Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 2509–2512

An efficient synthesis of new 1-*H*-4′-methyl-3′,4′-dihydrospiro[piperidine-4,2′(1′*H*)quinoline] scaffolds

Leonor Y. Vargas Méndez and Vladimir V. Kouznetsov*

Laboratorio de Química Orgánica y Biomolecular, Escuela de Química, Universidad Industrial de Santander, A.A. 678, Bucaramanga, Colombia

Received 18 January 2007; revised 6 February 2007; accepted 7 February 2007
Available online 13 February 2007

Abstract—Efficient synthesis of new 3′,4′-dihydrospiro[piperidine-4,2′(1′*H*)quinolines] by a four step synthetic route based on 1-benzyl-4-piperidone reactivity is reported.

Because the piperidine ring is the most common heterocyclic unit of many alkaloids, and is a key part of numerous drug candidates, a research in piperidine chemistry and synthesis continues to be prominent.[1,2] Watson et al. affirmed that in a decade (1988–1998) there were over 12.000 piperidine compounds mentioned in clinical and preclinical studies.[3] Thus, it is not surprising that the chemical literature reveals a much more increasing number of these derivatives with varied biological activities. Spiropiperidinyl compounds have attracted an increasing interest as the synthetic targets due to their important activity as pharmacophores in several biologically active compounds, mainly alkaloids.[4] The synthetic compounds with a 4-spiropiperidine motif (types **A**–**E**) possess interesting activities as well[5–9] (Fig. 1). The spiro system of 1-*H*-3′,4′-dihydrospiro[piperidine-4,2′(1′*H*)quinoline] **F** also shows interesting features that make it attractive for synthetic and pharmacological use. However, its chemistry is little studied. This is associated primarily with the lack of general and reliable procedures for the preparation of such spiropiperidinoquinoline derivatives.[10] All cited syntheses start from *N*-Boc-4-piperidone and have some difficulties in the synthesis of the key intermediates—4,4-disubstituted piperidines. Moreover, the final intramolecular cyclizations are not efficient.

With these facts in mind and as a continuation of our efforts on the synthetic potential of 4-*N*-aryl(benzyl)aminopiperidines to prepare a wide variety of nitrogen heterocycles, associated with various biological activities, we were particularly interested in N-unpro-

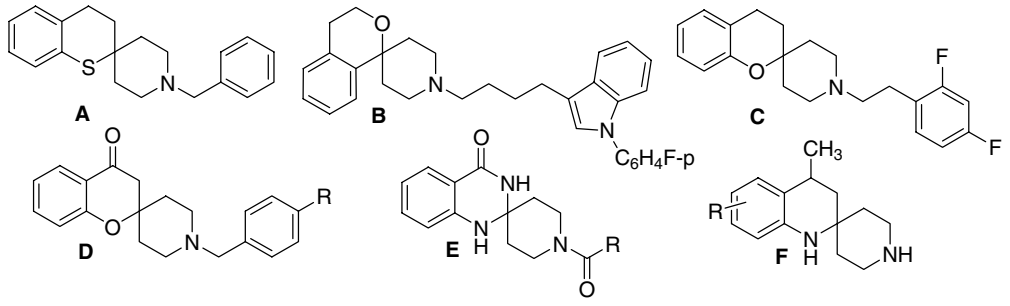
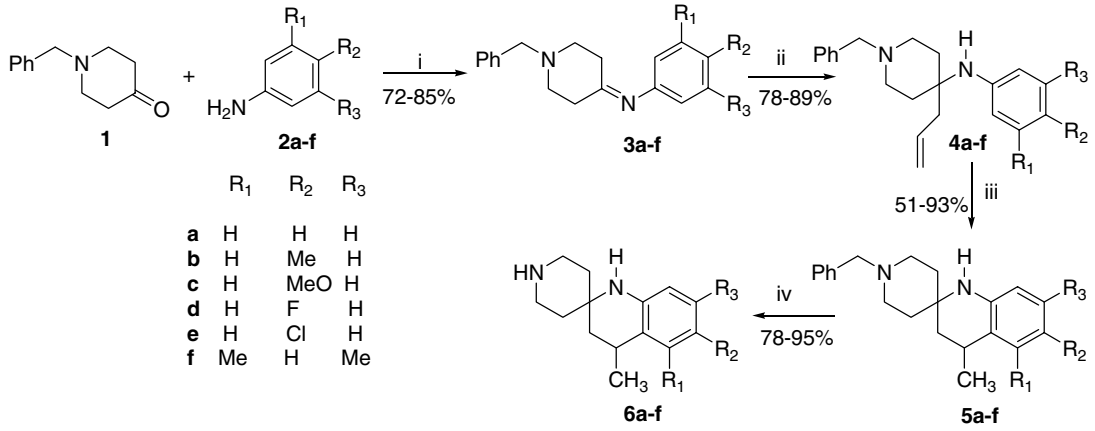


Figure 1. Compounds with 4-spiro piperidine skeleton as pharmaceuticals.

Keywords: Spiro-4-piperidines; Intramolecular alkene Friedel–Crafts alkylation; 3′,4′-Dihydrospiro[piperidine-4,2′(1′*H*)quinolines].
* Corresponding author. Tel.: +57 76 349069; fax: +57 76 349069/358210; e-mail: kouznet@uis.edu.co

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.02.037



Scheme 1. Reagents and conditions: (i) Toluene, reflux, 6–8 h, cat. AcOH; (ii) allylmagnesium bromide, Et_2O, 4–5 h and then work-up with NH_4Cl; (iii) 85% H_2SO_4, 80 °C, 4–6 h; (iv) $HCOONH_4$/Pd/C/MeOH, reflux, 10 min.

tected spiro-4-piperidines (type **F**) that could serve as useful precursors to many drug-like molecules. To the best of our knowledge, an efficient N-unprotected spiro-4-piperidines synthesis has not been described. The results of our quest for an efficient preparation of such spiro-4-piperidines are reported in this Letter.

Our synthetic route to the desired spirocyclic piperidines is outlined in Scheme 1. The synthesis of final type molecules **F** was planned from commercially available 1-benzyl-4-piperidone **1** in four steps. The condensation of this γ-piperidone with substituted anilines was achieved in boiling toluene in the presence of AcOH with azeotropic removal of water. Ketimines **3** were obtained and purified by distillation under reduced pressure in good yields (72–85%).

The new 4-allyl-1-benzyl-4-*N*-arylaminopiperidines **4** were prepared by addition of allylmagnesium bromide to the corresponding freshly distilled ketimines **3** using the Grignard procedure (allylmagnesium bromide has been prepared from allyl bromide and magnesium in anhydrous Et_2O). These aminopiperidine compounds were isolated as stable reddish or yellow oils in good yields (78–89%) following the distillation under reduced pressure and chromatographic techniques. The simplicity of the Grignard procedure and accessibility of the starting materials allowed us to prepare these aminopiperidines in large quantities, which are appropriate substrates to construct tetrahydroquinoline ring via an acid catalyzed intramolecular Friedel–Crafts alkylation—powerful and widely used methodology in the construction of diverse polycycles.[11] Thus, in the next key step, the treatment of γ-allyl-γ-*N*-arylaminopiperidines **4** with excess of 85% H_2SO_4 at 80 °C afforded effectively the new 1-benzyl-4′-methyl-3′,4′-dihydrospiro[piperidine-4,2′(1′*H*)quinolines] **5** in 51–93% yields[12] (Scheme 1).

Having in our hands diverse *N*-benzyl substituted spiro-4-piperidines **5**, we have dedicated our effort to find the best suited debenzylation procedures. This purpose is always achieved by a common debenzylation reaction with hydrogen gas in the presence of Pd on carbon,[13a,b] however an ammonium formate with Pd/C is also considered as a versatile agent in catalytic hydrogen transfer reductions.[13c] Thus, the last step of our synthetic route was realized with easily handled system $HCOONH_4$/Pd/C in methanol that allowed to obtain the desired 1-*H*-4′-methyl-3′,4′-dihydrospiro[piperidine-4,2′(1′*H*)quinolines] **6** in excellent yields (78–95%).[14] These final spiro piperidines are stable colorless crystalline substances with high melting points. Homonuclear and inverse-detected 2D NMR experiments allowed the assignment of all the signals and correlations, corroborating the obtained dihydrospiro[piperidine-4,2′(1′*H*)quinoline] core.

In conclusion, the synthesis described herein provides an efficient and original route in four-steps to 1-*H*-4′-methyl-3′,4′-dihydrospiro[piperidine-4,2′(1′*H*)quinolines] in excellent yields from commercially available 1-benzyl-4-piperidinone and anilines. The proposed method consists in mild reaction conditions, excellent yields, and simplicity. The obtained products should be useful intermediates for the assembly of novel diverse spiro-4-piperidine scaffolds. Preliminary results on the inhibitory activity at acetylcholinesterase enzyme indicated that some obtained compounds act as potent acetylcholinesterase inhibitors and will be reported in the immediate future.

Acknowledgments

This work was supported by the grant of Instituto Colombiano para el Desarrollo de la Ciencia y la Tecnología 'Francisco José de Caldas' (COLCIENCIAS-CENIVAM, Grant No. 432-2004). L.Y.V.M. thanks COLCIENCIAS and Universidad Industrial de Santander for her doctoral fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.02.037.

References and notes

1. (a) *Pharmaceutical Substances*; Kleemann, A., Engel, J., Kutscher, B., Reichert, D., Eds.; Stuttgart: Thieme, 1999; (b) Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine. Structure, Preparation, Reactivity and Synthetic Applications of Piperidine and its Derivatives*; Elsevier: Amsterdam, 1991.
2. (a) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953–2989; (b) Kouznetsov, V. V. *Khim.-Farm. Zh.* **1991**, *25*, 61–75, *Chem. Abstr*. **1991**, *115*, 158.846h; (c) Vartanyan, R. S. *Khim.-Farm. Zh.* **1983**, *17*, 540–550, *Chem. Abstr*. **1983**, *99*, 53629n.
3. Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679–3681.
4. (a) Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867–3870; (b) Chou, T.; Kuramoto, M.; Otani, Y.; Shikano, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3871–3874; (c) Ayer, W. A.; Ball, L. F.; Browne, L. M.; Tori, M.; Delbaere, L. T.; Silverberg, A. *Can. J. Chem.* **1984**, *62*, 298–302.
5. Spiro[[1]benzothiopyran-2,4′-piperidines], type **A**: Quaglia, W.; Gianella, M.; Piergentili, A.; Pigini, M.; Brasili, L.; Di Torso, R.; Rossetti, L.; Spompiato, S.; Melchiorre, C. *J. Med. Chem.* **1998**, *41*, 1557–1560.
6. Spiro[[2]benzopyran-1,4′-piperidine], type **B**: Moltzen, E. K.; Perregaard, J.; Meier, E. *J. Med. Chem.* **1995**, *38*, 2009–2017.
7. Spiro[[1]benzopyran-2,4′-piperidine], type **C**: Fletcher, S. R.; Burkamp, F.; Blurton, P.; Cheng, S. K. F.; Clarkson, R.; O'Connor, D.; Spinks, D.; Tudge, M.; van Niel, M. B.; Patel, S.; Chapman, K.; Marwood, R.; Shepheard, S.; Bentley, G.; Cook, G. P.; Bristow, L. J.; Castro, J. L.; Hutson, P. H.; MacLeod, A. M. *J. Med. Chem.* **2002**, *45*, 492–503.
8. Spiro[4-oxobenzo[1]pyran-2,4′-piperidines], type **D**: Harsanyi, K.; Szabadkai, I.; Borzá, I.; Karpati, E.; Kiss, B.; Pellionisz, M.; Farkas, S.; Horvath, C.; Csomov, K.; Lapis, E.; Laszlovszky, I.; Szabo, S.; Kis-Varga, A.; Laszy, J.; Gere, A. PTC Int. Appl. WO 9737,630, 1997; *Chem. Abstr*. **1997**, *127*, 346379e.
9. Spiro[4-oxoquinazoline-2,4′-piperidines], type **E**: Bartane, S., Schoen, I.; Pellioniszne, P. M.; Kiss, B.; Karpati, E.; Kis-Varga, A.; Lapis, E.; Gere, A.; Laszlovszky, I.; Farkas, S.; Csomov, K.; Horvath, C.; Szabo, S.; Horvath, P.; Laszy, J.; Szantay, C. Hung. Teljes HU 76,345, 1997; *Chem. Abstr*. **1998**, *128*, 154093f.
10. (a) Cossy, J.; Poitevin, C.; Gomez Pardo, D.; Peglion, J.-L.; Dessinges, A. *Tetrahedron Lett.* **1998**, *38*, 2965–2968; (b) Cossy, J.; Poitevin, C.; Gomez Pardo, D.; Peglion, J.-L.; Dessinges, A. *J. Org. Chem.* **1998**, *63*, 4554–4557; (c) Brown, D. W.; Mahon, M. F.; Ninan, A.; Sainsbury, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2329–2336; (d) Dorey, G.; Lockhart, B.; Lestage, P.; Casara, P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 935–939.
11. (a) Akita, H.; Naito, T.; Oishi, T. *Chem. Lett.* **1979**, 1365–1368; (b) Nasipuri, D.; Das, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2776–2778; (c) Kouznetsov, V.; Palma, A.; Rozo, W.; Stashenko, E.; Bahsas, A.; Amaro-Luis, J. *Tetrahedron Lett.* **2000**, *41*, 6899–6985; (d) Kouznetsov, V.; Palma, A.; Rozo, W.; Stashenko, E.; Bahsas, A.; Amaro-Luis, J. *Synth. Commun.* **2002**, *32*, 2965–2971; (e) Kouznetsov, V. V.; Avellaneda Duarte, L. D.; Stashenko, E. E. *Synth. Commun.* **2005**, *35*, 639–647.
12. *General procedure for the synthesis of 1-benzyl-3′,4′-dihydrospiro[piperidine-4,2′-(1′H)quinolines]* **5**. Sulfuric acid at 85% (w/v) (6 mL) was added dropwise to a mixture of aminopiperidine **4b** (2.00 g, 6.25 mmol) in CH_2Cl_2 (5 mL) 0 °C. The mixture was heated at 85 °C for 6 h with vigorous stirring. The reaction progress was monitored via TLC. Then the mixture was cooled down to 5 °C and was basified with NH_4OH solution, and extracted with CH_2Cl_2 (3×25 mL). The oily residue after dichloromethane separation was purified by column chromatography over alumina with ethyl acetate and heptane (1:15) to give 1.76 g (88%) of **5b** as a yellow viscous oil. IR (film): ν_{NH} 3406 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ): 1.31 (2H, d, $J = 6.7$ Hz, 4′-CH_3), 1.39 (1H, t, $J = 12.5$ Hz, 3′-Ha), 1.55–1.75 (4H, m, 3(5)-H), 1.84 (1H, dd, $J = 12.9$, 5.5 Hz, 3′-He), 2.22 (3H, s, 6′-CH_3), 2.27–2.37 (2H, m, 2(6)-Ha), 2.54 (1H, dd, $J = 11.8$, 6.3 Hz, 2- or 6-He), 2.63 (1H, dd, $J = 11.9$, 6.3 Hz, 2 or 6-He), 2.87 (1H, sept, $J = 6.5$ Hz, 4′-*H*), 3.52 (2H, s, CH_2–Ph), 3.84 (1H, br s, H–N), 6.64 (1H, d, $J = 8.0$ Hz, 8′-H), 6.79 (1H, d, $J = 8.0$ Hz, 7′-H), 6.95 (1H, s, 5′-H), 7.22–7.32 (5H, m, H_{Ph}); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 20.4 (+), 20.6 (+), 26.7 (+), 34.9 (−), 39.0 (−), 42.9 (−), 48.8, 49.4 (−), 49.5 (−), 63.4 (−), 114.5 (+), 125.8, 126.1, 127.0 (+), 127.3 (+), 127.4 (+), 128.2 (+, 2C), 129.1 (+, 2C), 138.4, 140.6; GC–MS: t_R 41.18 min; mass spectrum (EI): m/z (%) 320 (M^+, 51), 277 (4), 229 (7), 201 (13), 186 (75), 173 (47), 158 (36), 146 (46), 134 (24), 118 (7), 91 (100), 65 (9), 56 (7). Found: C, 82.51; H, 8.96; N, 8.75. Calcd for $C_{22}H_{28}N_2$: C, 82.45; H, 8.81; N, 8.74.
13. (a) Greene, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; (b) Bull, S. D.; Davies, S. G.; Fenton, G.; Mulvaney, A. W.; Prasad, R. S.; Smith, A. D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3765–3774; (c) Brieger, G.; Nestrick, T. J. *Chem. Rev.* **1974**, *74*, 567–580.
14. *General procedure for the synthesis of 3′,4′-dihydrospiro[piperidine-4,2′-(1′H)quinolines]* **6**. The spiro compound **5b** (1.00 g, 3.12 mmol) and $HCOONH_4$ (0.98 g, 15.6 mmol) were heated to reflux in MeOH (25 mL) for 10 min in the presence of 10% Pd/C (0.16 g). The reaction was monitored via TLC. The solid residue after methanol separation was purified by alumina column chromatography with methanol and ethyl acetate (1:10) to afford 0.64 g (89%) of **6b** as white crystals; mp >300 °C. IR (KBr): ν_{NH} 3445, 3311 cm^{-1}; ^1H NMR (400 MHz, D_2O, δ): 1.13 (3H, d, $J = 6.7$ Hz, 4′-CH_3), 1.19 (1H, t, $J = 12.8$ Hz, 3′-Ha), 1.54 (1H, ddd, $J = 12.7$, 7.9, 4.0 Hz, 3-Ha), 1.66–1.69 (2H, m, 5-H), 1.76 (1H, br t, $J = 4.0$ Hz, 3-He), 2.01 (1H, dd, $J = 13.7$, 6.2 Hz, 3′-He), 2.12 (3H, s, 6′-*CH*$_3$), 2.73 (1H, sept, $J = 6.4$ Hz, 4′-H), 2.98–3.07 (2H, m, 2-H), 3.09–3.23 (2H, m, 6-*H*), 6.51 (1H, d, $J = 8.1$ Hz, 8′-H), 6.77 (1H, d, $J = 8.0$ Hz, 7′-H), 6.98 (1H, s, 5′-H); ^{13}C NMR (100 MHz, D_2O + acetone-d_6, δ): 19.5 (+, 6′-CH_3), 20.1 (+, 4′-CH_3), 26.3 (+, 4′-C), 30.3 (−, 3-C), 34.6 (−, 5-C), 39.3 (−, 3′-C), 40.1 (−, 6-C), 40.4 (−, 2-C), 48.2 (4-C), 116.5 (+, 8′-C), 127.6 (+, 7′-C), 127.8 (4a′-*C*), 127.9 (+, 5′-C), 129.3 (6′-C), 139.4 (8a′-C); COSY correlations [δ_H/δ_H (H/H)]: 1.13/2.73 [4′-*CH*$_3$/4′-*H*], 1.19/2.01/2.73 [3′-Ha/3′-He/4′-H], 1.54/1.76/2.98–3.07 [3-Ha/3-He/2-H], 1.66–1.69/3.09–3.23 [5-H/6-H], 1.76/1.54/2.98–3.07 [3-He/3-Ha/2-H], 2.01/1.19/2.73 [3′-He/3′-Ha/4′-H], 2.73/1.13/2.01 [4′-H/4′-CH_3/3′-He], 2.98–3.07/1.54/1.76 [2-H/3-Ha/3-He], 3.09–3.23/1.66–1.69 [6-H/5-H], 6.51/6.77 [8′-H/7′-H], 6.77/6.51/6.98 [7′-H/8′-H/5′-H], 6.98/6.77 [5′-H/7′-H]; HMQC correlations [δ_H/δ_C (C/H)]: 19.5/2.12 [6′-CH_3/6′-CH_3], 20.1/1.13 [4′-CH_3/4′-CH_3], 26.3/2.73 [4′-C/4′-H], 30.3/1.54/1.76 [3-C/3-Ha/3-He], 34.6/1.66–1.69 [5-C/5-H], 39.3/1.19/2.01 [3′-C/3′-Ha/3′-He], 40.1/3.09–3.23 [6-C/6-H], 40.4/2.98–3.07 [2-C/2-H], 116.5/6.51 [8′-C/8′-H], 127.6/6.77 [7′-C/7′-H], 127.9/6.98 [5′-C/5′-H]; HMBC

correlations [δ_H/δ_C (C/H)]: 19.5/6.77/6.98[6′-CH_3/7′-H/5′-H], 20.1/1.19/2.73 [4′-CH_3/4′-H/3′-Ha], 26.3/1.13/1.19/2.01/6.98 [4′-C/4′-CH_3/3′-Ha/3′-He/5′-H], 30.3/1.19/1.66–1.69/2.98–3.07 [3-C/3′-Ha/5-H/2-H], 34.6/1.19/1.54/1.76/2.01/3.09–3.23 [5-C/3′-Ha/3-Ha/3-He/3′-He/6-H], 39.3/1.13/1.66–1.69 [3′-C/4′-CH_3/5-H], 40.1/2.98–3.07 [6-C/2-H], 40.4/1.66–1.69/3.09–3.23 [2-C/5-H/6-H], 48.2/1.19/1.54/1.66–1.69/1.76/2.01/2.98–3.07/3.09–3.23 [4-C/3′-Ha/3-Ha/5-H/3-He/3′-He/2-H/6-H], 116.5/6.77 [8′-C/7′-H], 127.6/2.12/6.98 [7′-C/6′-CH_3/5′-H], 127.8/1.13/6.51 [4a′-C/4′-CH_3/4′-H/8′-H], 127.9/2.73/6.77 [5′-C/4′-H/7′-H], 129.3/6.51 [6′-C/8′-H], 139.4/6.77/6.98 [8a′-C/7′-H/5′-H]; GC–MS: t_R 19.05 min; mass spectrum (EI): m/z (%) 230 (M^+, 52), 185 (100), 173 (54), 158 (84), 143 (29), 115 (18), 96 (16), 56 (45). Calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16. Found: C, 78.44; H, 9.86; N, 11.72.