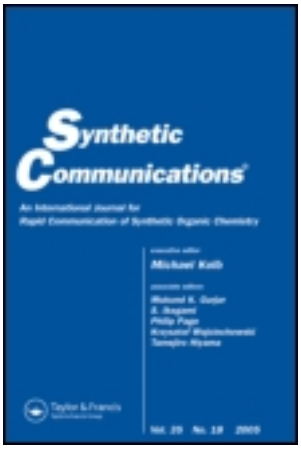

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A Simple and Efficient Synthesis of New Dihydrospiro[(1H)Quinoline-2,1′-Cyclohexane] Derivatives Via Internal Friedel-Crafts Alkene Alkylation of N-(1-Allylcyclohexanyl)Ethylphenylamine

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A Simple and Efficient Synthesis of New Dihydrospiro[(1*H*)Quinoline-2,1′-Cyclohexane] Derivatives Via Internal Friedel-Crafts Alkene Alkylation of N-(1-Allylcyclohexanyl)Ethylphenylamine

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Abstract: New substituted dihydrospiro[(1*H*)quinoline-2,1′-cyclohexanes] were prepared by the internal alkene alkylation of N-(1-allylcyclohexanyl) ethylphenylamine obtained from the corresponding ketimine and allylmagnesium bromide. The 1-allyl-6-ethyl-4-methyl-3,4-dihydrospiro[(1*H*)quinoline-2,1′-cyclohexane] undergoes an amino-Claisen transposition ($BF_3 \cdot Et_2O$) to afford the 8-allyl-6-ethyl-4-methyl substituted spiroquinolines or a second internal alkylation reaction promoted by Brönsted acid (H_2SO_4) to give a new unnatural lilolidine spiroderivative.

Keywords: Internal alkene Friedel-Crafts alkylation, amino-Claisen transposition, spiroquinolines

Despite the large number of published synthetic routes to quinoline and its derivatives there are only a few that describe the construction of the tetra- or dihydroquinoline ring spiro annulated at positions C-2 cycloalkanes or heterocycles.[1,2] The chemistry and biological activity of this type of spiro

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heterocompounds remain largely unexplored. Nevertheless, these particular heterocycles are useful for many sectors of the chemical industry and have attracted the attention of synthetic organic chemists recently due to antibacterial, anti-inflammatory, and herbicidal properties.[3,4]

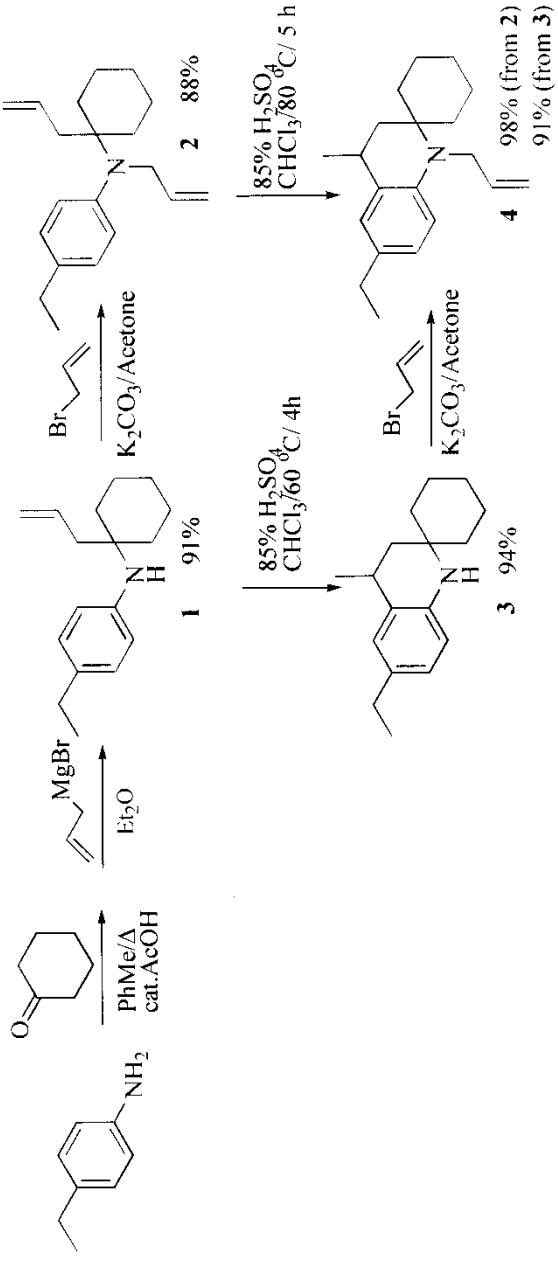
On the other hand, the condensed tricyclic system of 1,2,5,6-tetrahydropyrrolo[3,2,1-*ij*]quinolines is the basic skeleton of lilolidine alkaloids and its derivatives possess a wide spectrum of biological activity.[5–8]

Over a period of years we were involved in the preparation of bioactive nitrogen-containing heterocycles from imines. As results of these studies a new practical synthesis of the dihydrospiro[(1*H*)quinoline-2,1′-cycloalkanes] developed which allowed us to investigate some chemical and biological properties of this spiro heterosystem.[9,10] Herein, we report an efficient synthesis of new spiranes **3** and **4** and the chemical behavior of 1-allyl-6-ethyl-4-methyl-dihydrospiro[(1*H*)quinoline-2,1′-cyclohexane] (**4**). The latter compound undergoes an amino-Claisen transposition ($BF_3 \cdot Et_2O$) to afford the 8-allyl-6-ethyl-4-methyl substituted spiroquinoline **5** or a second internal alkylation reaction promoted by Brönsted acid (H_2SO_4) to give a new unnatural lilolidine spiroderivative **6**.

RESULTS AND DISCUSSION

The starting material for this work, 4-N-(1-allylcyclohexanyl)ethylphenylamine **1**, was obtained from *p*-ethylaniline via a well-known two-step procedure: ketimine formation and addition of allyl magnesium bromide to the obtained imine.[10] N-Allylation of this amine in common way gave N-allyl ethylphenylamine **2**, which possesses an π-electron rich aromatic ring and two allyl (electrophilic C_3 synthon) fragments that make it a versatile source of synthetic materials for constructing (1*H*)-quinolines spiro-annulated at C-2. The acid cyclization (85% $H_2SO_4/CHCl_3/60^\circ C/4$ h) of *p*-ethylphenylamine **1** and N-allyl substituted amine **2** proceeded smoothly to give respective 4,6-dialkyl substituted quinoline **3** and 1-allyl-4,6-dialkyl substituted quinoline **4** in excellent yield. Both quinolines are 6-exo-trig products of internal alkene Friedel-Crafts alkylation. The ^1H NMR spectroscopic data allowed an unambiguous statement of the formation of the 4-methylquinoline ring of **3** and **4**. In the case of the quinoline **4**, the NMR data indicated the presence of the N-allyl moiety. Moreover, conversion of **3** into **4** was realised under the same allylation reaction conditions in good yield (Scheme 1).

The N-allyl spiroquinoline **4** is a suitable precursor for the construction of diverse unknown heterospiranes containing a nitrogen atom. Thus, a mixture of the quinoline **4** and equimolar amounts of Lewis acid ($BF_3 \cdot Et_2O$) was heated at 90°C for 1 h to give amino-Claisen rearranged product **5**, which was isolated by silica gel column chromatography as a viscous oil in 72%



Scheme 1.

yield. The same quinoline precursor was heated at 90°C with 85% sulfuric acid for prolonged time to give a new unnatural lilolidine spiroderivative **6** in moderate yield. This tetracyclic molecule is a 5-exo-trig product of an internal alkylation reaction promoted by Brönsted acid (Scheme 2).

Both analytical and spectral data of final products **5**,**6** are in full agreement with the proposed structures. The best spectral proof for these structures is the appearance of two singlets assignable to aromatic protons 5-H (δ 6.94) and 7-H (δ 6.76) in compound **5**, and 7-H (δ 6.87) and 9-H (δ 6.65) in tricyclic molecule **6**, while the three aromatic protons of the precursor **4** give one singlet (δ 7.01) and two doublets (δ 6.91 and 6.50, J = 8.5 Hz). The presence of a pyrrolidine moiety in compound **6** was proven by a set of signals, that is a quartet (δ 2.41, J = 7.5 Hz), multiplet (δ 2.92) and doublet (δ 1.20, J = 7.8 Hz) assignable to corresponding protons 1-H, 2-H and 1-CH_3.

CONCLUSION

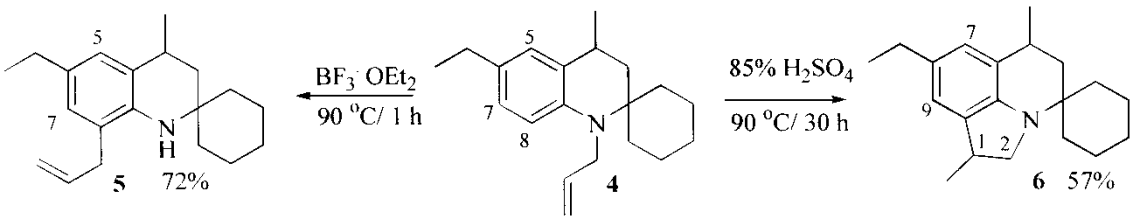
Using the classical Friedel-Crafts internal alkylation we synthesized new 8-allyl-6-ethyl-3,4-dihydro-4-methylspiro[(1*H*)quinoline-2,1′-cyclohexane] (**5**) and 1,6-dimethyl-8-ethyl-1,2,5,6-tetrahydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline (**6**), which were structurally related to the tricyclic nuclei of the basic skeleton of lilolidine alkaloids.

EXPERIMENTAL

IR spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer as KBr pellets. The ^{1}H spectra were determined on Bruker AM-300, in $CDCl_3$ with tretramethylsilane as internal standard. Data are reported as follows: chemical shifts (multiplicity, number of protons, coupling constants, and group). Mass spectra were recorded with a HP 5890 A Series II, link to a network mass selective detector HP 5972, a spectrometer with 70 eV electron impact ionization. The purities of the obtained substance were monitoring by thin-layer chromatography on Silufol UV_{254} sheets. Solvents and common reagents obtained from Merck and Aldrich were reagent grade.

N-(1-Allylcyclohexanyl)ethylphenylamine (1)

Imine obtained from *p*-ethylaniline and cyclohexanone (10.44 g, 0.052 mol) was dissolved in 50 mL of absolute ether and added slowly at 10°C to a magnetically stirred solution (170 mL of Et_2O) of allyl magnesium bromide,



Scheme 2.

prepared from allyl bromide (18.85 g, 0.156 mol) and magnesium (6.31 g, 0.259 mol). The reaction mixture was heated to 30–35°C during 6 h, cooled to 0°C and treated with water and then with saturated ammonium chloride solution. The organic layer was separated and the aqueous layer was extracted with ether (3 × 40 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was fractionated at reduced pressure to give 11.48 g of **1** as yellowish liquid.

Yield 91%; b.p. 125–130°C/10 mm Hg, n_D^{20} 1.5340; IR (KBr): ν 3419, 1637, 911 cm^{-1}; ^1H NMR (300 MHz): δ 7.02 (1H, d, J = 8.0 Hz, 3(5)-H), 6.64 (1H, d, J = 8.3 Hz, 2(6)-H), 5.90–5.84 (2H, m, =CH-), 5.16–5.00 (1H, m, $=CH_2$), 3.38 (1H, br.s, N-H), 2.58 (2H, q, J = 7.6 Hz, $—\underline{CH_2}CH_3$), 2.45 (2H, d, J = 7.3 Hz, $-CH_2-$), 2.32–1.36 (10H, m, H-cyclohexane), 1.24 (3H, t, J = 7.6 Hz, $—CH_2\underline{CH_3}$); GC-MS: t_R 22.43 min., (m/z, %): 243 (M^+, 3), 202 (100); Anal. Calcd for $C_{17}H_{25}N$: C, 83.89; H, 10.35; N, 5.75. Found: C, 83.55; H, 10.76; N, 5.43.

N-(1-Allylcyclohexyl)-N-(4-ethylphenyl)allylamine (2)

A suspension of **1** (1.0 g, 0.004 mol) in 10 mL acetone with allyl bromide (2.48 g, 0.020 mol) and potassium carbonate (1.70 g, 0.012 mol) was allowed to reflux for 4 days. The reaction was monitored by TLC. The mixture was treated with water. The products were extracted with CH_2Cl_2 (3 × 20 mL) Organic layer was dried (sodium sulfate) and the residue purified by chromatography on a short column (alumina) to give 1.02 g of **2** as yellowish viscous oil.

Yield 88%; n_D^{20} 1.5260; IR (KBr):ν 910 cm^{-1}; ^1H NMR (300 MHz): δ 7.11–7.03 (4H, m, HPh), 6.08–5.97 (2H, m, $N\text{-}CH_2\underline{CH}—CH_2$), 5.69–5.59 (2H, m, $=CH_2$), 5.08–5.03 (1H, m,—CH=), 4.95 (1H, dd, J = 17.3,1.8 Hz, $N\text{-}CH_2CH=\underline{CH_2}$, Ha), 4.82 (1H, dd, J = 10.0, 1.8 Hz, $N\text{-}CH_2CH=\underline{CH_2}$, Hb), 3.75 (2H, d, J = 5.9 Hz, $N\text{-}CH_2-$), 2.61 (2H, q, J = 7.7 Hz, $—\underline{CH_2}CH_3$), 2.37 (2H, d, J = 7.4 Hz, $—CH_2—$), 1.58–1.32 (10H, m, H-cyclohexane), 1.23 (3H, t, J = 7.7 Hz, $—CH_2\underline{CH_3}$); GC-MS: t_R 24.07 min., (m/z, %): 283 (M^+, 1), 242(100); Anal. Calcd for $C_{20}H_{29}N$: C, 84.75; H, 10.31; N, 4.94. Found: C, 84.34; H, 10.67; N, 4.68.

6-Ethyl-3,4-dihydro-4-methylspiro[(1*H*)quinoline-2,1′-cyclohexane] (3)

85% Sulfuric acid (5.0 mL) was added dropwise at 0°C to a solution of the amine **1** (2.5 g, 0.010 mol) in $CHCl_3$ (5 mL). The resulting mixture was heated at 60–80°C for 4 h while stirring vigorously. The reaction progress was monitored via TLC. At the end of the reaction the mixture was cooled down to room temperature and concentrated ammonium hydroxide solution

was added to pH 10. Three 20 mL extractions with ether were performed. The organic layers were combined, dried (sodium sulfate) and concentrated. The oily residue was purified by column chromatography over silica gel with heptane: ethyl acetate = 20 : 1 to give 2.35 g of **3** as yellow viscous oil.

Yield 94%; n_D^{20} 1.5400; IR (KBr): ν 3408 cm^{-1}; ^1H NMR (300 MHz): δ7.00 (1H, s, 5-H), 6.84 (1H, d, J = 8.4 Hz, 7-H), 6.44 (1H, d, J = 8.0 Hz, 8-H), 3.83 (1H, br.s, N-H), 2.96–2.87 (1H, m, 4-H), 2.55 (2H, q, J = 7.7 Hz, —$\underline{CH_2}CH_3$), 1.90 (1H, dd, J = 12.7, 5.7, 3-He), 1.69–1.41 (11H, m, H-cyclohexane and 3-Ha), 1.35 (3H, d, J = 6.7 Hz, 4-CH_3), 1.22 (3H, t, J = 7.7 Hz, –$CH_2\underline{CH_3}$); GC–MS: t_R 24.46 min., (m/z, %): 243 (M^+, 26), 228 (37), 214 (2), 200 (100), 187 (7), 172 (16), 149 (1), 91 (2), 77 (2) 41 (10); Anal. Calcd for $C_{17}H_{25}N$: C, 83.89; H, 10.35; N, 5.75. Found: C, 83.62; H, 10.76; N, 5.63.

Synthesis of 1-Allyl-6-ethyl-3,4-dihydro-4-methylspiro[quinoline-2,1′-cycloxane] (4)

Method A. 85% Sulfuric acid (2.5 mL) was added dropwise at 0°C to a solution of **2** (1.0 g, 0.004 mol) in $CHCl_3$ (5 mL). The resulting mixture was heated at 80–90°C for 5 h while stirring vigorously. The reaction progress was monitored via TLC. At the end of the reaction the mixture was cooled down to room temperature and concentrated ammonium hydroxide solution was added to pH 10. Three 20 mL extractions with dichloromethane were performed. The organic layers were combined, dried (sodium sulfate) and concentrated. The oily residue was purified by column chromatography over silica gel with heptane: ethyl acetate = 20 : 1 to give 0.98 g of **4** as pale yellow oil.

Yield 98%; n_D^{20} 1.5410; IR (KBr): ν1644, 914 cm^{-1}; ^1H NMR (300 MHz): δ 7.01 (1H, s, 5-H), 6.91 (1H, d, J = 8.5 Hz, 7-H), 6.50 (1H, d, J = 8.0 Hz, 8-H), 5.95–5.87 (1H, m, –CH═), 5.26 (1H, dd, J = 10.3, 1.8 Hz, ═CH_2, Ha), 5.13 (1H, dd, J = 17.7, 1.8 Hz, ═CH_2, Hb), 4.51(1H, dt, J = 1.8 Hz, N-CH_2), 3.69 (1H, dt, J = 1.8 Hz, N-CH_2), 2.90–2.81 (1H, m, 4-H), 2.57 (2H, q, J = 7.7 Hz, —$\underline{CH_2}CH_3$), 2.40 (1H, dd, J = 13.3, 4.4 Hz, 3-He), 1.84–1.51 (10H, m, H-cyclohexane), 1.28 (1H, t, J = 13.3, 3-Ha), 1.39 (3H, d, J = 6.6 Hz, 4-CH_3), 1.23 (3H, t, J = 7.7 Hz, —$CH_2\underline{CH_3}$); GC-MS: t_R 27.24 min., (m/z, %): 283 (M^+, 29), 268 (70), 254 (12), 240 (61), 227 (38), 212 (100), 41 (55); Anal. Calcd for $C_{20}H_{29}N$: C, 84.75; H, 10.31; N, 4.94. Found: C, 84.53; H, 10.43; N, 5.06.

Method B. A suspension of **3** (1.0 g, 0.004 moles)) in 10 mL acetone with allyl bromide (2.48 g, 0.020 mol) and potassium carbonate (1.70 g, 0.012 mol) was allowed to reflux for 4 days. The reaction was monitored by TLC. The mixture was treated with water. The products were extracted with CH_2Cl_2 (3 × 20 mL) Organic layer was dried (sodium sulfate) and the residue

purified by chromatography on a short column (alumina) to give 1.06 g (91%) of oily compound those chemical data were identical to **4**.

Synthesis of 8-Allyl-6-ethyl-3,4-dihydro-4-methylspiro[(1*H*)quinoline-2,1′-cyclohexane] (5)

Allylamine **4** (0.23 g, 8 mmol) was heated at 90°C for 1 h in $BF_3 \cdot Et_2O$ (0.46 mL), cooled and poured into ice. The pH was brought to 8 with Na_2CO_3. The organic products were extracted with Ch_2Cl_2 (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The oily residue was purified by column chromatography (silica gel, heptane/ethyl acetate, from 25:1 to 20:1) to afford 0.16 g of **5** as brown oil.

Yield 72%; IR (KBr): ν3410, 1634, 912 cm^{-1}; ^{1}H NMR (300MHz): δ 6.94 (1H, s, 5-H), 6.76 (1H, d, J = 1.2, 7-H), 6.10–5.68 (1H, m, -CH═), 5.21–5.10 (2H, m, ═CH_2), 3.29 (2H, d, J = 6.4, —CH_2), 4.00 (1H, br.s, N-H), 2.96–2.88 (1H, m, 4-H), 2.54 (2H, q, J = 7.7 Hz, —$\underline{CH_2}CH_3$), 1.87–1.25 (10H, m, H-cyclohexane), 1.85–1.80 (1H, dd, J = 12.8, 4.3 Hz, 3-He), 1.37 (1H, t, J = 12.6, 3-Ha), 1.34 (3H, d, J = 6.8 Hz, 4-CH_3), 1.25 (3H, t, J = 7.7 Hz, —$CH_2\underline{CH_3}$); GC-MS: t_R 26.66 min., (m/z, %): 283 (M^+, 32), 268 (40), 254 (3), 240 (100), 227 (3), 212 (15), 41 (6); Anal. Calcd for $C_{20}H_{29}N$: C, 84.75; H, 10.31; N, 4.94. Found: C, 84.94; H, 10.53; N, 4.60.

Synthesis of 1,6-Dimethyl-8-ethyl-1,2,5,6-tetrahydro-4*H*-spiro[pyrrolo-[3,2,1-*ij*]quinoline-4,1-cyclohexane] (6)

85% Sulfuric acid (3.2 mL) was added dropwise at 0°C to a solution of the amine **1** (0.32 g, 1 mmol) in $CHCl_3$ (5 mL). The resulting mixture was heated at 60–80°C for 4 h while stirring vigorously. The reaction progress was monitored via TLC. At the end of the reaction the mixture was cooled down to room temperature and concentrated ammonium hydroxide solution was added to pH 10. Three 20 mL extractions with chloroform were performed. The organic layers were combined, dried (sodium sulfate) and concentrated. The oily residue was purified by column chromatography over silica gel with a heptane–ethyl acetate mixture to give 0.18 g of **6** as brown oil.

Yield 57%; n_D^{20} 1.5560; ^{1}H NMR (300 MHz): δ 6.87 (1H, s, 7-H), 6.65 (1H, s, 9-H), 2.92 (1H, m, 2-H), 2.85 (1H, m, 6-H), 2.53 (2H, q, J = 7.7 Hz, —$\underline{CH_2}CH_3$), 2.41 (1H, q, J = 7.5, 1-H), 1.62–1.10 (12H, m, H-cyclohexane and 5-H), 1.33 (3H, d, J = 6.8 Hz, 6-CH_3), 1.20 (3H, d, J = 7.8 Hz, 1-CH_3), 1.09 (3H, t, J = 7.7 Hz, —$CH_2\underline{CH_3}$); GC–MS: t_R 27.68 min., (m/z, %): 283 (M^+, 32), 268 (40), 254 (3), 240 (100), 227 (3), 212 (15), 41 (6); Anal. Calcd for $C_{20}H_{29}N$: C, 84.75; H, 10.31; N, 4.94. Found: C, 84.58; H, 10.63; N, 4.81.

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