Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 1981–1984
Tetrahedron Letters

Intramolecular alkene Friedel–Crafts cyclization of 1-allyl-1-*N*-(*ortho*-alkylphenylamino)cyclohexanes. A useful route to alkyl substituted dihydrospiro[(1*H*)quinoline-2,1′-cyclohexanes]. Unprecedented *ipso*-substitution of alkyl groups ☆

Vladimir V. Kouznetsov,[a,*] Fedor I. Zubkov,[b,*] Eugenia V. Nikitina[b] and Luz Dary Avellaneda Duarte[a]

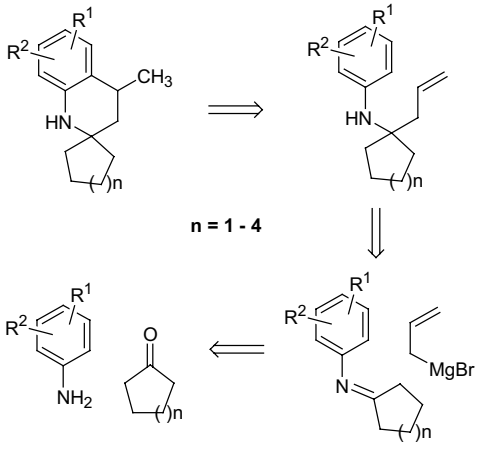
[a]*Laboratory of Fine Organic Synthesis, Research Center for Biomolecules, School of Chemistry, Industrial University of Santander, A.A. 678, Bucaramanga, Colombia*

[b]*Organic Chemistry Department of the Russian Peoples Friendship University, 6, Miklukho-Maklayia St, Moscow 117198, Russian Federation*

Received 11 November 2003; revised 8 December 2003; accepted 18 December 2003

Abstract—An unprecedented intramolecular Friedel–Crafts *ipso*-alkylation at the *ortho*-alkyl group of the *N*-arylamino moiety of 1-allyl-1-*N*-arylaminocycloalkanes to give alkyl substituted dihydrospiro[(1*H*) quinoline-2,1′-cycloalkanes] is reported. Unexpected results were explained in the context of intramolecular *ipso*-substitution of alkyl groups and their 1,2-rearrangement. A plausible mechanism for this type of Friedel–Crafts alkylation by an alkene moiety promoted by a Brönsted acid (H_2SO_4) is proposed.

Many biologically and pharmacologically active alkaloids bear quinoline or tetrahydroquinoline fragments. The most general method to obtain tetrahydroquinolines involves intramolecular cyclizations starting from substituted aniline derivatives. Among these, intramolecular Friedel–Crafts reactions[1] promoted by Brönsted and Lewis acids are considered to be a powerful method for the effective construction of these heterocyclic compounds[2] or carbocyclic compounds.[3] Moreover, many new methods for the synthesis of tetrahydroquinoline derivatives have been developed.[4,5] However, there are very few examples that describe the construction of the di- or tetrahydroquinoline ring spiro annulated at position C-2 with cycloalkanes or heterocycles. Thus, the chemistry and biological activity of this type of spiroheterocompounds remain largely unexplored. As part of our research program aimed at the preparation of bioactive nitrogen-containing heterocycles from imines, we developed a practical synthesis of the dihydrospiro[(1*H*)quinoline-2,1′-cycloalkanes], which is based on the reactivity of accessible ketimines[6] (Scheme 1).



Scheme 1.

Keywords: Spiroquinolines; *ipso*-Intramolecular electrophilic alkylation; Intramolecular Friedel–Crafts reaction.

☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2003.12.148

* Corresponding authors. Fax: +57-76-349069; e-mail addresses: kouznet@uis.edu.co; fzubkov@sci.pfu.edu.co

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.12.148

The ketimines are transformed into the corresponding *gem*-allyl-*N*-arylaminocycloalkanes via an addition of the Grignard reagent—allyl magnesium bromide. These amines, possessing a π-electron rich aromatic ring, a basic nitrogen atom, and an allyl fragment—an electrophilic C_3 synthon, represent a versatile source of synthetic material for constructing (1*H*)-quinolines spiro-annulated at C-2.

Whereas the synthetic potential of intramolecular Friedel–Crafts alkylation is well documented, there has been no report of intramolecular alkene alkylation where an *ipso*-attack at the carbon attached to an alkyl group plays a pivotal role in preparing alkyl substituted dihydrospiro[(1*H*) quinoline-2,1′-cycloalkanes]. Herein, we wish to report an unexpected intramolecular Friedel–Crafts alkylation with the internal alkene group in a series of *ortho*-methyl (-ethyl) substituted 1-allyl-1-*N*-arylaminocyclohexanes that easily undergo *ipso*-substitution of the alkyl groups to give some poorly accessible heterospiranes, which can be regarded as intermediates in drug preparation.

To obtain the alkyl substituted dihydrospiro[(1*H*)quinoline-2,1′-cyclohexanes], which are useful synthons in our investigations on marine alkaloid spiroanalogs,[7] the 1-allyl-1-*N*-arylaminocyclohexanes **1a**–**d**[8] (Fig. 1) were used as starting compounds. Compounds **1** were prepared from the easily accessible cyclohexanone imines and allyl magnesium bromide in yields of 75–95% (calculated after distillation and purification).

The acid catalyzed cyclization (97% H_2SO_4/$CHCl_3$/60–65 °C/3–5 h) of *o*-methylphenylamine **1a** and its ethyl substituted analog **1b** proceeded smoothly to give 8-alkyl substituted quinolines **2a** and **2b** in 85% and 65% yield, respectively (Scheme 2). GC–mass analysis of the crude reaction product **2a** (R = Me) indicated no side products.

However, during the cyclization of **1b** (R = Et) we isolated the unexpected 5-ethyl substituted quinoline **3b** in 25% yield.Compounds **2b** and **3b** were purified by alumina column chromatography as colorless oils with similar retention coefficients. The mass and IR spectra

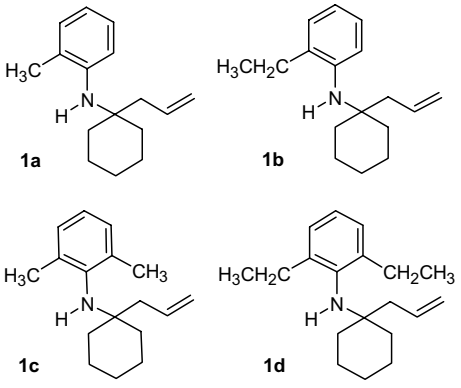
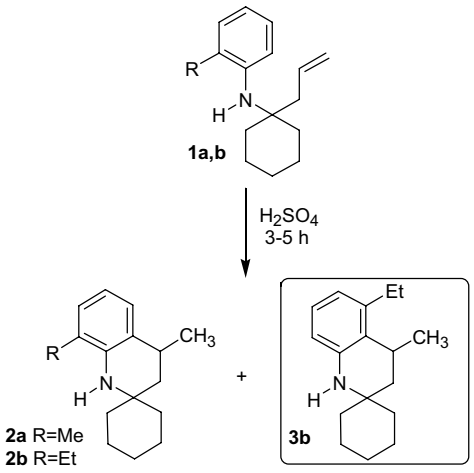


Figure 1. *ortho*-Methyl (-ethyl) substituted 1-allyl-1-*N*-arylaminocyclohexanes, the key substrates in the synthesis of substituted 3,4-dihydro-4-methylspiro[(1*H*)quinoline-2,1′-cyclohexanes].



Scheme 2.

of the isomeric quinolines **2b** and **3b** were virtually the same. The ^1H and ^{13}C NMR spectroscopic data indicated the formation of the 4-methylquinoline ring. X-ray analysis of the hydrochloride salt of **3b** led to the identification of the structure as 4-methyl-5-ethyl-3,4-dihydrospiro[(1*H*)quinoline-2,1′-cyclohexane] realized as two forms **A** and **B** (Fig. 2).[9]

These results could be explained in the context of an intramolecular *ipso*-substitution–alkylation of the ethyl group in compound **1b**. A plausible mechanism for this type of intramolecular Friedel–Crafts alkylation promoted by the Brönsted acid is proposed in Scheme 3. In most cases, the carbon atom of the arene that acts as the nucleophile has an attached hydrogen.[10,11] Thus, in our case, the normal Wheland intermediates **2*a**,**b**, appeared as a result of electrophilic attack at the free *ortho*-position, followed by loss of H^+ from the C-4a position to afford the 8-alkyl substituted quinolines **2a**,**b**.

However, when the carbocation attacks the aryl moiety at the alkyl substituted carbon (*ipso*-attack), Wheland

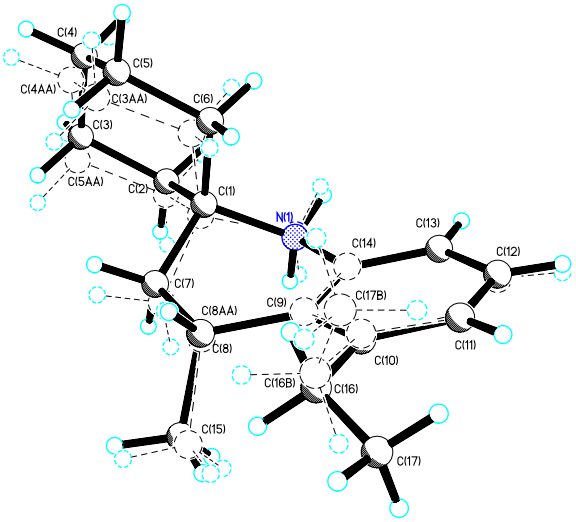
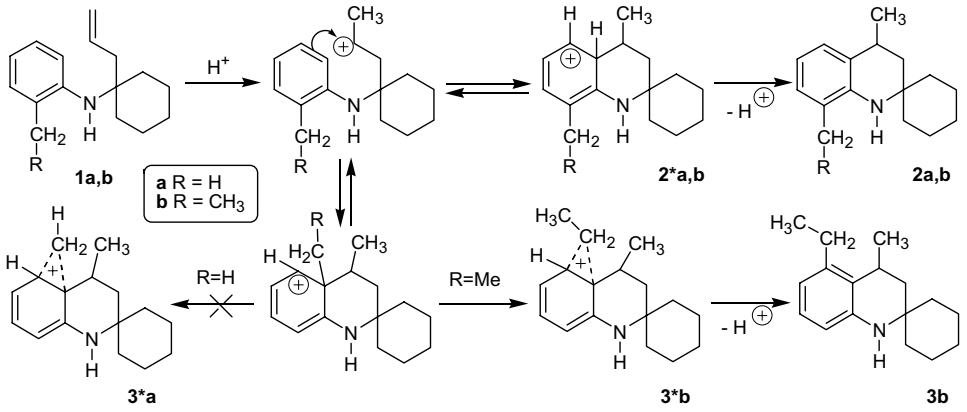


Figure 2. The X-ray crystal structure of **3b** (form **A** (solid line) and **B** (dotted line)).



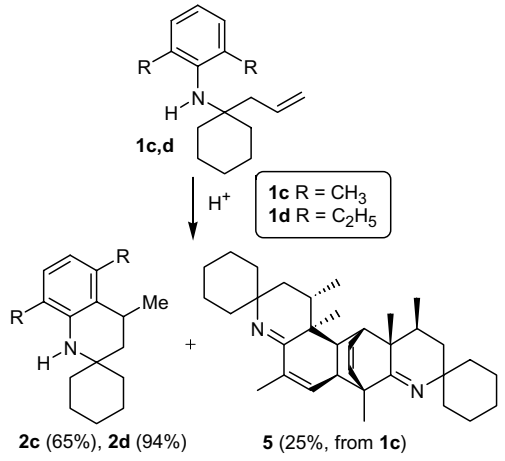
Scheme 3.

intermediates are formed that could give the three-center cationic especies **3*a**,**b**. A 1,2-shift of the ethyl group from C-4a to C-5 followed by loss of H^+ leads to the 5-alkyl substituted quinoline **3b**.

We assume that the methyl group of the ethyl radical can stabilize the three-center cationic species **3*b** due to both induction and hyperconjugation effects. In the case of **1a**, the cationic center of the intermediate **3*a** is not stabilized enough by the hydrogen atom (Scheme 3).

To the best of our knowledge, examples of the intramolecular *ipso*-substitution of an *ortho*-alkyl group in the presence of the second free *ortho*′-position have not been observed.

This interesting result stimulated us to investigate further the intramolecular alkylation process in the case of *ortho*′-dialkylsubstituted compounds **1c**,**d**. Treatment of the *ortho*,*ortho*′-diethyl substituted allylarylaminocyclohexane **1d** under the same reaction conditions furnished the expected 5,8-diethyl substituted spirane **2d** in almost quantitative yield (Scheme 4). In this case, as both *ortho*-carbon atoms attached to the ethyl group are equivalent, *ipso*-attack proceeds easily followed by a 1,2-shift of an ethyl group and loss of H^+ to produce the aromatic derivative.



Scheme 4.

In the case of *ortho*,*ortho*′-dimethyl substituted allylarylaminocyclohexane **1c**, the intramolecular alkylation proceeds more fascinatingly. Besides the *ipso*-substitution product **2c**, which was obtained in 65% yield, we isolated the heterocycle **5** (25%) possessing an unprecedented spiro structure. The spectroscopic data (^1H and ^{13}C NMR and mass spectra) did not allow the assignment of its structure, which was unambiguously established by X-ray analysis.[8,12] As indicated,[8,12] the central bicyclo[2.2.0]octane fragment is *endo*-fused with a piperidine ring and *exo*-fused with a cyclohexene ring.

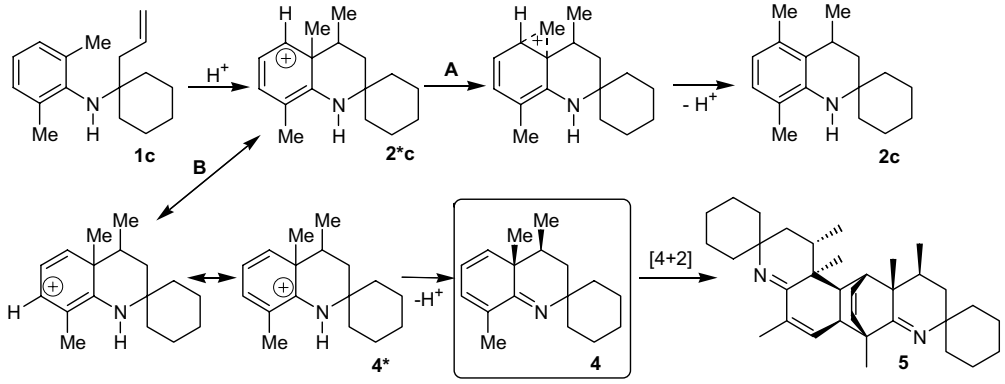
This interesting finding could also be explained in the context of intramolecular *ipso*-attack at the carbon attached to the methyl group. A plausible mechanism for the formation of these products is proposed in Scheme 5. The Wheland intermediate **2*c** can lead both to the 1,2-shift product **2c** (the main route A) and to the dimeric product **5** via the loss of H^+ from the resonance-stabilized structure **4*** (route B). The existence of the precursor **4** in the reaction mixture was proved by ^1H NMR spectroscopic data, but all attempts to isolate it by chromatography failed.

This compound has a *cis*-diene structure and presumably rapidly dimerizes acting as a diene and as a dienophile. It is noteworthy that this [4+2] cycloaddition proceeds in a highly regio- and diastereoselective manner affording the *endo*-adduct **5**.

In summary, we disclose a previously unknown electrophilic alkylation process via an intramolecular *ipso*-substitution of the *ortho*-alkyl group in the the *N*-arylamino moiety of 1-allyl-1-*N*-arylaminocycloalkanes. The new method provides an attractive and alternative route to alkyl substituted C-2-spiroannulated quinolines. Efforts are in progress to elucidate the mechanistic details of this intramolecular Friedel–Crafts alkylation and to determine its scope and limitations.

Acknowledgements

The authors would like to thank Konstantin F. Turchin (Center for Chemistry of Drugs—All-Russian Institute



Scheme 5.

for Chemical and Pharmaceutical Research, Moscow, Russia) and Grigorii G. Aleksandrov (Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, Moscow, Russia) for the useful discussion during the preparation of this manuscript. Financial support from the Colombian Institute for Science and Research (Colciencias, proyecto 1115-05-353-96) are acknowledged.

References and notes

1. (a) Heaney, H. The Intramolecular Aromatic Friedel–Crafts Reaction. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991, 2, pp 753–768; (b) Roberts, R. M.; Khalaf, A. A. *Friedel–Crafts Alkylation Chemistry: A Century of Discovery*; Marcel Dekker: New York, 1984; (c) Olah, G. A. *Friedel–Crafts Chemistry*; Wiley-Interscience: London, 1973.
2. (a) Beck, J. B.; Booher, R. N.; Brown, A. C.; Kwok, R.; Pohland, A. *J. Am. Chem. Soc.* **1967**, *89*, 3934–3935; (b) Conley, R. T.; Knopka, W. N. *J. Org. Chem.* **1964**, *29*, 496–497; (c) Plostnieks, J. U.S. Patent 3,706,522, 1973; *Chem. Abstr*. **1973**, *78*, 29641f.
3. (a) Majetich, G.; Zhang, Y. *J. Am. Chem. Soc.* **1994**, *116*, 4979–4980; (b) Gan, Y.; Li, A.; Pan, X.; Chan, A. S. C.; Yang, T.-K. *Tetrahedron: Asymmetry* **2000**, *11*, 781–787.
4. Kouznetsov, V.; Palma, A. R.; Ewert, C. A.; Varlamov, A. V. *J. Heterocycl. Chem.* **1998**, *35*, 761–785.
5. Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031–15070.
6. (a) Palma, A. R.; Rozo, W.; Stashenko, E.; Molina, D.; Kouznetsov, V. *J. Heterocycl. Chem.* **1998**, *35*, 183–186; (b) Palma, A. R.; Vargas, L. Y.; Silva, J.; Kouznetsov, V. *Heterocycl. Commun.* **1998**, *4*, 455–462; (c) Palma, A.; Silva, A. J.; Carrillo, C.; Kouznetsov, V.; Stashenko, E.; Bahsas, A.; Amaro-Luis, J. *Tetrahedron* **2002**, *58*, 8719–8727; (d) Kouznetsov, V.; Palma, A.; Rozo, W.; Stashenko, E.; Bahsas, A.; Amaro-Luis, J. *Tetrahedron* **2003**, *59*, 419–425.
7. Kouznetsov, V.; Zubkov, F.; Palma, A.; Restrepo, G. *Tetrahedron Lett.* **2002**, *43*, 4707–4709.
8. All starting and final compounds (**1a–d**, **2a–d**, **3b**, **5**) were fully characterized by spectral and elemental analyses. Crystallographic data for structures **3b** and **5** have been deposited with the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication numbers CCDC 220116 (**3b**) and 220117 (**5**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
9. Both crystallographic independent cations **A** and **B** have similar geometrical parameters but different orientations of the ethyl group [torsion angles C(9)C(10)C(16)C(17) and C(11)C(10)C(16)C(17)], 154.6° and −30.3°, in **A**; and −123.4° and 53.8° in **B**, respectively.
10. (a) Perrin, C. L.; Skinner, D. A. *J. Am. Chem. Soc.* **1971**, *93*, 3389–3394; (b) Traynham, J. G. *J. Chem. Educ.* **1983**, *60*, 937–941.
11. Moodie, R. B.; Schofield, K. *Acc. Chem. Res.* **1976**, *9*, 287–292.
12. Crystal data for **5**: crystal dimensions: $0.81\times0.31\times0.12$ mm, colorless rhombuses, $C_{34}H_{50}N_2$, M 486.76, space group P-2(1)/c, monoclinic, $a = 12.510(3)$, $b = 10.140(2)$, $c = 22.570(5)$ Å, $\alpha = 90$, $\beta = 102.16(3)$, $\gamma = 90°$, $Z = 4$, $V = 2798.8(11)$ Å^3, $\rho_{calcd} = 1.155$ g cm^{-3}, $\mu = 0.660$ cm^{-1}, $F(000) = 1072$. Intensities of 4407 reflections with $I \geqslant 0.5\sigma I$ (4212 are independent of symmetry) were measured. The final R_1 value is 0.0747 ($wR_2(F^2) = 0.2359$) for 1614 with $I \geqslant 2\sigma I$ $R_{int} = 0.1238$) reflections, GOOF = 1.096.