New and Efficient Synthesis of 6,11-Dihydro-11-ethyl-5*H*-dibenz[*b*,*e*]azepine Derivatives Starting from *N*-Benzylanilines via Amino-Claisen and Friedel–Crafts Methodologies

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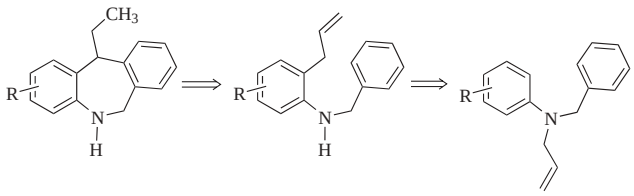
Abstract: New and efficient synthesis of 6,11-dihydro-11-ethyl-5*H*-dibenz[*b*,*e*]azepine derivatives, using the key steps of BF_3·OEt_2-catalyzed aromatic amino-Claisen rearrangement and the intramolecular alkene Friedel–Crafts alkylation, is reported.

Key words: dibenz[*b*,*e*]azepine derivatives, amino-Claisen rearrangement, N-allylation, intramolecular alkene Friedel–Crafts alkylation



Scheme 1

The synthesis of the dibenz[*b*,*e*]azepine ring has attracted a wide interest as several derivatives of this heterocyclic unit have been found to be biologically active as anti-depressive,[1,2] anxiolytic,[3,4] anti-inflammatory,[5–7] and anti-allergic[8] agents.

In the synthesis of dibenz[*b*,*e*]azepines, anthranilic acid[9] and *ortho*-aminobenzylic alcohol[4,10] derivatives as well as anthraquinone derivatives[11] are the most widely used precursors. However, to the best of our knowledge, the possibility to easily prepare this heterocyclic core using the broad scope of intramolecular alkene Friedel–Crafts alkylation in the series of *N*-benzyl-*o*-allylanilines has not been explored yet.

We have been studying for several years the intramolecular Friedel–Crafts alkylation process as the key step in the construction of diverse N-containing polyheterocycles.[12–17]

In continuation of our research program on the preparation of new potential CNS-active molecules, we needed a simple and inexpensive synthesis of 6,11-dihydro-11-ethyl-5*H*-dibenz[*b*,*e*]azepine derivatives. Analyzing the retro synthetic pathway for the dibenz[*b*,*e*]azepine structures depicted in Scheme 1, we inferred that the *N*-benzyl-*o*-allyl-anilines could be useful precursors in its synthesis.

To obtain these key intermediates, we addressed to powerful Claisen rearrangement methodology, taking into consideration that the amino-Claisen rearrangement in the aromatic systems has received a great attention in the last decades due to its potential synthetic utility in organic synthesis,[18–20] and that the *ortho*-allylation of anilines by Friedel–Crafts alkylation reaction becomes troublesome.[21] We wish here to report a new and efficient synthesis of 6,11-dihydro-11-ethyl-5*H*-dibenz[*b*,*e*]azepine derivatives starting from readily available substituted anilines and benzaldehyde.

Thus, a wide range of substituted anilines and benzaldehyde were subjected to the reductive amination process[22] to produce secondary *N*-benzylanilines **1a**–**e** in high yields. N-Allylation reaction of anilines **1a**–**e** was performed by the conventional procedure with an excess (2 equiv) of allylbromide in DMF at room temperature or in acetone in the presence of potassium carbonate (K_2CO_3) under reflux to afford the *N*-allyl-*N*-benzylanilines **2a**–**e** in 53–91% yields as clear viscous oils (Scheme 2).

In the second step, a solution of compounds **2** and equimolar amounts of boron trifluoride–diethyl ether complex (BF_3·OEt_2) in sulpholane was heated at 140–155 °C.[23] The reaction mixture was then allowed to react for 2–3 h (TLC control) to give the desired rearranged products **3a**–**d**,[24] which were isolated by silica gel column chromatography as viscous oils in good yields, essentially unaffected by the nature of substituents on the benzene ring of anilines (Table 1). In the case of the amino-Claisen rearrangement of compound **2e**, the allylic group migrates to both free *ortho* positions with formation of two regioisomeric products corresponding to 2-allyl-*N*-benzyl-5-methylaniline (**3e**) and 2-allyl-*N*-benzyl-3-methylaniline (**3e′**) in a 0.8:1 ratio (determined by NMR spectroscopy), which we could not separate.

Finally, compounds **3a**–**d** were heated at 80–90 °C with concentrated sulfuric acid for 1.5–2.5 h. Under these acidic conditions, the allyl moiety of molecules **3** provides an appropriate handle to generate the necessary and thermodynamically stable benzyl cation. Therefore the

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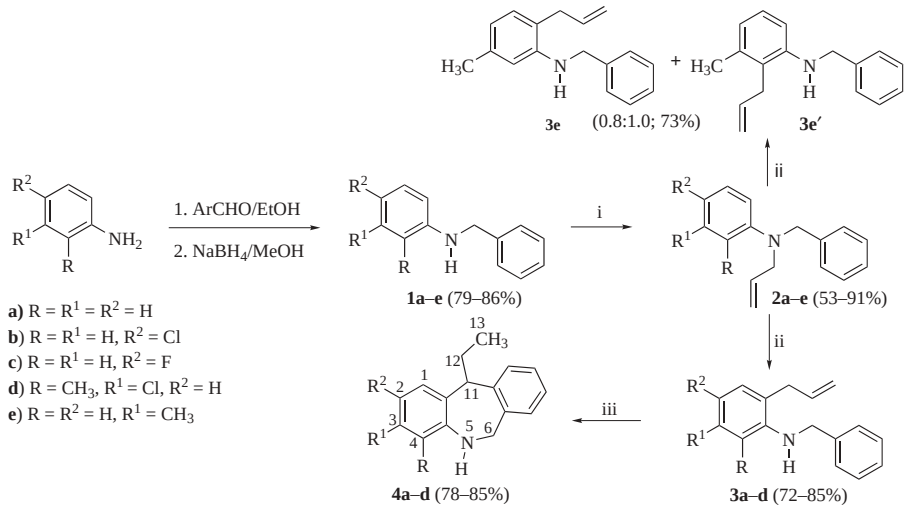


Scheme 2 *Reagents and conditions*: (i) $BrCH_2CH{=}CH_2$ (2 equiv), DMF, r.t. or acetone, K_2CO_3, reflux, 6–7 h; (ii) $BF_3{\cdot}OEt_2$ (1 equiv), sulpholane (3–5 mL), 140–155 °C, 2–3 h; (iii) concd H_2SO_4, 80–90 °C, 1.5–2.5 h.

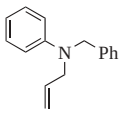
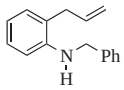
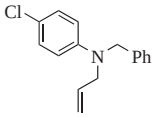
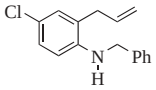
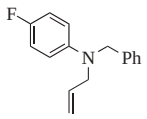
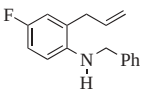
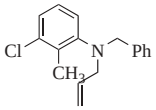
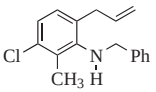
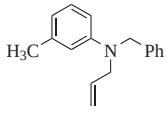
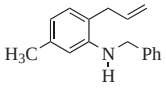
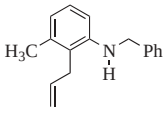
intramolecular Friedel–Crafts alkylation of the second benzene ring can be realized. Treatment of the reaction mixture with 25% ammonia solution, and extraction and purification by silica gel column chromatography afforded compounds **4a**–**d** in good yields (78–85%). Longer reaction times and higher temperatures resulted in the decomposition of key intermediates **3a**–**d**.

All spectroscopic data (IR, MS and ^1H NMR, ^{13}C NMR) of final products **4a**–**d** are in full agreement with the proposed structures.[25] These compounds showed absorption bands at 3446–3405 cm^{-1} due to amino group (N-H) in the IR spectra. In the electron impact (EI) MS, molecular ion peaks were observed at *m/z* (%) = 223 (14) [M^+], 257 (^{35}Cl, 17) [M^+], 241 (17) [M^+] and 271 (^{35}Cl, 13) [M^+] together with their fragment ion peaks $M^+ - C_2H_5$ as base peaks.

The most clear spectral proof for the structures **4** was the appearance of two triplets assignable to 11-CH (δ = 3.84–3.63 ppm, *J* = 7.7–7.3 Hz) and 13-CH_3 (δ = 0.96–0.91 ppm, *J* = 7.4–7.0 Hz), and a multiplet assignable to 12-CH_2 protons (δ = 2.23–2.14 ppm). The spectra also showed two doublets (δ = 4.95–4.71 and 4.30–4.00 ppm, *J* = 14.8–14.4 Hz) attributed to 6-CH_AH_B protons, while the corresponding peaks of precursors **3** were singlets (δ = 4.34–4.09 ppm). The signal of NH proton is observed only in spectrum of compound **4d** at δ = 4.09 ppm, while for other compounds this signal is not evident because it may be overlapped with the signal of proton 6-H_B.

This way, we have been demonstrated that $BF_3{\cdot}Et_2O$-catalyzed aromatic amino-Claisen rearrangement and intramolecular alkene Friedel–Crafts alkylation could gain prominence as a synthetically useful reactions to build the dibenz[*b*,*e*]azepine structural unit, which occurs in a number of bioactive molecules for a variety of biological targets, in particular, the tetracyclic antidepressants such as mianserin and its close relative analogues. The good yields of intermediates and final products as well as the

Table 1 Amino-Claisen Rearrangement of **2a**–**e** to **3a**–**e**

Entry	*N*-Allylaniline	Conditions	Rearranged product	Yield (%)
1	 **2a**	155 °C 2.5 h	 **3a**	80
2	 **2b**	140 °C 3 h	 **3b**	73
3	 **2c**	140 °C 3 h	 **3c**	72
4	 **2d**	140 °C 2 h	 **3d**	85
5	 **2e**	155 °C 2.5 h	 **3e**  **3e′**	73

general applicability accommodating a variety of substitutions on both aromatic rings are the main advantages of our approach. Further application of these methodologies in synthesis of other nitrogen containing heterocycles is currently under way in our laboratory.

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(23) Anderson, W. K.; Lai, G. *Synthesis* **1995**, 1287.
(24) **Spectral Data for Selected Compounds 3**.
Compound **3b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.29 (2 H, d, *J* = 6.0 Hz, -CH_2-), 4.10 (1 H, br s, NH), 4.34 (2 H, s, N-CH_2-), 5.15 (2 H, m, =CH_2), 5.95 (1 H, m, -CH=), 6.54 (1 H, d, *J* = 8.0 Hz, 6-H), 7.06 (1 H, d, *J* = 2.0 Hz, 3-H), 7.08 (1 H, dd, *J* = 8.0, 2.0 Hz, 5-H), 7.30–7.43 (5 H, m, H-phenyl). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.1 (-CH_2-), 48.2 (N-CH_2-), 111.8 (6-C), 116.9 (=CH_2), 122.0 (4-C), 125.2 (2-C), 127.3 (*ortho*-C), 127.4 (5-C), 128.7 (3-C), 129.0 (*para*-C), 129.5 (*meta*-C), 135.0 (-CH=), 139.0 (1′-C), 144.6 (1-C). MS (EI): *m/z* (%) = 257 (^{35}Cl, 8) [M^+], 242 (<1), 228 (1), 180 (11), 166 (26), 152 (11), 131 (40), 91 (100), 77 (10).
Compound **3c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.32 (2 H, d, *J* = 6.4 Hz, -CH_2-), 4.06 (1 H, br s, NH), 4.34 (2 H, s, N-CH_2-), 5.15 (2 H, m, =CH_2), 5.97 (1 H, m, -CH=), 6.56 (1 H, dd, *J* = 9.0, 5.0 Hz, 6-H), 6.83 (1 H, d, *J* = 3.0 Hz, 3-H), 6.85 (1 H, dd, *J* = 9.0, 3.0 Hz, 5-H), 7.30–7.39 (5 H, m, H-phenyl). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.2 (-CH_2-), 48.7 (N-CH_2-), 111.5 (d, *J* = 10.0 Hz. 6-C), 113.4 (d, *J* = 20.0 Hz, 3-C), 116.5 (d, *J* = 20.0 Hz, 5-C), 116.9 (=CH_2), 125.3 (d, *J* = 10.0 Hz, 2-C), 127.2 (*para*-C), 127.5 (*ortho*-C), 128.5 (*meta*-C), 135.1 (-CH=), 139.3 (1′-C), 142.3 (1-C), 155.6 (d, *J* = 206.1 Hz, 4-C). MS (EI): *m/z* (%) = 241 (28) [M^+], 212 (8), 198 (4), 164 (9), 150 (66), 135 (17), 91 (100), 77 (6), 65 (21).
Compound **3d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (3 H, s, 2-CH_3), 3.29 (2 H, dt, *J* = 6.0, 1.6 Hz, -CH_2-), 3.04 (1 H, br s, NH), 4.09 (2 H, s, N-CH_2-), 5.05 (2 H, m, =CH_2), 5.93 (1 H, m, -CH=), 6.95 (1 H, d, *J* = 8.0 Hz, 5-H), 7.07 (1 H, d, *J* = 8.0 Hz, 4-H), 7.33–7.40 (5 H, m, H-phenyl). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.6 (2-CH_3), 36.3 (-CH_2-), 53.6 (N-CH_2-), 116.9 (=CH_2), 123.4 (4-C), 127.4 (*ortho*-C), 127.8 (5-C), 128.3 (*para*-C), 128.6 (*meta*-C), 129.4 (3-C), 130.4 (6-C), 133.7 (2-C), 136.5 (-CH=), 139.0 (1′-C), 147.4 (1-C). MS (EI): *m/z* (%) = 271 (^{35}Cl, 11) [M^+], 256 (2), 242 (4), 194 (7), 180 (33), 166 (18), 145 (46), 130 (14), 115 (8), 91 (100), 77 (8), 65 (22).
(25) **NMR and Analytical Data for Compounds 4**.
Compound **4a**: IR (KBr): 3405 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (3 H, t, *J* = 7.4 Hz, 13-H), 2.17 (2 H, m, 12-H), 3.69 (1 H, t, *J* = 7.3 Hz, 11-H), 4.00 (1 H, d, *J* = 14.8 Hz, 6-H_B), 4.95 (1 H, d, *J* = 14.8 Hz, 6-H_A), 6.50 (1 H, d, *J* = 8.0 Hz, 4-H), 6.67 (1 H, td, *J* = 8.0, 1.0 Hz, 2-H), 6.96 (1 H, td, *J* = 8.0, 1.0 Hz, 3-H), 7.12 (1 H, dd, *J* = 8.0, 1.0 Hz, 1-H), 7.19–7.30 (4 H, m, 7-H-10-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.0 (13-C), 31.6 (12-C), 51.1 (6-C), 54.8 (11-C), 117.9 (4-C), 118.2 (2-C), 127.2 (3-C), 127.6-129.5 (7-C-10-C), 130.2 (11a-C), 130.8 (1-C), 136.5 (6a-C), 142.1 (10a-C), 146.2 (4a-C). MS (EI): *m/z* (%) = 223 (14) [M^+], 194 (100), 178 (8), 165 (11), 116 (10), 96 (10). Anal. Calcd for $C_{16}H_{17}N$: C, 86.06; H, 7.67; N, 6.27. Found: C, 86.13; H, 7.81; N, 6.14.
Compound **4b**: IR (KBr): 3406 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (3 H, t, *J* = 7.3 Hz, 13-H), 2.14 (2 H, m, 12-H), 3.63 (1 H, t, *J* = 7.7 Hz, 11-H), 4.17 (1 H, d, *J* = 14.4 Hz, 6-H_B), 4.77 (1 H, d, *J* = 14.4 Hz, 6-H_A), 6.40 (1 H, d, *J* = 8.5 Hz, 4-H), 6.91 (1 H, dd, *J* = 8.5, 2.3 Hz, 3-H), 7.10

(1 H, d, 2.3 Hz, 1-H), 7.12–7.34 (4 H, m, 7-H-10-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3 (13-C), 31.5 (12-C), 49.5 (6-C), 51.5 (11-C), 119.4 (4-C), 122.9 (2-C), 127.4 (3-C), 127.4–128.7 (7-C-10-C), 129.1 (11a-C), 130.7 (1-C), 136.5 (6a-C), 142.0 (10a-C), 145.1 (4a-C). MS (EI): *m/z* (%) = 257 (^{35}Cl, 17) [M^+], 228 (100), 193 (46), 165 (17), 115 (6), 89 (5). Anal. Calcd for $C_{16}H_{16}ClN$: C, 74.56; H, 6.26; N, 5.43. Found: C, 74.38; H, 6.49; N, 5.35.

Compound **4c**: IR (KBr): 3429 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (3 H, t, *J* = 7.1 Hz, 13-H), 2.18 (2 H, m, 12-H), 3.76 (1 H, t, *J* = 7.6 Hz, 11-H), 4.20 (1 H, d, *J* = 14.6 Hz, 6-H_B), 4.71 (1 H, d, *J* = 14.6 Hz, 6-H_A), 6.49 (1 H, dd, *J* = 8.0, 5.0 Hz, 4-H), 6.72 (1 H, ddd, *J* = 8.0, 3.0 Hz, 3-H), 6.82 (1 H, dd, *J* = 10.0, 3.0 Hz, 1-H), 7.13–7.22 (4 H, m, 7-H-10-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.9 (13-C), 30.8 (12-C), 49.7 (6-C), 53.1 (11-C), 113.7 (d, *J* = 20 Hz, 3-C), 116.7 (d, *J* = 20 Hz, 1-C), 119.5 (d, *J* = 10 Hz, 4-C), 126.8 (8-C), 127.4 (9-C), 128.2 (7-C), 129.1 (10-C), 130.0 (11a-C), 136.5 (6a-C), 141.3 (10a-C), 142.5 (4a-C), 156.4 (d, *J* = 230 Hz, 2-C). MS (EI): *m/z* (%) = 241 (17) [M^+], 212 (100), 196 (15), 183 (17), 165(10), 116 (9). Anal. Calcd for $C_{16}H_{16}FN$: C, 79.64; H, 6.68; N, 5.80.Found: C, 79.70; H, 6.80; N, 5.65.

Compound **4d**: IR (KBr): 3446 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (3 H, t, *J* = 7.4 Hz, 13-H), 2.20 (3 H, s, 4-CH_3), 2.23 (2 H, m, 12-H), 3.84 (1 H, t, *J* = 7.6 Hz, 11-H), 4.09 (1 H, br s, N-H), 4.3 (1 H, d, *J* = 14.6 Hz, 6-H_B), 4.90 (1 H, d, *J* = 14.6 Hz, 6-H_A), 6.78 (1 H, d, *J* = 8.3 Hz, 2-H), 6.92 (1 H, d, *J* = 8.3 Hz, 1-H), 7.18–7.29 (4 H, m, 7-H-10-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9 (13-C), 13.3 (4-CH_3), 29.9 (12-C), 48.0 (6-C), 52.5 (11-C), 117.5 (3-C), 120.3 (2-C), 124.9 (4-C), 125.9 (9-C), 126.5 (7-C), 127.0 (8-C), 127.7 (10-C), 127.8 (1-C), 131.8 (11a-C), 135.3 (6a-C), 140.9 (10a-C), 144.4 (4a-C). MS (EI): *m/z* (%) = 271 (^{35}Cl, 13) [M^+], 242 (100), 227 (6), 207 (31), 191 (10), 178 (11), 165 (8), 152 (6), 139 (2), 89 (4). Anal. Calcd for $C_{17}H_{18}ClN$: C, 75.13; H, 6.68; N, 5.15. Found: C, 75.29; H, 6.83; N, 5.08.