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 quinolines1 and their hydrogenated derivatives2,3 have been of considerable interest to heterocyclic and medicinal chemists for many years as medicines4 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 cruzii, 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 homoallylamines10-12 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 reaction13 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 aldimes to preformed allyl magnesium bromide in ether (THF) afforded the 4-N-p-methylphenylamino-4-[α-(β- or γ-)pyridyl]-1-butenes 4-6 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 aldimes. 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. Similar fact has been observed previously for the related compounds. Attempts to separate these diastereoisomers by conventional column chromatography led to the isolation of major diastereoisomer for tetrahydroquinoline 8. Its NMR analysis revealed that it possess a cis-configuration of the methyl group and the pyridine moiety disposed both equatorially at C-4 ($J_{4,3a} = 12.1$ Hz, $J_{4,3e} = 6.0$ 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.

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.

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 CDCl₃ 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. Intramolecular acid cyclisation of aminobutenes 4-6 were effectuated by described method. Aromatization of tetrahydroquinolines 7-9 was carried out with the excess of sulphur by known procedure.

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References

4-N-Aryl(phenyl)amino-4-tertary-l-butenes as building blocks in heterocyclic synthesis. 1. New route to 4,6-dimethyl-2-pyridylquinolines from


14 Selected physical data for 4: yield 54%; white crystals, m.p. 102-103 ºC; IR (KBr): δ = 3277, 1618, 1592, 916 cm⁻¹; ¹H NMR (90 MHz): δ 8.59 (1H, m, α'-Hpy), 7.69-7.05 (3H, m, β-β' and γ-H), 6.91 (2H, d, J = 8.6 Hz, 3(5)-H), 6.45 (2H, d, J = 8.6 Hz, 2(6)-H), 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, CH₃); GC-MS fₐ 26.83 min., m/z = 238 (M⁺); Anal. Calcd for C₁₆H₁₈N₂: 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 fₐ 27.58 min., m/z (%): 238 (M⁺, 100), 223 (50), 208 (6), 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).


17 Selected physical data for isolated and purified cis-isomer 8: yield 75%; yellow crystals, m.p. 169-170 ºC; IR (KBr): δ = 3266, 1594 cm⁻¹; ¹H NMR (400 MHz): δ 8.54 (1H, d, J = 2.0 Hz, α-Hpy), 8.45 (1H, dd, J = 3.0 and 1.9 Hz, α'-Hpy), 7.68 (1H, dt, J = 8.1 and 1.9 Hz, γ-Hpy), 7.20 (1H, dd, J = 8.1 and 3.0 Hz, β'-Hpy), 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-CH₃), 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-CH₃); ¹³C NMR (100 MHz): δ 149.0 (α'-Cpy), 148.6 (α-Cpy), 141.9 (8a-C), 139.8 (β-Cpy), 134.2 (γ-Cpy), 127.4 (5-C), 127.4 (7-C), 127.2 (6-C), 125.9 (4a-C), 123.6 (β'-Cpy), 114.5 (8-C), 54.7 (2-C), 41.6 (3-C), 31.1 (4-C), 20.6 (6-CH₃), 20.2 (4-CH₃); GC-MS, fₐ 28.31 min., m/z = 238 (M⁺); Anal. Calcd for C₁₆H₁₈N₂: 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 ºC; ¹H NMR (300 MHz): δ 9.32 (1H, d, J = 2.1 Hz, α-Hpy), 8.67 (1H, dd, J = 4.7 and 1.7 Hz, α'-Hpy), 8.46 (1H, dt, J = 8.0, 2.1 and 1.7 Hz, γ-Hpy), 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'-Hpy), 2.74 (3H, s, 6-CH₃), 2.57 (3H, s, 4-CH₃); ¹³C NMR (75 MHz): δ 153.8 (2-C), 150.3 (α'-Cpy), 149.1 (α-Cpy), 147.1 (8a-C), 145.0 (4a-C), 136.8 (6-C), 135.7 (β-Cpy), 135.2 (γ-Cpy), 132.2 (7-C), 130.4 (8-C), 127.7 (4-C), 124.0 (β'-Cpy), 123.1 (5-C), 119.7 (3-C), 22.33 (4-CH₃), 19.46 (6-CH₃); GC-MS, fₐ 24.25 min., m/z = 234 (M⁺); Anal. Calcd for C₁₆H₁₈N₂: C: 80.92, H, 7.31, N, 11.61.


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