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Reaction of benzyne with 1,2,3,4-tetrahydroisoquinolines as an access to 1*H*-3-benzazepines

Natalia I. Guranova,[a] Alexey V. Varlamov,[a] Roman A. Novikov,[b] Alexander V. Aksenov,[c] Tatiana N. Borisova,[a] Elena A. Sorokina[a] and Leonid G. Voskressensky*[a]

[a] *Organic Chemistry Department, Peoples Friendship University of Russia (RUDN University), 117198 Moscow, Russian Federation. Fax: +7 495 955 0779; e-mail: lvoskressensky@sci.pfu.edu.ru*

[b] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

[c] *North-Caucasus Federal University, 355009 Stavropol, Russian Federation*

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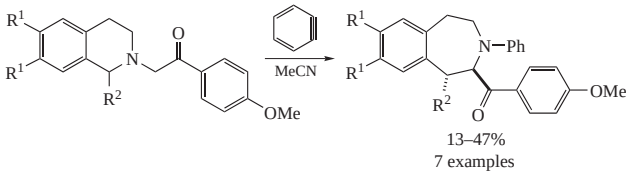
1,2,3,4-Tetrahydroisoquinolines bearing phenacyl group at the nitrogen atom in their reaction with benzyne in acetonitrile undergo ring expansion to give 1*H*-3-benzazepines.

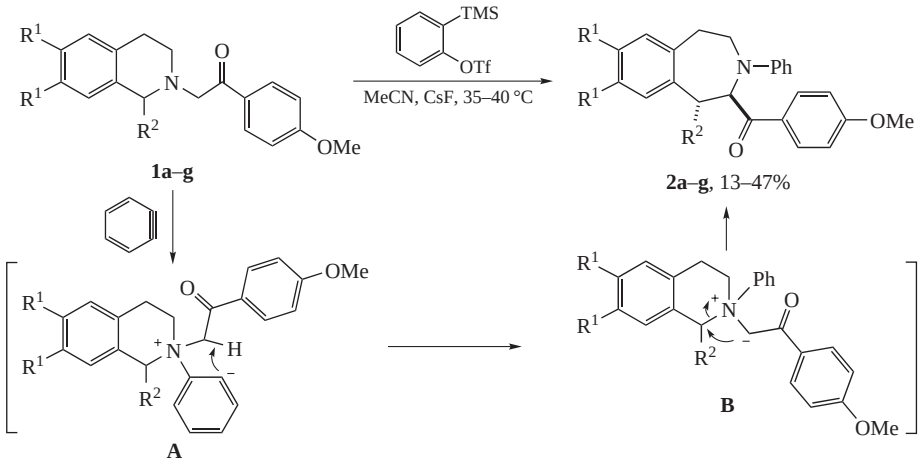


Benzazepine motif can be found in natural compounds such as lennoxamine,[1–5] clavizepine[6–8] and cephalotaxine.[9,10] Substituted benzazepines have a wide range of biological activity.[11–17] 1-Aryl-3-benzazepines possess analgesic, antihistamine, anticholinergic activities. Fenoldopam is an antihypertensive drug for patients with renal failure. The derivatives of 3-benzazepine are known as agonists and antagonists of D_1[18–21] and D_3 dopamine receptors.[22] 1-Methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine is a selective 5-HT_{2C} receptor agonist prospective for treatment of obesity.[23] Some 3-benzazepine derivatives exhibit *in vivo* activity in experiments on animals against neurological abnormalities including Parkinsons[25] and Alzheimer[26] diseases.

The known methods for constructing benzazepine are based on the acid-catalyzed intramolecular Friedel–Crafts reaction,[27–31] the rearrangement of 1-(α-hydroxybenzyl)tetrahydroisoquinolines[32,33] under acidic conditions, or the Stevens rearrangement of isoquinolines.[12] Examples for the synthesis of 1,2-disubstituted benzazepines[34–39] are few in number. To date, only one synthesis of 1-arylsubstituted 3-benzazepines using arynes has been described,[40] in this case the substituent being introduced into already existing seven-membered cycle.

Here, we propose a novel method for construction of 1,2-disubstituted 3-benzazepines based on reaction of 1,2,3,4-tetrahydroisoquinolines with generated *in situ* benzyne (Scheme 1). Arynes are known to react with nitrogen nucleophiles with the formation of zwitterions.[41–45] The presence of activated methylene group near nitrogen atom in such zwitterion would cause the formation of ylide that can further undergo Stevens rearrangement leading to ring expansion products.

Phenacyl substituted tetrahydroisoquinolines **1a**–**g** (Scheme 1) were obtained by alkylation of the corresponding NH-tetrahydroisoquinolines[46] with *p*-methoxyphenacyl bromide. Compounds **1a**–**g** reacted with benzyne upon moderate heating in acetonitrile in the presence of CsF. The reaction proceeded smoothly within 24 h to afford 1-R-2-phenacyl substituted 1,2,4,5-tetrahydro-1*H*-3-benzazepines **2a**–**g** in 13–47% yields. The lowest yield was observed for 1-(2-fluorophenyl)benzazepine **2e** (13%), presumably due to steric hindrance caused by *ortho*-fluorine



a $R^1 = R^2 = H$
b $R^1 = H$, $R^2 = Ph$
c $R^1 = OMe$, $R^2 = Ph$
d $R^1 = OMe$, $R^2 = 4\text{-}NO_2C_6H_4$
e $R^1 = OMe$, $R^2 = 2\text{-}FC_6H_4$
f $R^1 = OMe$, $R^2 = 4\text{-}MeOC_6H_4$
g $R^1 = OMe$, $R^2 = 3,4,5\text{-}(MeO)_3C_6H_2$

Scheme 1

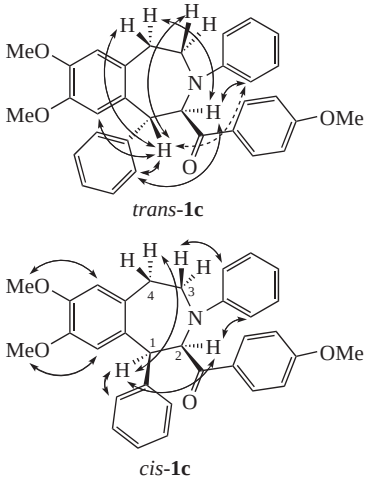


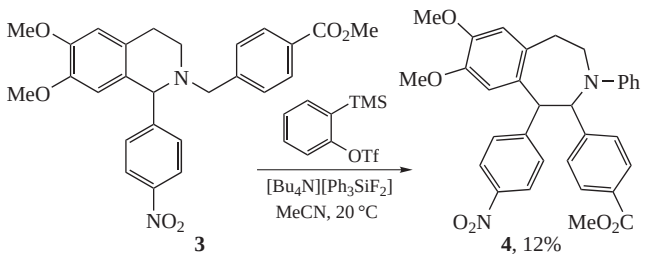
Figure 1 NOESY correlations between benzazepine **1c** protons.

atom. Unsubstituted at C-1 position benzazepine **2a** was also formed in moderate yield (26%). Therefore, we performed the reactions of compounds **1a**,**c**,**e** with benzyne in microwave reactor at 110 °C. To our delight, the microwave irradiation allowed us to minimize the reaction time to 15 min and increase the yields of benzazepines **2e** and **2a** to 55 and 34%, respectively. The yield of product **2c**, however, remained unchanged. The formation of 7-membered ring was not observed in the reaction of tetrahydroisoquinoline **1c** with benzyne in DMSO/CsF and THF/TMAF systems even upon heating.

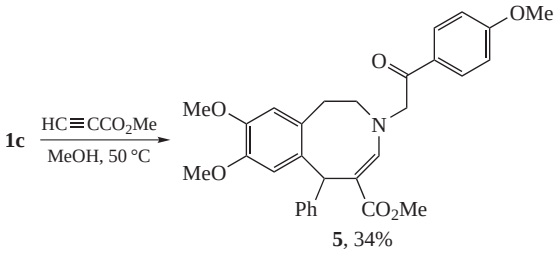
We suppose that zwitterion **A** generated through addition of benzyne to tetrahydroisoquinoline **1** due to the acidic nature of methylene group transforms into ylide **B** (see Scheme 1). The Stevens rearrangement of the latter leads to benzazepines **2** forming predominantly as *trans* isomers. According to NMR analysis of crude reaction product **2c** (Figure 1), both *trans* and *cis* isomers are formed (7 : 1 ratio). Purification on SiO_2 allows one to obtain pure *trans*-azepines. It is of note that highly stereospecific formation of tetrahydrobenz-3-azepines from the quaternary salts of 4-methoxycarbonylmethyl-4-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolines in the presence of amines was described.[34]

In the major isomer, the protons 1-H and 2-H are *trans* located as evidenced by a large $J_{1,2}$ 8.3 Hz. Conversely, the 1-H and 2-H protons of the minor *cis*-isomer resonate as broad unresolved doublets. No cross peaks between 1-H and 2-H protons are observed in the NOESY spectra of the major isomer, while they, as well as 1-H and 4-H correlations, are characteristic of the *cis*-isomer. The ^{1}H NMR spectra of *trans*-isomers contain two doublets from hydrogen atoms at C-1 and C-2 at 5.22–5.42 and 5.54–5.61 ppm, respectively, with $J_{1,2}$ 7.7–8.3 Hz.

To assess the effect of the phenacyl substituent, we carried out the reaction between benzyne and isoquinoline **3** that does not bear strong activating group at the nitrogen atom. A complex mixture was formed in this case, from which azepine **4** was isolated in 12% yield (Scheme 2). This could be due to the high nucleophilicity of the anion center in the initially formed zwitterion of type **A** (see Scheme 1).



Scheme 2



Scheme 3

Note that the reaction of tetrahydroisoindoline **1c** with methyl propiolate leads to azocine **5** (Scheme 3). The formation of benzazepine was not observed in this case.

In summary, we have demonstrated that 1,2,3,4-tetrahydroisoquinolines bearing at the nitrogen atom a substituent with activated methylene group in their reaction with benzyne undergo the Stevens rearrangement furnishing 1,2-disubstituted 3-benzazepines with *trans* configuration of the major isomer. Microwave irradiation promotes the reaction and raises the yields of the products. The method is convenient since it allows one to avoid preliminary preparation of quaternary salts and the use of strong bases.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.01.005.

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