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2-Allyl-*N*-benzyl substituted α-naphthylamines as building blocks in heterocyclic synthesis. New and efficient syntheses of benz[*e*]naphtho[1,2-*b*]azepine and naphtho[1,2-*b*]azepine derivatives

Andrés Felipe Yépez,[a] Alirio Palma,[a,*] Elena Stashenko,[a] Ali Bahsas[b] and Juan M. Amaro-Luis[b]

[a]*Laboratorio de Síntesis Orgánica, Centro de Investigación en Biomoléculas, Escuela de Química, Universidad Industrial de Santander, A.A. 678, Bucaramanga, Colombia*
[b]*Laboratorio de RMN, Grupo de Productos Naturales, Departamento de Química, Universidad de los Andes, Mérida 5101, Venezuela*

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Abstract—A new series of 13-acetyl-7,12-dihydro-7-ethylbenz[*e*]naphtho[1,2-*b*]azepine (**4a–d**) and 2-aryl-4-hydroxy-2,3,4,5-tetrahydronaphtho[1,2-*b*]azepine derivatives (**6a–d**) have been synthesized from *N*-allyl-*N*-benzyl substituted α-naphthylamines (**1a–d**) by utilizing aromatic amino-Claisen rearrangement, intramolecular Friedel–Crafts alkylation and intramolecular dipolar 1,3-cycloaddition nitrone-olefin reactions.

During the last 50 years, dibenz[*b*,*e*]azepine and tetrahydro-1-benzazepine rings have attracted wide interest as several derivatives of these heterocyclic units have been found to possess useful pharmacological activities.[1–8] This fact has fuelled research, which focuses mainly in the development of methodologies for the preparation of many derivatives of these heterocyclic systems.[9–15]

Although a large number of synthetic routes to dibenz[*b*,*e*]azepine and tetrahydro-1-benzazepine derivatives are described in the literature, there is very few information about benz[*e*]naphtho[1,2-*b*]azepines[9] and tetrahydronaphtho[1,2-*b*]azepines,[16–18] which may, in part, be due to lack of general methods for the synthesis of such derivatives.

Lately, our attention has been focused on studying both the intramolecular Friedel–Crafts alkylation[19–21] and dipolar 1,3-cycloaddition reactions[22] as key steps in the construction of several nitrogen-containing heterocycles. In a more recent communication,[23] we described an expedient synthetic route to dihydrodibenz[*b*,*e*]azepine derivatives, from the readily available *N*-allyl-*N*-benzylanilines, through aromatic amino-Claisen rearrangement and Friedel–Crafts alkylation, as main transformations.

To broaden the scope of our approach, and the utility of intramolecular Friedel–Crafts alkylation and 1,3-dipolar cycloaddition processes as appropriate methodologies to dihydrobenz[*e*]naphtho[1,2-*b*]azepines and tetrahydronaphtho[1,2-*b*]azepines, we have been testing the chemistry of several 2-ally-*N*-benzyl-α-naphthylamines, the common key intermediate in the synthesis of these heterocyclic systems, in both acidic and oxidative conditions. The results of these studies are reported in this letter.

Synthesis of the 13-acetyl-7,12-dihydrobenz[*e*]naphtho-[1,2-*b*]azepines (**4a–d**) is depicted in Scheme 1. The starting *N*-allyl-*N*-benzyl substituted α-naphthylamines (**1a–d**) were prepared in good yields (70–85%) from the corresponding secondary aromatic amines and an excess

Keywords: Benz[*e*]naphtho[1,2-*b*]azepines; Tetrahydronaphtho[1,2-*b*]-azepines; Amino-Claisen rearrangement; Intramolecular Friedel–Crafts alkylation; Intramolecular dipolar 1,3-cycloaddition.
* Corresponding author. Fax: +57 76 349069/358210; e-mail: apalma@uis.edu.co

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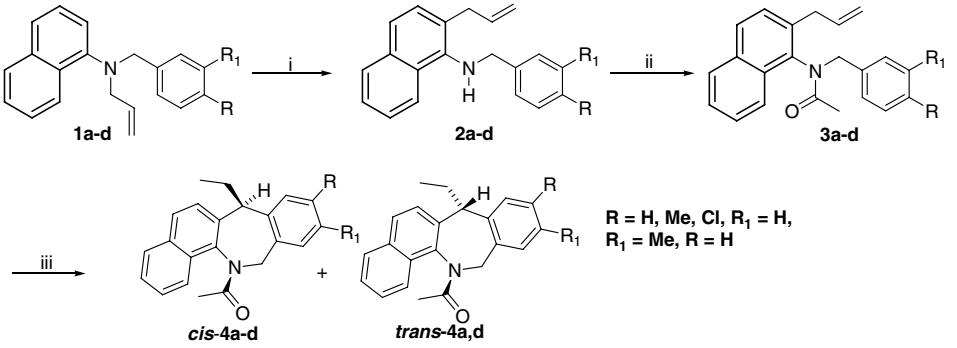


Scheme 1. Reagents and conditions: (i) $BF_3{\cdot}OEt_2$ (1 equiv), 118–120 °C, 1–2 h; (ii) Ac_2O, reflux, 3 h; (iii) PPA, 90 °C, 2 h.

(2 equiv) of allyl bromide, as an alkylating agent, in boiling acetone in the presence of K_2CO_3. The key intermediates (**2a**–**d**) were obtained in 61–88% yields by aromatic amino-Claisen rearrangement of *N*-allyl derivatives (**1a**–**d**) in the presence of equimolar amounts of $BF_3{\cdot}OEt_2$.[24] The reaction was completed within 1–2 h at 118–120 °C.

In the next step, we chose to use the N-acetylated 2-allyl-α-naphthylamines, instead of non-protected 2-allylnaphthylamines, to avoid the potential sulfonation of the naphthalene ring. Additionally, polyphosphoric acid (PPA) was used as promoter of the intramolecular Friedel–Crafts alkylation. Thus, N-acetylation of intermediates (**2a**–**d**) with excess of acetic anhydride (4 equiv) at reflux gave the corresponding *N*-acetyl derivatives (**3a**–**d**) in quantitative yields, which in turn were reacted with PPA at 90 °C to give the desired products (**4a**–**d**) in 34–64% yields.

The structures of (**4a**–**d**) were confirmed by ^1H NMR and ^{13}C NMR spectroscopy in $CDCl_3$ solution, and were fully assigned on the basis of COSY and HMQC as well as HMBC experiments.[25] Thus, the ^1H NMR spectra of **4a** (R = R_1 = H) and **4d** (R = H, R_1 = CH_3) indicate that these derivatives are formed as a mixture of two stereoisomers, in a 6:1 and 8:1 ratio, with cis and trans configurations relative to the spatial orientation of the ethyl group at C-7 with respect to the acetyl moiety at the nitrogen atom in the central ring. These isomers could be separated by recrystallization from heptane–ethyl acetate. The spectra displayed two set of signals for each of the diastereotopic 12-H_AH_B and 7-H protons, as well as for 7-ethyl protons. In contrast, the ^1H NMR spectra of **4b** (R = Me, R_1 = H) and **4c** (R = Cl, R_1 = H) displayed only one set of signals for the same protons, indicating that they are formed as unique stereoisomers. The NOESY spectra revealed the cis isomer as the major product, as indicated by the observation of a cross-peak between the methyl protons of the ethyl substituent at 7-position with the methyl protons of acetyl group at nitrogen atom.

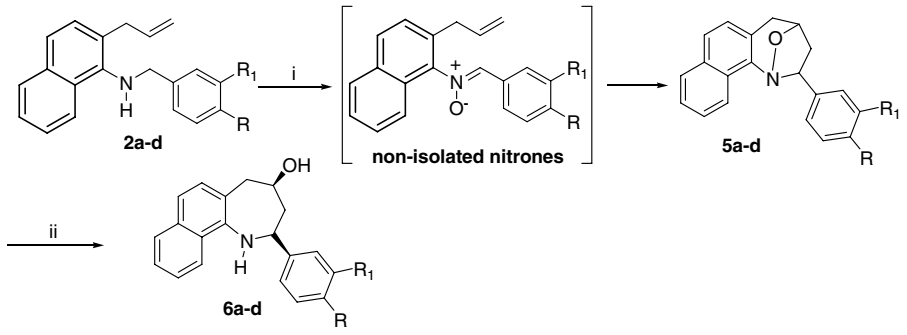
Synthesis of 2-aryl-4-hydroxy-2,3,4,5-tetrahydronaphtho[1,2-*b*]azepines (**6a**–**d**) is depicted in Scheme 2. The key intermediates (**2a**–**d**) were oxidized with hydrogen peroxide (H_2O_2) in the presence of catalytic amounts of sodium tungstate in acetone/H_2O (9:1), at low temperature (0–25 °C).[26] The reactions were completed within 45–50 h, and the isolated products were the cycloadducts (**5a**–**d**) in 30–66% yields.

Oxidation of (**2a**–**d**) is assumed to proceed via initial generation of reactive nitrones as unstable intermediates, which in the reaction conditions undergo intramolecular dipolar cycloaddition-[3+2] with the double bond of the allylic moiety to provide the cycloadducts (**5a**–**d**). The ^1H and ^{13}C NMR spectra of these compounds were assigned unambiguously using a combination of heteronuclear (HETCOR) spectra and chemical shifts.[27] The data derived from these spectra and NOESY experiments were used to identify the isolated cycloadducts as the *exo* isomer.

Finally, the reductive cleavage of the N–O bond of the *exo*-cycloadducts (**5a**–**d**) was carried out by simply heating the substrates with zinc powder in glacial acetic acid.[28] The reactions are typically completed within 5–10 h, and gave, after basic workup to remove the excess of acetic acid and column chromatographic purification, the desired tetrahydronaphtho[1,2-*b*]azepines (**6a**–**d**) in 64–78% yields.

The ^1H NMR spectra of these compounds[29] showed a single resonance for 2-H, 4-H and 3-CH_2 protons at 3.99–3.96, 3.96–3.92 and 2.31–2.22 ppm, respectively, and distinctive resonances for each of the diastereotopic 5-H_AH_B protons at 3.36–3.29 and 3.19–3.14 ppm. These data indicate that reductive cleavage of the N–O bond of the *exo*-cycloadducts was stereospecific with the formation of only one stereoisomer. The relative spatial orientation of subtituents at positions C-2 and C-4 was determined by means of NOESY experiments on the protons of the azepine ring. These experiments revealed that the target compounds contain both the 2-phenyl (aryl) and 4-hydroxy substituents on the same side of the molecule, consequently the isomers were identified as the *cis*-2-aryl-4-hydroxy-2,3,4,5-tetrahydronaphtho[1,2-*b*]azepines.

In summary, this contribution represents an extension of our studies dealing with the synthesis of heterocyclic compounds having the dibenz[*b*,*e*]azepine and tetrahydro-1-benz-azepine cores in their structure. Further studies will be carried out, in the near future, to test their potential biological activities.



Scheme 2. Reagents and conditions: (i) H_2O_2/Na_2WO_4, acetone/H_2O, 0–25 °C, 45–50 h; (ii) Zn/AcOH, 80–82 °C, 5–10 h.

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25. NMR data for cis isomer **4a**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.15 (3H, t, $J = 7.3$, –CH_2–CH_3), 1.83 (3H, s, CH_3—C═O), 2.40 (2H, m, 7-CH_2–), 4.28 (1H, d, $J = 17.2$, 12-H_B), 4.56 (1H, t, $J = 8.0$, 7-H), 6.33 (1H, d, $J = 17.2$, 12-H_A), 6.97 (1H, d, $J = 7$, 11-H), 7.05 (1H, t, $J = 7.0$, 10-H), 7.10 (1H, t, $J = 7.0$, 9-H), 7.26 (1H, d, $J = 7$, 8-H), 7.42 (1H, d, $J = 8.4$, 6-H), 7.47 (1H, td, $J = 8.0$, 1.2, 3-H), 7.56 (1H, td, $J = 8.0$, 2.0, 2-H), 7.80 (1H, d, $J = 8.4$, 5-H), 7.84 (1H, d, $J = 8.0$, 1-H), 7.86 (1H, d, $J = 8.0$, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 12.6 (–CH_2–CH_3), 22.6 (CH_3—C═O), 20.7 (7-CH_2–), 42.6 (7-C), 47.7 (12-C), 121.9 (1-C), 121.9 (6-C), 123.9 (8-C), 125.8 (3-C), 126.3 (10-C), 126.4 (9-C), 127.5 (2-C), 128.3 (11-C), 128.5 (5-C), 128.6 (4-C), 130.5 (4b-C), 133.0 (4a-C), 134.4 (6a-C), 134.8 (11a-C), 140.2 (7a-C), 141.3 (6b-C), 171.2 (C═O). NMR data for trans isomer **4a**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.93 (3H, t, $J = 7.2$, –CH_2–CH_3), 1.83 (3H, s, CH_3—C═O), 2.01 (2H, m, 7-CH_2–), 3.83 (1H, t, $J = 8.0$, 7-H), 4.18 (1H, d, $J = 16.8$, 12-H_B), 6.20 (1H, d, $J = 16.8$, 12-H_A), 7.14 (1H, d, $J = 6.8$, 11-H), 7.16 (1H, t, $J = 7.0$, 10-H), 7.18 (1H, t, $J = 7.0$, 9-H), 7.21 (1H, d, $J = 6.8$, 8-H), 7.42 (1H, d, $J = 8.4$, 6-H), 7.51 (1H, td, $J = 8.0$, 1.3, 3-H), 7.59 (1H, td, $J = 8.4$, 1.3, 2-H), 7.80 (1H, d, $J = 8.4$, 5-H), 7.84 (1H, d, $J = 8.4$, 1-H), 7.89 (1H, d, $J = 8.0$, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 13.2 (–CH_2–CH_3), 21.5 (CH_3—C═O), 30.7 (7-CH_2–), 46.7 (12-C), 55.8 (7-C), 121.2 (1-C), 125.6 (3-C), 126.1 (10-C), 126.3 (9-C), 127.2 (2-C), 127.8 (5-C), 128.1 (4-C), 128.2 (11-C), 128.7 (6-C), 129.7 (4b-C), 130.9 (8-C), 133.3 (4a-C), 134.8 (11a-C), 135.6 (6a-C), 137.9 (7a-C), 138.0 (6b-C), 170.6 (C═O).
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27. NMR data for cycloadduct **5a**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.63 (1H, dd, $J = 16.8$, 2.0, 5-H_B), 2.68 (2H, m,

3-H_AH_B), 3.59 (1H, dd, $J = 16.8$, 5.6, 5-H_A), 4.77 (1H, dd, $J = 8.0$, 3.2, 2-H), 5.09 (1H, td, $J = 5.2$, 2.0, 4-H), 7.23 (1H, d, $J = 8.4$, 6-H), 7.36 (1H, t, $J = 7.6$, 4′-H), 7.45 (2H, t, $J = 7.6$, 3′-H), 7.47 (1H, m, 9-H), 7.47 (1H, m, 10-H), 7.60 (2H, d, $J = 7.6$, 2′-H), 7.65 (1H, d, $J = 8.4$, 7-H), 7.81 (1H, dd, $J = 9.2$, 3.4, 8-H), 8.26 (1H, dd, $J = 9.6$, 3.6, 11-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 35.2 (5-C), 43.0 (3-C), 74.4 (2-C), 75.4 (4-C), 120.9 (5a-C), 122.0 (11-C), 125.4 (7-C), 125.7 (9-C), 125.7 (10-C), 126.4 (2′-C), 127.0 (4′-C), 127.3 (6-C), 127.5 (11a-C), 127.7 (8-C), 128.6 (3′-C), 132.5 (7a-C), 143.8 (1′-C), 145.5 (5b-C).

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29. NMR data for compound **6a**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.22 (2H, m, 3-H_AH_B), 3.14 (1H, dd, $J = 13.2$, 1.6, 5-H_B), 3.29 (1H, dd, $J = 13.2$, 10.0, 5-H_A), 3.92 (1H, qd, $J = 9.8$, 2.2, 4-H), 3.99 (1H, dd, $J = 13.4$, 7.2, 2-H), 4.37 (1H, br s, O–H), 7.30 (1H, d, $J = 8.4$, 6-H), 7.37 (1H, m, 4′-H), 7.39 (2H, m, 3′-H), 7.41 (1H, m, 9-H), 7.41 (1H, m, 10-H), 7.41 (2H, m, 2′-H), 7.46 (1H, dd, $J = 8.4$, 1.6, 7-H), 7.59 (1H, d, $J = 8.0$, 11-H), 7.79 (1H, dd, $J = 7.6$, 1.6, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 44.5 (5-C), 47.4 (3-C), 61.1 (2-C), 69.9 (4-C), 119.9 (11-C), 121.6 (7-C), 124.2 (5a-C), 125.2 (10-C), 125.7 (9-C), 126.3 (11a-C), 126.6 (2′-C), 127.9 (4′-C), 128.7 (8-C), 129.1 (3′-C), 129.9 (6-C), 133.4 (7a-C), 144.1 (1′-C), 144.6 (5b-C).