Sequential Amino-Claisen Rearrangement/Intramolecular 1,3-Dipolar Cycloaddition/Reductive Cleavage Approach to the Stereoselective Synthesis of *cis*-4-Hydroxy-2-aryl-2,3,4,5-tetrahydro-1(1*H*)-benzazepines

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Abstract: A novel stereoselective synthesis of *cis*-2-aryl-4-hydroxy-2,3,4,5-tetrahydro-1-benzazepines from *N*-allylanilines utilizing aromatic amino-Claisen rearrangement and intramolecular 1,3-dipolar cycloaddition methodologies is described. This sequence involves N-allylation of corresponding *N*-benzylanilines followed by amino-Claisen rearrangement, subsequent oxidation with in situ 1,3-dipolar cycloaddition affording isoxazolidines, and finally reductive cleavage of the isoxazolidinic N–O bond.

Key words: amino-Claisen rearrangement, intramolecular 1,3-dipolar cycloaddition, tetrahydro-1-benzazepines, *ortho*-allylanilines, reductive cleavage

Tetrahydro-1-benzazepine derivatives have been extensively investigated synthetically and pharmacologically. The diverse biological activities of these derivatives are well known as highly potent and orally active non-peptide arginine vasopressin antagonists for both V_{1A} and V_2 receptors,[1] potent inhibitors of cyclin-dependent kinases,[2] potent and orally bioavailable growth hormone secretagogue,[3] antagonists of *N*-methyl-D-aspartate and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors,[4] antagonists of platelet-activating factor,[5] and promising agents against HIV-1 infection.[6] The interesting biological activity of tetrahydro-1-benzazepines make them attractive targets in organic synthesis, consequently several synthetic strategies for their synthesis have already been developed. This heterocyclic system can be synthesized by the intramolecular Claisen-type reaction,[7] transition-metal-catalyzed oxidative N-heterocyclization of amino alcohols,[8] palladium- and nickel-catalyzed intramolecular amination of aryl bromides[9] and aryl chlorides.[10] Recently, the ring-closing metathesis (RCM) methodology was also conveniently applied for the synthesis of tetrahydro-1-benzazepines.[11]

Our continuing interest in *ortho*-allylaniline chemistry[12] led us to explore a new and efficient synthetic approach for the stereoselective synthesis of *cis*-2-aryl-4-hydroxy-tetrahydro-1-benzazepines applying intramolecular 1,3-dipolar cycloaddition as the key reaction.

The synthetic route to the novel compounds is outlined in Scheme 1. The starting materials, anilines **1a**–**g**, obtained by direct reductive amination of the corresponding benzaldehydes with sodium cyanoborohydride ($NaBH_3CN$),[13] were alkylated by treatment with an excess (2 equiv) of allyl bromide in the presence of potassium carbonate in acetone at reflux for 6–8 hours affording the corresponding *N*-allylanilines **2a**–**g** in good yield (65–95%). Introduction of an allyl moiety at the *ortho*-position of the aniline amino group was achieved by the aromatic amino-Claisen rearrangement[14] of the *N*-allyl derivatives **2a**–**g**. Thus, rearrangement of these derivatives by heating in the presence of 1.5 equivalents of boron trifluoride–diethyl ether complex ($BF_3{\cdot}OEt_2$), as acid catalyst, at 140–150 °C for 2–5 hours (monitored by TLC) gave the expected rearranged products **3a**–**g** in moderate to good yields (55–75%).

In the past three decades, much attention has been focused on the 1,3-dipolar cycloaddition of nitrone to olefin. This type of reaction has proven to be a very powerful method for the synthesis of five- and six-membered nitrogen-containing heterocycles.[15] However, to the best of our knowledge the intramolecular 1,3-dipolar cycloaddition using *N*-benzyl-*ortho*-allylanilines as appropriate building blocks in the construction of tetrahydro-1-benzazepine ring has not been explored yet. For this reason we examined its applicability to the synthesis of 4-hydroxy-2-aryl-2,3,4,5-tetrahydro-1-benzazepines.

Thus, *ortho*-allyl-*N*-benzylanilines **3a**–**g** were subjected to oxidation with 30% H_2O_2 in the presence of catalytic amounts of sodium tungstate (Na_2WO_4) according to a methodology described by Murahashi to obtain the corresponding nitrones.[16] Under the conditions employed, not only the amino group was transformed to a nitrone, but surprisingly an in situ intramolecular 1,3-dipolar cycloaddition of nitrone to olefin also took place affording the corresponding isoxazolidines **4a**–**g** in low yield (20–30%), and the starting *ortho*-allylanilines were recovered in 40–50%. To increase the yield of cycloadducts, the organic residue obtained after removing the solvent (acetone–H_2O) and the catalyst was dissolved in toluene and heated under reflux for 3–4 hours. In this thermal condition, cycloadducts were obtained in 40–60%, after column

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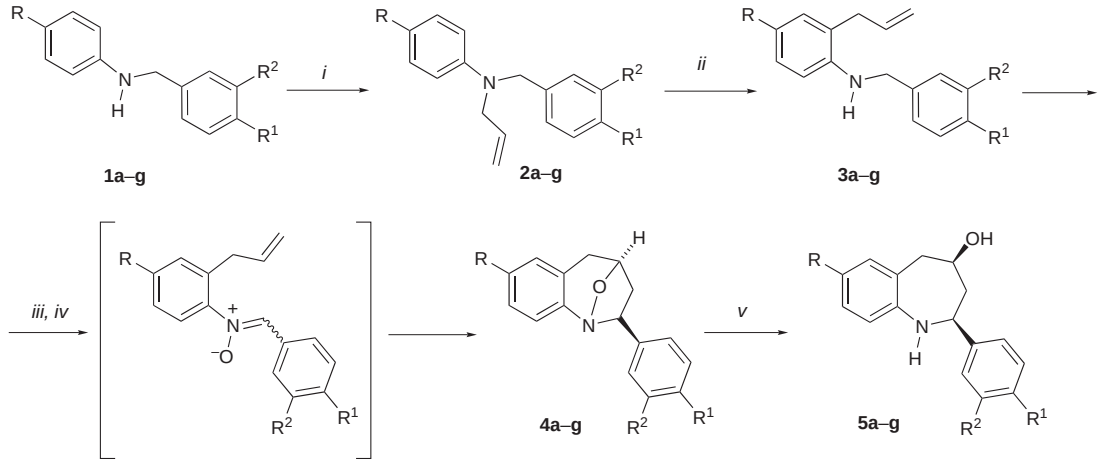

a: R = R^1 = R^2 = H; **b**: R = CH_3, R^1 = R^2 = H; **c**: R = Cl, R^1 = R^2 = H; **d**: R = F, R^1 = R^2 = H; **e**: R = OCF_3, R^1 = R^2 = H; **f**: R = R^2 = H, R^1 = Cl; **g**: R = R^1 = H, R^2 = CH_3

Scheme 1 *Reagents and conditions*: (i) $BrCH_2CH{=}CH_2$ (2 equiv), acetone, K_2CO_3, reflux, 6–8 h; (ii) $BF_3{\cdot}OEt_2$ (1.5 equiv), 140–155 °C, 2–5 h, 25 °C then sat. Na_2CO_3 solution and extraction with CH_2Cl_2; (iii) 30% H_2O_2 (3–4 mol), $Na_2WO_4{\cdot}2H_2O$ (4–6 mol%), acetone–H_2O (9:1 v/v), 25 °C to –5 °C, 40–50 h, then H_2O and extraction with CH_2Cl_2; (iv) toluene, reflux, 3–4 h; (v) Zn (6 mol), 80% AcOH (excess), 80–85 °C, 2–5 h, 25 °C then 5% NH_4OH solution and extraction with EtOAc.

chromatographic purification on silica gel, together with a considerable amount of polymeric material.

In all cases only one of the two possible diastereomers was isolated. Cycloadducts **4a**–**g** were shown to be *exo*-cycloadducts as evidenced by NOESY experiments.[17]

Even though oxidation of *ortho*-allylanilines **3a**–**g** afforded in one-pot the desired cycloadducts **4a**–**g** with high regio- and stereocontrol, the relative poor yield of this interesting transformation was a cause for concern. However, our attempts to improve the yields of cycloadducts by changing the reaction temperature or by increasing the relative quantity of the reagents and the reaction time were unsuccessful. The scope and mechanistic details of this one-pot transformation are under investigation and will be described in a forthcoming publication.

Finally, when *exo*-cycloadducts **4a**–**g** were subjected to reductive cleavage of N–O bond using Zn in excess of 80% acetic acid at 80–85 °C for 2–5 hours, as expected, the exclusive *cis*-2-aryl-4-hydroxytetrahydro-1-benzazepines **5a**–**g** were obtained in nearly quantitative yield after column chromatographic purification on silica gel. The relative configurations at the stereocenters of new compounds **5a**–**g** were assigned on the basis of NOESY experiments, in which the methynic protons 4-H and 2-H gave unambiguous cross signal. The 2-aryl groups are in equatorial positions, according to the geminal methine protons 2-H_{ax} showing one large coupling about 11.1 Hz and one small coupling about 2.1 Hz and therefore having exactly one *trans*-axial and one *cis*-equatorial coupling partners, namely 3-H_{ax} and 3-H_{eq}. The 4-hydroxy groups are also positioned equatorially, according to the geminal methine proton 4-H_{ax} showing one large coupling about 10.1 Hz and two small couplings about 3.7 and 1.6 Hz and therefore having two *trans*-axial coupling partners (3-H_{ax} and 5-H_{ax}) and two *cis*-equatorial coupling partners (3-H_{eq} and 5-H_{eq}).[18] The exclusive formation of *cis*-diastereomers may be explained by the stereospecific ring-opening of *exo*-cycloadducts during the reductive cleavage of N–O bond.

In summary, the stereoselective synthesis of *cis*-2-aryl-4-hydroxytetrahydro-1-benzazepines, based on one-pot oxidation–intramolecular 1,3-dipolar cycloadditon of *ortho*-allylanilines followed by reductive cleavage of the isoxazolidinic cycloadducts has been achieved. The method is flexible enough to allow the synthesis of many *cis*-tetrahydro-1-benzoazepine derivatives, by simply varying the substituents on both benzene nuclei. Furthermore, this method could be potentially extended to the synthesis of important bioactive molecules analogues.

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(17) NMR data for *exo*-cycloadduct **4a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.58 (1 H, d, *J* = 16.5 Hz, 5-H_A), 2.61–2.69 (2 H, m, 3-H_AH_B), 3.45 (1 H, dd, *J* = 16.6, 5.4 Hz, 5-H_B), 4.62 (1 H, dd, *J* = 11.2, 4.4 Hz, 2-H), 4.97 (1 H, m, 4-H), 7.12 (1 H, dd, *J* = 6.6, 2.1 Hz, 9-H), 7.15–7.24 (3 H, m, 6-H, 7-H, 8-H), 7.30 (1 H, t, *J* = 7.6 Hz, 4′-H), 7.39 (2 H, t, *J* = 7.6 Hz, 3′-H, 5′-H), 7.50 (2 H, d, *J* = 7.2 Hz, 2′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.6 (5-C), 42.7 (3-C), 75.1 (4-C), 75.3 (2-C), 121.9 (9-C), 125.2 (5a-C), 125.9 (7-C), 126.4 (2′-C, 6′-C), 126.5 (8-C), 126.9 (4′-C), 128.4 (3′-C, 5′-C), 129.8 (6-C), 143.8 (1′-C), 150.9 (9a-C).

(18) NMR data for *cis*-stereoisomer **5a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14 (1 H, ddd, *J* = 11.0, 10.7, 10.5 Hz, 3-H_{ax}), 2.22 (1 H, ddt, *J* = 11.0, 2.9, 1.9 Hz, 3-H_{eq}), 3.03 (1 H, dt, *J* = 13.6, 1.9 Hz, 5-H_{eq}), 3.13 (1 H, dd, *J* = 13.6, 10.5 Hz, 5-H_{ax}), 3.88 (1 H, tdd, *J* = 10.5, 2.9, 1.9 Hz, 4-H_{ax}), 3.98 (1 H, dd, *J* = 11.0, 1.9 Hz, 2-H_{ax}), 6.70 (1 H, d, *J* = 7.6 Hz, 9-H), 6.92 (1 H, t, *J* = 7.6 Hz, 7-H), 7.10 (1 H, t, *J* = 7.6 Hz, 8-H), 7.18 (1 H, d, *J* = 7.6 Hz, 6-H), 7.35 (1 H, t, *J* = 6.9 Hz, 4′-H), 7.39 (2 H, d, *J* = 6.9 Hz, 2′-H, 6′-H), 7.43 (2 H, t, *J* = 6.9 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.7 (5-C), 48.5 (3-C), 61.3 (2-C), 70.0 (4-C), 120.1 (9-C), 121.8 (7-C), 126.6 (2′-C, 6′-C), 127.4 (8-C), 127.8 (4′-C), 128.0 (5a-C), 128.9 (3′-C, 5′-C), 131.6 (6-C), 145.1 (1′-C), 149.4 (9a-C).