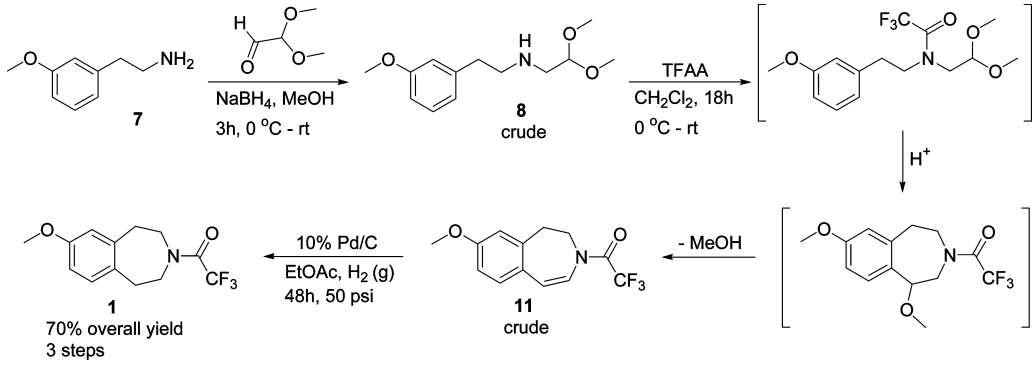
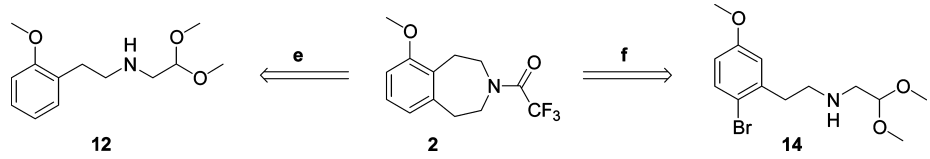
Scheme 5. **Friedel-Crafts cyclization**



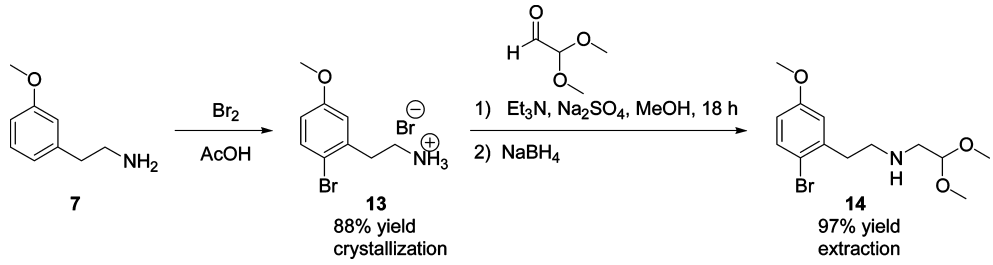
Scheme 6. **Synthesis of compound 1**



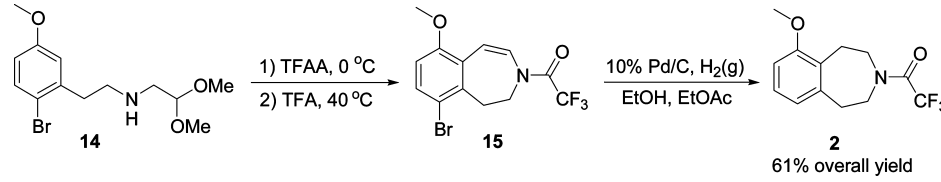
Scheme 7. **Two possible synthetic pathways to construct tetrahydro-3-benzazepine 2**



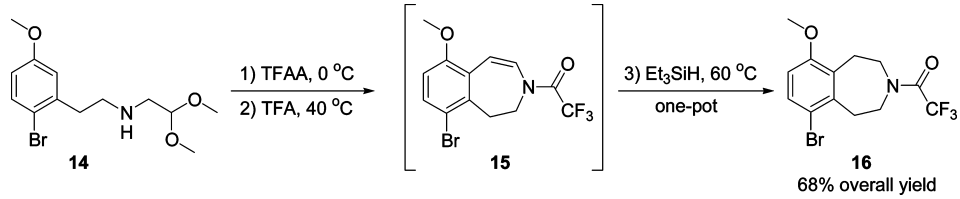
Scheme 8. **Synthesis of dimethyl acetal 14**



Scheme 9. **Synthesis of tetrahydrobenzazepine isomer 2**



Scheme 10. **Three-step, one-pot synthesis**



and excellent purity. Thus, we established a highly efficient one-pot, four-step transformation for the synthesis of tetrahydrobenzazepine **16** from intermediate **14**.

Conclusion

In summary, we have developed a highly efficient and versatile route for the synthesis of regioisomeric 6- and 7-methoxytetrahydrobenzazepines **1**, **2**, and **16** in three chromatography-free steps from the same commercially available amine **7**. In the key step, acylation, Friedel−Crafts cyclization, enamine formation, and reduction (in the case of **16**) are all accomplished with a simple one-pot procedure. Compared to the literature precedence, this route offers significant advantages

and should be applicable to the synthesis of many interesting tetrahydrobenzazepine building blocks. While we have not carried out the synthesis beyond 20 g scales, the crystalline nature of the benzazepines and the simple modifications of replacing stripping operations with solvent exchanges along with other minor changes should allow this chemistry to successfully operate at multikilogram scale.

Experimental Section

General. All reagents were purchased from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker (^{1}H, 400, 500, 600 MHz; ^{13}C, 126, 151 MHz) NMR spectrometer. HRMS (ESI) was performed on a Bruker μToF apparatus. Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. Analytical HPLC conditions were the following: Agilent ZORBAX Eclipse XDB-C8, 5 μm, 4.6 mm × 150 mm, flow rate 1 mL/min, gradient (acetonitrile/water with 0.05% TFA): 1% acetonitrile/99% water to 99% acetonitrile/1% water ramp over 8 min, then hold.

***N*-(2,2-Dimethoxyethyl)-2-(3-methoxyphenyl)ethylamine (8).** A mixture of 2-(3-methoxyphenyl)ethylamine (**7**) (20.0 g, 0.132 mol, 1.0 equiv), dimethoxyacetaldehyde solution 60 wt % in H_2O (23.9 mL, 0.158 mol, 1.2 equiv), and MeOH (75 mL) was stirred overnight at room temperature and then cooled to 0 °C. $NaBH_4$ (4.0 g, 0.106 mol, 0.8 equiv) was added in small portions over 15 min, and then the mixture was warmed to 25 °C. After stirring for 3 h at room temperature, the reaction was quenched with H_2O (200 mL) and extracted with CH_2Cl_2 (200 mL). The organic layer was collected, dried over Na_2SO_4, filtered, and concentrated to obtain *N*-(2,2-dimethoxyethyl)-2-(3-methoxyphenyl)ethylamine (**8**) as oil (34 g, 107% crude yield). The material was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.21 (dd, J = 8.9, 7.5 Hz, 1H), 6.80 (d, J = 7.6 Hz, 1H), 6.76−6.74 (m, 2H), 4.45 (t, J = 5.5 Hz, 1H), 3.79 (s, 3H), 3.36 (s, 6H), 2.89 (t, J = 6.8 Hz, 2H), 2.79−2.75 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 159.7, 141.4, 129.4, 121.0, 114.4, 111.50, 103.8, 55.1, 54.0, 51.0, 36.4; HRMS (ESI+): calculated for $[C_{13}H_{21}NO_3 + H]^+$, 240.1594; *m/z* found, 240.1596.

8-Methoxy-3-trifluoroacetyl-2,3-dihydro-1H-benzo[*d*]azepine (11). A solution of *N*-(2,2-dimethoxyethyl)-2-(3-methoxyphenyl)ethylamine (**8**) (34 g, 0.142 mol, 1 equiv) in CH_2Cl_2 (250 mL) was slowly treated with TFAA (100.4 mL, 0.711 mol, 5 equiv) in a cooled ice bath. The ice bath was removed, and the reaction mixture was stirred for 18 h. The reaction was quenched with ice cold aq saturated NaCl solution. The organic layer was separated, dried with Na_2SO_4, filtered, and concentrated to recover 8-methoxy-3-trifluoroacetyl-2,3-dihydro-1*H*-benzo[*d*]azepine (**11**) as a yellow-orange oil (44.38 g, 115% crude yield). The material was used in the next step without further purification. The product exists as two rotamers at room temperature in the NMR spectra. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.19−6.61 (m, 4H), (5.98, 5.84) (d, J = 10.4 Hz, 1H), (4.07, 3.96) (t, J = 4.9 Hz, 2H), 3.82 (s, 3H), (3.13, 3.09) (t, J = 4.9 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 159.0, 154.6 (q, J_{C-F} = 36.8 Hz), (140.4, 140.1), (133.2, 133.1), 126.0, 121.9, 120.8 (q, J_{C-F} = 4.5 Hz), 116.4 (q, J_{C-F} = 287.9 Hz), (116, 115.6), (115.0, 114.9), (112.0, 111.9), 55.3, (45.8, 44.2), (37.0, 36.5); HRMS (ESI+): calculated for $[C_{13}H_{12}F_3NO_2 + H]^+$, 272.0893; *m/z* found, 272.0881.

7-Methoxy-3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine (1)[4]. In a 1-L, one-neck, Parr bottle, crude 8-methoxy-3-trifluoroacetyl-2,3-dihydro-1*H*-benzo[d]azepine (**7**) (44 g, 0.162 mol) was diluted with EtOAc (250 mL) and then charged with 10% Pd/C (5 g) and H_2 (50 psi). After 18 h at room temperature, the reaction was approximately 70% complete. The catalyst was filtered off with a pad of Celite. The filtrate was resubmitted to hydrogenation, utilizing fresh 10% Pd/C (5 g) to complete the reaction. The catalyst was filtered off and the filtrate concentrated to an oily solid. The crude product was slurried in 1:1 TBME/hexane (200 mL) overnight and then filtered to recover 25.20 g of 7-methoxy-3-trifluoroacetyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (**1**) as a white solid in 70% yield over three steps. The product exists as two rotamers at room temperature in the NMR spectra. Mp 105−107 °C; ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.08−7.03 (dd, J = 7.7, 3.4 Hz, 1H), 6.72−6.68 (m, 2H), 3.79 (s, 3H), 3.76−3.73 (m, 2H), 3.70−3.65 (m, 2H), 2.96−2.90 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$, δ): (158.5, 158.3), (156.2, 155.9), (141.4, 140.7), (132.1, 131.4), (130.9, 130.8), 116.8 (q, J_{C-F} = 287.7 Hz), (116.0, 115.9), 111.4, 55.2, (48.7, 48.3), (47.2, 46.8), (38.1, 37.0), (36.9, 35.7); HRMS (ESI+): calculated for $[C_{13}H_{14}F_3NO_2 + H]^+$, 274.1049; *m/z* found, 274.1057.

2-(2-Bromo-5-methoxyphenyl)ethylammonium Bromide (13). A solution of 3-methoxyphenethylamine (**7**) (15.0 mL, 0.103 mol, 1.0 equiv) in acetic acid (50 mL) was treated with a solution of bromine (5.55 mL, 0.108 mol, 1.05 equiv) in acetic acid (10 mL) over 50 min, during which the internal temperature never exceeded 25 °C. After stirring for 10 min, Et_2O (100 mL) was added over 5 min. The suspension was cooled to 0 °C and filtered. The filter cake was rinsed with Et_2O and hexanes and dried in a vacuum oven at 45 °C for 4 h to afford product **13** as a white solid (28.3 g, 88%). Mp 152−154 °C; ^{1}H NMR (400 MHz, d_6-DMSO, δ): 7.95 (br s, 3H), 7.52 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 3.1 Hz, 1H), 6.84 (dd, J = 8.8, 3.1 Hz, 1H), 3.77 (s, 3H), 3.08−3.01 (m, 2 H), 2.99−2.92 (m, 2H). ^{13}C NMR (151 MHz, d_6-DMSO, δ): 158.8, 137.4, 133.3, 116.7, 114.6, 113.9, 55.4, 38.2, 33.2. HRMS (ESI+): calculated for $[C_9H_{13}BrNO + H]^+$, 230.0175; *m/z* found, 230.0194.

***N*-(2,2-Dimethoxyethyl)-2-(2-bromo-5-methoxyphenyl)-ethylamine (14).** A mixture of 2-(2-bromo-5-methoxyphenyl)-ethylammonium bromide (**13**) (20.0 g, 0.064 mol, 1.0 equiv) in MeOH (200 mL), anhydrous Na_2SO_4 (20.0 g, 0.141 mol, 2.2 equiv), triethylamine (9.4 mL, 0.067 mol, 1.05 equiv), and dimethoxyacetaldehyde solution (60 wt % in H_2O, 14.5 mL, 0.096 mol, 1.5 equiv) was stirred at room temperature for 18 h. The reaction was then cooled to −15 °C. Sodium borohydride (2.4 g, 0.063 mol, 1.0 equiv) was added in small portions over 12 min, during which the internal temperature never exceeded 20 °C. The reaction was warmed to room temperature and stirred for 30 min and filtered. Saturated $NaHCO_3$ solution (100 mL) was added, and methanol was removed by rotovap. The solution was diluted with water (150 mL) and extracted with CH_2Cl_2 (150 mL). The organic layer was washed with aq saturated $NaHCO_3$ solution (100 mL) and aq saturated NaCl (100 mL) solution, dried over Na_2SO_4, and concentrated to

afford product **14** as a light-yellow oil (19.8 g, 97%). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.42 (d, J = 8.8 Hz, 1H), 6.81 (d, J = 3.1 Hz, 1H), 6.65 (dd, J = 8.7, 3.1 Hz, 1H), 4.49 (t, J = 5.5 Hz, 1H), 3.78 (s, 3H), 3.40 (s, 6H), 2.90 (s, 4 H), 2.80 (d, J = 5.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 158.9, 140.2, 133.3, 116.3, 114.9, 113.5, 104.0, 55.4, 54.1, 51.0, 49.5, 36.9; MS (ESI+): calculated for $[C_{13}H_{21}BrNO_3 + H]^+$, 318.1; *m*/*z* found, 318.0.

6-Methoxy-3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine (2). Under neat conditions, *N*-(2,2-dimethoxyethyl)-2-(2-bromo-5-methoxyphenyl)ethylamine (**14**) (2.3 g, 7.2 $\times$ 10^{-3} mol, 1.0 equiv) was added dropwise to TFAA (3.22 mL, 0.023 mol, 3.2 equiv) at −15 °C over 15 min, during which the internal temperature never exceeded −10 °C. The reaction was warmed to room temperature and stirred for 25 min. Trifluoroacetic acid (5.52 mL, 0.074 mol, 10.3 equiv) was added over 2 min, and the reaction was heated to 40 °C for 18 h. The mixture was diluted with toluene (40 mL) and ice/water (40 mL). The organic layer was washed with water (2 $\times$ 20 mL) and passed through a short silica gel pad with CH_2Cl_2. The solvents were removed to afford a red oil, which was then redissolved in 1:1 EtOH/EtOAc (30 mL). The flask was purged with N_2(g) and charged with Pd/C (10%, 0.76 g, 0.71 mmol, 0.1 equiv). The reaction was connected to a H_2 balloon and stirred at room temperature for 3 days. The mixture was filtered through a Celite pad and concentrated to afford red oil. After trituration from 1:1 MTBE/hexanes, the product **2** was obtained as a white solid (1.2 g, 61% yield). The product exists as two rotamers (1:1 ratio) at room temperature in NMR spectra. Mp 74−75 °C; ^{1}H NMR of the mixture (500 MHz, $CDCl_3$, δ): 7.17−7.10 (m, 1H), 6.80 (dd, J = 8.7, 4.7 Hz, 1H), 6.78−6.72 (m, 1H), 3.81 (s, 3H), 3.79−3.71 (m, 2H), 3.71−3.62 (m, 2H), 3.14−3.05 (m, 2H), 2.99−2.96 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$, δ): 156.9, 156.1 (q, J_{C-F} = 35.4 Hz), (141.8, 141.2), (128.3, 127.7), (127.5, 127.3), 122.1, 116.7 (q, J_{C-F} = 288.0 Hz), (109.5, 109.3), 55.7, [47.9 (q, J_{C-F} = 3.5 Hz), 47.8 (q, J_{C-F} = 3.2 Hz)], (46.4, 46.3), (37.5, 36.3), (27.2, 25.9); HRMS (ESI+): calculated for $[C_{13}H_{15}F_3NO_2 + H]^+$, 274.1049; *m*/*z* found, 274.1051.

(6-Bromo-9-methoxy-3-2,2,2-trifluoro-trifluoroacetyl-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine (16). A 250-mL, two-neck, round-bottom flask under a nitrogen atmosphere was charged with TFAA (19.6 mL, 0.14 mol, 3.2 equiv) and cooled to 0 °C. Under neat conditions, *N*-(2,2-dimethoxyethyl)-2-(2-bromo-5-methoxyphenyl)ethylamine (**14**) (14.0 g, 0.044 mol, 1.0 equiv) was added dropwise to TFAA (19.6 mL, 0.14 mol, 3.2 equiv) at 0 °C over 5 min, during which the internal temperature never exceeded 15 °C. The reaction was warmed to room temperature and stirred for 20 min. Trifluoroacetic acid (32.7 mL, 0.440 mol, 10.0 equiv) was added over 3 min, and the reaction was heated to 40 °C for 2 h. Triethylsilane (31.6 mL, 0.198 mol, 4.5 equiv) was added over 6 min, and the reaction was heated to 60 °C for 24 h. The reaction was diluted with toluene (90 mL), washed with water (2 $\times$ 200 mL) and $NaHCO_3$ solution (150 mL), dried over Na_2SO_4, and concentrated. Hexanes (60 mL) was added to the residue over 5 min. The resulting suspension was cooled to 0 °C and filtered to afford product **16** as a white solid (10.6 g, 68%). The product exists as two rotamers (1:1 ratio) at room temperature in NMR spectra. Mp 88−89 °C; ^{1}H NMR of the mixture (500 MHz, $CDCl_3$, δ): [7.44 (d, J = 8.8 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H)], 6.69 (d, J = 8.9 Hz, 1H), [3.82 (s, 3H), 3.81 (s, 3H)], 3.80−3.74 (m, 2H), 3.73−3.65 (m, 2 H), 3.28−3.24 (m, 2H), 3.17−3.11 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$, δ): 156.2 (q, J_{C-F} = 36.5 Hz), 156.1, (140.3, 140.0), (131.6, 131.4), (130.2, 129.7), 116.7 (q, J_{C-F} = 288.0 Hz), (115.6, 115.5), (111.1, 110.8), 55.9, [47.1 (q, J_{C-F} = 3.1 Hz), 46.6 (q, J_{C-F} = 3.3 Hz)], (45.4, 45.1), (35.5, 34.6), (27.2, 26.0); HRMS (ESI+): calculated for $[C_{13}H_{14}BrF_3NO_2 + H]^+$, 352.0155; *m*/*z* found, 352.014. Anal. Calcd for $C_{13}H_{13}BrF_3NO_2$: C, 44.34; H, 3.72; N, 3.98. Found: C, 44.11; H, 3.41; N, 3.91.

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Supporting Information Available

This material is available free of charge via the Internet at http://pubs.acs.org.

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