4-N-ARYL(BENZYL)AMINO-4-HETARYL-1-BUTENES AS BUILDING BLOCKS IN HETEROCYCLIC SYNTHESIS. 1. NEW ROUTE TO 4,6-DIMETHYL-2-PYRIDYLQUINOLINES FROM THE 4-N-p-METHYLPHENYLAMINO-4-PYRIDYL-1-BUTENES

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Abstract: Mediated-acid intramolecular cyclisation of 4-N-p-methylphenylamino-4-pyridyl-1-butenes **4-6** was used to obtain new C-2 pyridyl substituted 4,6-dimethyl-1,2,3,4-tetrahydroquinolines **7-9**, which were oxidised then to their aromatic analogues **10-12** in good yields.

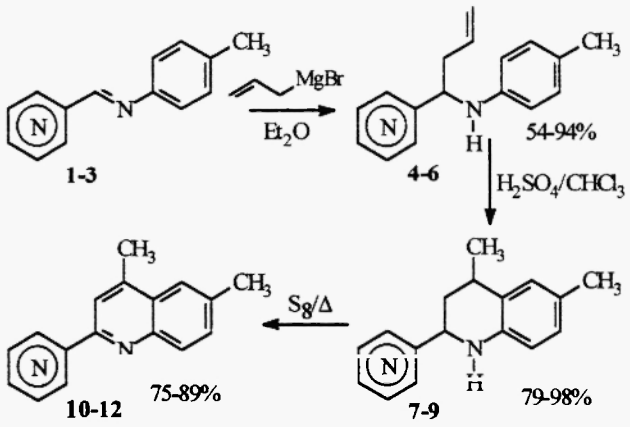
Introduction

The synthesis of quinolines[1] and their hydrogenated derivatives[2,3] have been of considerable interest to heterocyclic and medicinal chemists for many years as medicines[4] and as the basic unit of series of natural alkaloids.[5] Substituted 4-methylquinolines are useful starting products for ring construction of complex natural N-heterocycles.[6,7] Moreover, the 8-(diethylaminohexylamino)-6-methoxy-4-methylquinoline is highly effective against the protozoan parasite *Trypanosoma cruzy*, which is the agent of Chagas' disease.[8] Several antitumor antibiotics are based on the 2-(α-pyridyl)quinoline-quinone tricyclic molecule.[9] Keeping in view the above facts, we developed a simple and general method for the preparation of C-2 pyridyl substituted 4,6-dimethyl-(tetrahydro)quinolines. As part of our current investigation on the synthetic potential of homoallylamines[10-12] obtained from the simple ald- and ketimines, we describe here an efficient synthesis of 4,6-dimethyl-2-[α-(β- or γ-)pyridyl]quinolines starting from the corresponding 4-N-p-methylphenylamino-4-pyridyl-1-butenes (homoallylamines).

Results and Discussion

Our strategy is based on the use of a very useful allylation Grignard reaction[13] of aldimines which leads to the preparation of homoallylamines. The requisite known N-pyridinyliden-p-toluidines **1-3** were

simply prepared from p-toluidine and corresponding pyridine-α-(β- or γ-)carboxaldehydes heating the mixture in dry ethanol. The addition of a ether or THF solution of aldimines to preformed allyl magnesium bromide in ether (THF) afforded the 4-N-p-methylphenylamino-4-[α-(β- or γ-)pyridyl]-1-butenes **4-6**[14] which are suitable molecule precursors for tetrahydroquinoline derivatives (Scheme). It is worth noting that the use of ether is limited by the solubility of utilized aldimines. Gentle heating of aminopyridylbutenes **4-6** with 85% sulfuric acid in chloroform afforded the respective 4,6-dimethyl-2-pyridyl-1,2,3,4-tetrahydroquinolines **7-9** in 72-79 % yields. According to the GC-MS analysis of crude reaction, these tetrahydroquinolines exist as a mixture of the two geometric isomers (trans-cis: 4-Me/2-Py) in the ratio 1 : 2.5, 1 : 7.0 and 1 : 2.0, respectively.[15] Similar fact has been observed previously for the related compounds.[16] Attempts to separate these diastereoisomers by conventional column chromatography led to the isolation of major diastereoisomer for tetrahydroquinoline **8**. Its NMR analysis[17] revealed that it possess a cis-configuration of the methyl group and the pyridine moiety disposed both equatorially at C-4 ($J_{4a,3a}$ = 12.1 Hz, $J_{4a,3e}$ = 6.0 Hz) and C-2 ($J_{2a,3a}$ = 11.6 Hz, $J_{2a,3e}$ = 2.5 Hz), respectively. Thus, we succeeded in separating of major cis-isomer, however, we were enable to isolate minor trans-isomer.



Scheme

These diastereoisomeric mixture of tetrahydroquinolines were subjected to the aromatization process. Rapid fusion of these reduced quinoline forms with elementary powdered sulphur (270-300°C, 10-20 min) furnished 4,6-dimethylquinolines **10-12** containing α-, β- or γ-pyridyl fragment at C-2. The structures of the C-2 pyridyl substituted quinolines **10-12** were strongly confirmed by IR, ^{1}H- and ^{13}C-NMR spectra and were supported by the mass spectrometric data.[18]

The simplicity of this elegant protocol and accessibility of the starting materials allowed us to prepare these new pyridyl substituted 4-methylquinolines that should have wide applicability in heterocyclic chemistry.

Experimental

Melting points were measured in open capillaries with a Fisher-Johns melting point apparatus and uncorrected. Infrared spectra were recorded on a Nicolet Avatar 360 FT spectrometer as KBr pellets unless otherwise indicated. NMR spectra were determined on a Jeol 300 and Bruker AM-400 spectrometer in $CDCl_3$ with TMS as internal standard. A Hewlett-Packard 5890A Series II Gas Chromatograph interfaced to an HP 5972 Mass Selective Detector (MSD) with an HP 5 [5%-phenyl-poly(dimethyl-siloxane)] capillary column (60 m x 0.25 mm x 0.25 mm) was used for MS identification at 70 eV and for the determination of the ratio of geometric isomers presented in the mixtures **7-9**. Elemental analyses were performed on a Perkin Elmer 2400 Series II analyzer. Column chromatography was performed on aluminium oxide 90 active neutral (70-230 mesh). Elemental analyses were in satisfying agreement with the calculated data. The allylation reactions of aldimines **1-3** were carried out using known procedures.[10,11] Intramolecular acid cyclisation of aminobutenes **4-6** were effectuated by described method.[12] Aromatization of tetrahydroquinolines **7-9** was carried out with the excess of sulphur by know procedure.[19]

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References

1 Jones G., Pyridines and Their Benzo Derivatives: (v). Synthesis, in Comprehensive Heterocyclic Chemistry, Katritzky A. R., ed., Pergamon Press, Oxford, 1984, V.2, pp 395.

2 Kouznetsov V., Palma A., Ewert C., Varlamov A., *J. Heterocycl .Chem.*, 35, 761 (1998).

3 Katrizky A. R., Rachwal S., Rachwal B., *Tetrahedron*, 52, 15031 (1996).

4 Pharmaceutical Substances, Kleemann A., Engel J., Kutscher B., Reichert D., eds., Thieme, Stuttgart, 1999.

5 Phytochemical Dictionary. A Handbook of Bioactive Compounds from Plants, Harborne J. B., Baxter H., eds., Taylor & Francis, London, 1993, pp267.

6 Roberts D., Joule J. A., Antonieta Bros M., Alvarez M., *J. Org. Chem.*, 62, 568 (1997).

7 Alvarez M., Antonieta Bros M., Gras G., Ajana W., Joule J. A., *Eur. J. Org. Chem.*, 1173 (1999).

8 Chiari E., Oliveira A. B., Prado M. A. F., Alves R. J., Galvão L. M. C., Araujo F. G., *Antimicrob. Agents Chemother.*, 40, 613 (1996).

9 Boger D. L., Diels-Alder Reactions of Heterocyclic Azadienes: Development of a Strategy for The Total Synthesis of Streptonigrin, Lavendamycin, and Synthetic Quinoline-5,8-Quinones, in Strategies and Tactics in Organic Synthesis, Linberg, Th., ed., Academic Press, New York, 1989, V. 2, pp 2.

10 Kouznetsov V. V., Palma A.R., Aliev A. E., *Anales de Quimica. Int. Ed.*, 94, 132 (1998).

11 Kouznetsov V., Ocal N., Turgut Zh., Zubkov F., Kaban S., Varlamov A., *Monatsh. Chem.*, 129, 671 (1998).

12 Vargas L. Y, Rozo R., Kouznetsov V., *Heterocycles*, 53, 785 (2000).

13 Bloch R., *Chem. Rev.*, 98, 1407 (1998).

14 Selected physical data for 4: yield 54%; white crystals, m.p. 102-103 °C; IR (KBr): ν = 3277, 1618, 1592, 916 cm^{-1}; ^1H NMR (90 MHz): δ 8.59 (1H, m, α'-H_{Py}), 7.69-7.05 (3H, m, β-,β'- and γ-H_{Py}), 6.91 (2H, d, J = 8.6 Hz, 3(5)-H_{Ph}), 6.45 (2H, d, J = 8.6 Hz, 2(6)-H_{Ph}), 6.00-5.55 (1H, m, 1-H), 5.13 (2H, td, J = 4.4 and 1.0 Hz, 2-H), 4.49 (1H, br.s, 4-H), 4.32 (1H, br.s, H-N), 2.84-2.52 (2H, m, 3-H), 2.19 (3H, s, CH_3); GC-MS t_R 26.83 min., *m/z* = 238 (M^+); Anal. Calcd for $C_{16}H_{18}N_2$: C: 80.67, H: 7.56, N: 11.76. Found: C, 80.85; H, 7.33; N, 11.61.

15 Crude reaction for 8 GC-MS: minor isomer with t_R 27.58 min., *m/z* (%): 238 (M^+, 100), 223 (50), 208 (6), 194 (4), 180 (2), 168 (1), 160 (71), 152 (1), 144 (20), 130 (12), 115 (8), 104 (6), 91 (10), 77 (8), 65 (5), 51 (7), 41 (3); major isomer with t_R 28.31 min., *m/z* (%): 238 (M^+, 100), 223 (49), 208 (9), 194 (3), 180 (2), 168 (1), 160 (69), 152 (1), 144 (20), 130 (13), 115 (9), 104 (6), 91 (10), 77 (8), 65 (5), 51 (7), 41 (3).

16 Kuznetsov V.V., Aliev A.E., Prostakov N.S., *Khim. Geterotsikl. Soedin.*, 73 (1994). Chem. Abst. 121, 300.738 (1994).

17 Selected physical data for isolated and purified cis-isomer 8: yield 75%; yellow crystals, m.p. 169-170 °C; IR (KBr): ν = 3266, 1594 cm^{-1}; ^1H NMR (400 MHz): δ 8.54 (1H, d, J = 2.0 Hz, α-H_{Py}), 8.45 (1H, dd, J = 3.0 and 1.9 Hz, α'-H_{Py}), 7.68 (1H, dt, J = 8.1 and 1.9 Hz, γ-H_{Py}), 7.20 (1H, dd, J = 8.1 and 3.0 Hz, β'-H_{Py}), 6.92 (1H, s, 5-H), 6.75 (1H, d, J = 8.0 Hz, 7-H), 6.39 (1H, d, J = 8.0 Hz, 8-H), 4.37 (1H, dd, J = 11.6 and 2.5 Hz, 2-Ha), 3.78 (1H, br.s, H-N), 3.00 (1H, ddd, J = 12.1, 6.8 and 6.0 Hz, 4-Ha), 2.17 (3H, s, 6-CH_3), 2.00 (1H, ddd, J = 12.6, 6.0 and 2.5 Hz, 3-He), 1.67 (1H, q, J = 12.6 and 12.1 Hz, 3-Ha), 1.26 (3H, d, J = 6.8 Hz, 4-CH_3); ^{13}C NMR (100 MHz): δ 149.0 (α'-C_{Py}), 148.6 (α-C_{Py}), 141.9 (8a-C), 139.8 (β-C_{Py}), 134.2 (γ-C_{Py}), 127.4 (5-C), 127.4 (7-C), 127.2 (6-C), 125.9 (4a-C), 123.6 (β'-C_{Py}), 114.5 (8-C), 54.7 (2-C), 41.6 (3-C), 31.1 (4-C), 20.6 (6-CH_3), 20.2 (4-CH_3); GC-MS, t_R 28.31 min., *m/z* = 238 (M^+); Anal. Calcd for $C_{16}H_{18}N_2$: C: 80.67, H: 7.56, N: 11.76. Found: C, 80.92; H, 7.31; N, 11.61.

18 Selected data for **10**: yield 89%; yellow crystals, m.p.109-110 °C; ^1H NMR (300 MHz): δ 9.32 (1H, d, J = 2.1 Hz, α-H_{Py}), 8.67 (1H, dd, J = 4.7 and 1.7 Hz, α'-H_{Py}), 8.46 (1H, dt, J = 8.0, 2.1 and 1.7 Hz, γ-H_{Py}), 8.05 (1H, d, J = 8.6 Hz, 8-H), 7.75 (1H, s, 5-H), 7.65 (1H, s, 3-H), 7.56 (1H, dd, J = 1.6 and 8.6 Hz, 7-H), 7.42 (1H, dd, J = 8.0 and 4.7 Hz, β'-H_{Py}), 2.74 (3H, s, 6-CH_3), 2.57 (3H, s, 4-CH_3); ^{13}C NMR (75 MHz): δ 153.8 (2-C), 150.3 (α'-C_{Py}), 149.1 (α-C_{Py}), 147.1 (8a-C), 145.0 (4a-C), 136.8 (6-C), 135.7 (β-C_{Py}), 135.2 (γ-C_{Py}), 132.2 (7-C), 130.4 (8-C), 127.7 (4-C), 124.0 (β'-C_{Py}), 123.1 (5-C), 119.7 (3-C), 22.33 (4-CH_3), 19.46 (6-CH_3); GC-MS t_R 24.25 min., *m/z* = 234 (M^+); Anal. Calcd for $C_{16}H_{14}N_2$: C: 82.05, H: 5.98, N: 11.97. Found: C 81.79, H 6.01, N 12.08.

19 Methods for the Oxidation of Organic Compounds, Haines, A.H ; ed., Academic Press, New York, 1985, pp 16.

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