4-N-ARYL(BENZYL)AMINO-4-HETARYL-1-BUTENES AS BUILDING BLOCKS IN HETEROCYCLIC SYNTHESIS. 3. A SIMPLE SYNTHESIS OF FLUORINATED 4-METHYL-2-(3-PYRIDYL)-1,2,3,4-TETRAHYDROQUINOLINES AND THEIR RESPECTIVE QUINOLINES

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Abstract: 6-Fluoro- and 6,8-difluro-4-methyl-2-(3-pyridyl)-1,2,3,4-tetrahydroquinolines (**5,6**) and their respective quinolines (**7,8**) were obtained by a two or three step synthesis, starting from the corresponding aldimines (**1,2**) preformed from 4-fluoro- or 2,4-difluoroanilines and 3-pyridinecarboxaldehyde via a sequence of reactions that included nucleophilic addition of Grignard reagents to the aldimines and an acid-mediated intramolecular cyclisation of the homoallylamines with fluorinated substituents (**3,4**).

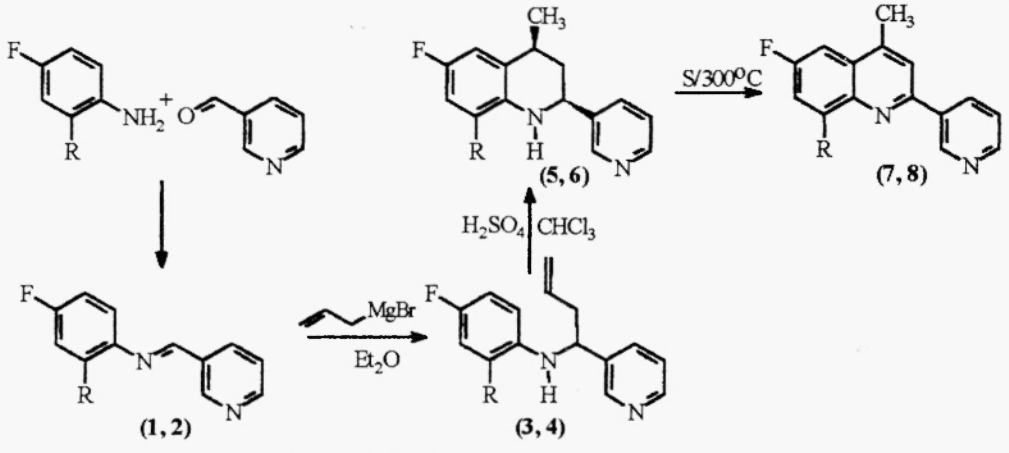
Introduction

The applicability of fluorinated quinolines and quinolones in heterocyclic and medicinal chemistry is well known. These compounds have wide and diverse applications in organic synthesis and drug preparation. Modern antibacterial fluoroquinolones such as norfloxacin and ciprofloxacin (the third generation antibiotics) are commercially available.[1,2] The 4-fluoroquinolines[3] and analogs are valuable precursors to amino-substituted quinoline derivatives that are DNA triple-helix specific interalators.[3,4] Therefore, fluorinated quinolines have received much interest due to the increased recognition of their biomedical and synthetic importance.[5] On the other hand, a large number of tetrahydroquinoline derivatives are involved in the manufacture of a wide variety of medicinals and pharmaceuticals. However, the conventional chemical fluorination of (tetrahydro)quinolines is not easy to perform and often requires hazardous reagents.[6] The general synthetic routes to fluoroquinolines and fluorotetrahydroquinolines are based on the cyclocondensation of fluoroanilines and α,β-unsaturated carbonyl compounds (the Skraup synthesis)[7,8] or cyclisation of β-(N-fluorophenyl)aminopropionic acids in the presence polyphosphoric acid at 120-130 °C.[9] With these facts in mind, we consider that the fluorinated tetrahydroquinolines with a pyridine moiety constitute an interesting class of organic compounds which can serve as starting materials for the preparation of drug. As a continuation of our current efforts directed toward exploring the synthetic potential of homoallylamines (4-N-

arylamino-1-butenes),[10-13] we describe here an simple two step synthesis of 6-fluoro- and 6,8-difluro-4-methyl-2-(3-pyridyl)-1,2,3,4-tetrahydroquinolines starting from the corresponding aldimines, which are obtained from 4-fluoro- or 2,4-difluoroanilines and 3-pyridinecarboxaldehyde.

2 Results and Discussion

The allylation Grignard reaction[14] of ald- and ketimines is a powerful method for the preparation of homoallylic amines which are useful intermediates for the construction of bioactive substances.[15-18] As outlined in the scheme 1, our strategy for the synthesis of the fluorinated tetrahydroquinolines (**5,6**) started from aldimines (**1,2**), which were easily prepared from 3-pyridinecarboxaldehyde and 4-fluoroaniline or 2,4-difluoroaniline. Both isolated solid imines showed in their IR spectra the characteristic C=N bands appearing in the region of 1670-1631 cm^{-1}. The addition of an ether solution of these aldimines to preformed allyl magnesium bromide in ether furnished the expected 3-butenilamines (**3,4**), which are valuable precursors to tetrahydroquinolines with fluorinated substituents. The intramolecular cationic cyclisation of the compounds (**3,4**) was readily achieved by heating these compounds in 85% sulfuric acid in chloroform affording the respective 6-fluoro- and 6,8-difluro-4-methyl-2-(3-pyridyl)-1,2,3,4-tetrahydroquinolines (**5,6**) in good yields (Scheme 1).



R = H (1, 3, 5, 7), F (2, 4, 6, 8)

Scheme 1.

According to the GC-MS spectra of the crude reaction product for tetrahydroquinoline (**5**), a mixture of the two geometric isomers (cis-trans: 4-Me/2-Py) is observed in the ratio 7 : 1. The observation of diastereoisomeric 1,2,3,4-tetrahydroquinolines during the cyclisation of 4-N-arylamino-1-butenes agrees to previous reports for related compounds.[19] We have found that purification by column chromatography led to the enrichment of the cis-isomer, however we were unable to isolate minor trans-isomer. The same analysis of the crude reaction product for tetrahydroquinoline (**6**) revealed the formation of a unique diasteroisomer (2e-Py/4e-Me). ^{1}H and ^{13}C NMR analysis of both isolated and purified tetrahydroquinolines indicated a cis

configuration of the methyl group and the pyridine moiety disposed both equatorially at C-4 and C-2, respectively.[20]

Fusion of obtained tetrahydroquinolines (**5,6**) with powdered sulphur (270-300°C, 10-20 min) afforded the 4-methylquinolines (**7,8**) containing fluorine atoms and the 3-pyridyl fragment at C-2. The products (**5-8**) were purified by column chromatography on alumina, as stable solids. The structures of the C-2 pyridyl tetrahydroquinolines (**5,6**) and their respective quinolines (**7,8**) were confirmed by IR, ^{1}H, ^{13}C, and ^{19}F NMR spectra and were supported by the mass spectrometric data.[21] The carbon assignations were confirmed by COSY and NOESY experiments.

The simplicity of the procedure and accessibility of the starting materials allowed us to prepare these new 6-fluorinated and 6,8-difluorinated 2-(3-pyridyl)-4-methyltetrahydroquinolines in large quantities and their chemistry is in progress in our laboratory. Moreover, all fluorinated products (**3-8**) were evaluated for antifungal and antichagasic properties. Study on the antifungal activity showed that compounds (**3,4**) and (**7**) displayed significant activity (MICs < 25 μg/mL) against the fungus *A. niger*, *M. canis*, *E. floccosum* and *T. rubrum*. Results on the anti-trypanocidal activity showed that compounds (**3-5**) were active (96-98%) at 100 μg/mL against the parasite *T. cruzi* (epimasigotes) with low non specific citotoxicity (12-40%).[22]

Experimental

Experimental conditions were described in previous communication of this series.[10] Elemental analyses were in satisfying agreement with the calculated data. The allylation reactions of aldimines **1,2** and were Intramolecular acid cyclisation of aminobutenes **3,4** carried out using known procedures.[11,12] Aromatization of tetrahydroquinolines **5,6** was carried out with the excess of sulphur by know procedure.[23]

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20. The detailed results from these studies will be published elsewhere.

21. Some selected data: for **5** - ^{13}C NMR (100 MHz) δ. 156.20 (d, 6-C, $^{1}J_{CF}$ = -235.0 Hz); 149.20 (2'-C_{Py}); 148.62 (6'-C_{Py}); 140.51 (d, 8a-C, $^{4}J_{CF}$ = 2.0 Hz); 139.48 (3'-C_{Py}); 134.18 (4'-C_{Py}); 127.46 (d, 4a-C, $^{3}J_{CF}$ = 6.1 Hz); 123.62 (5'-C_{Py}), 115.08 (d, 8-C, $^{3}J_{CF}$ = 7.4 Hz); 113.48 (d, 5-C, $^{2}J_{CF}$ = 23.0 Hz), 113.43 (d, 7-C, $^{2}J_{CF}$ = 22.3 Hz), 54.72/50.07 (2-C), 40.99/37.79 (3-C), 31.34/36.54 (4-C), 20.07/23.87 (4-CH_3). ^{19}F NMR (188.31 MHz) δ: -125.64 (quintet, 6-F, $^{4}J_{FH}$ = 5.6 Hz); for **6** -^{13}C NMR (100 MHz) δ: 155.22 (dd, 6-C, $^{1}J_{CF}$ = -239.0 Hz, $^{4}J_{CF}$ = 12.8 Hz); 151.46 (dd, 8-C, $^{1}J_{CF}$ = -241.0 Hz, $^{4}J_{CF}$ = 12.8 Hz); 148.44 (2'-C_{Py}); 148.03 (6'-C_{Py}); 139.00 (3'-C_{Py}); 134.91 (4'-C_{Py}); 131.88 (dd, 4a-C, $^{3}J_{CF}$ = 7.4 Hz, $^{3}J_{CF}$ = 7.4 Hz); 128.59 (dd, 8a-C, $^{2}J_{CF}$ = 12.8 Hz, $^{4}J_{CF}$ = 3.4 Hz); 123.42 (5'-C_{Py}); 108.90 (dd, 5-C, $^{2}J_{CF}$ = 22.3 Hz, $^{4}J_{CF}$ = 3.4 Hz); 101.70 (dd, 7-C, $^{2}J_{CF}$ = 23.6 Hz, $^{2}J_{CF}$ = 24.3 Hz); 56.01 (2-C); 46.89 (3-C); 37.16 (4-C); 19.09 (4-CH_3). ^{19}F NMR (188.31 MHz) δ: -122.47 (d, 6-F, $^{3}J_{FH}$ = 16.7 Hz); -129.7 (s, 8-F); for **7**- ^{13}C NMR (50 MHz) δ: 160.54 (d, 6-C, $^{1}J_{CF}$ = -247.2 Hz); 153.65 (2-C); 150.14 (2'-C_{Py}); 148.65 (6'-C_{Py}); 145.25 (3'-C_{Py}); 144.74 (d, 8a-C, $^{4}J_{CF}$ = 6.1 Hz); 134.88 (4-C); 134.70 (4'-C_{Py}); 132.76 (d, 8-C, $^{3}J_{CF}$ = 9.2 Hz); 128.15 (d, 4a-C, $^{3}J_{CF}$ = 9.2 Hz); 123.60 (5'-C_{Py}), 119.69 (3-C); 119.68 (d, 5-C, $^{2}J_{CF}$ = 25.9 Hz); 107.31 (d, 7-C, $^{2}J_{CF}$ = 22.9 Hz); 19.0 (4-CH_3). ^{19}F NMR (188.31 MHz) δ: -125.64 (q, $^{3}J_{FH}$ = 8.3 Hz, $^{4}J_{FH}$ = 5.6 Hz); for **8** - ^{13}C RMN (50 MHz) δ: 159.61 (dd, 6-C, $^{1}J_{CF}$ = -247.2 Hz, $^{3}J_{CF}$ = 12.2 Hz); 159.23 (dd, 8-C, $^{1}J_{CF}$ = -260.9 Hz, $^{3}J_{HF}$ = 13.7 Hz); 153.77 (2-C); 150.44 (2'-C_{Py}); 148.62 (6'-C_{Py}); 146.98 (3'-C_{Py}); 135.01 (4'-C_{Py}); 132.97 (4-C); 128.91 (dd, 4a-C, $^{3}J_{CF}$ = 10.7 Hz, $^{3}J_{CF}$ = 3.1 Hz); 123.75 (5'-C_{Py}); 120.84 (3-C); 111.41 (dd, 8a-C, $^{2}J_{CF}$ = 21.4 Hz, $^{4}J_{CF}$ = 3.1 Hz); 105.35 (dd, 7-C, $^{2}J_{CF}$ = 29.0 Hz, $^{2}J_{CF}$ = 22.9 Hz); 103.33 (dd, 5-C, $^{2}J_{CF}$ = 21.4 Hz, $^{4}J_{CF}$ = 4.6 Hz), 19.35 (4-CH_3). ^{19}F NMR (188.31 MHz) δ: -108.42 (q, 6-F, $^{3}J_{FH}$ = 8.5 Hz, $^{3}J_{FH}$ = 8.3 Hz); -117.44 (t, 8-F, $^{3}J_{FH}$ = 8.9 Hz).

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