Pergamon

Tetrahedron Letters 41 (2000) 9829–9833

TETRAHEDRON LETTERS

A simple, efficient method for regioselective synthesis of 7-aminomethyl-7,8-dihydro-6*H*-quinolin-5-ones, new potential CNS agents

Beatriz Pita, Christian F. Masaguer and Enrique Raviña*

Departamento de Química Orgánica, Laboratorio de Química Farmacéutica, Facultad de Farmacia, Universidad de Santiago de Compostela, 15706 Santiago de Compostela, Spain

Received 20 August 2000; accepted 10 October 2000

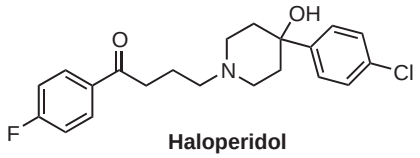
Abstract

We have developed an efficient and convenient strategy for the regioselective synthesis of new conformationally restricted butyrophenones of the quinoline series. The 7-aminomethyl-7,8-dihydro-6*H*-quinolin-5-ones **9** were obtained from protected alcohol **5** via the tosylate, and also in a one-pot reaction via bromo derivative **6**, with moderate-to-good overall yields in both cases.

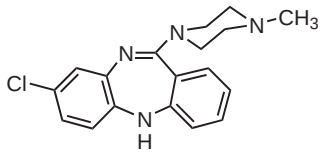
Schizophrenia is a serious mental illness that afflicts nearly 1% of the world's population. Front-line therapy consists of administration of conventional neuroleptics (or conventional antipsychotics) such as haloperidol, the prototype of a group of very potent antipsychotic butyrophenone derivatives. Because these drugs appear to act mainly via blockade of central D_2 dopamine receptors, the hypothesis that activation of these receptors is a primary factor in the pathogenesis of schizophrenia has gained wide acceptance.[1] Unfortunately, dopamine receptor blockade is also intimately associated with the extrapyramidal side effects (EPS, a short-term parkinsonism like condition) of these drugs. Furthermore, classical antipsychotics are not effective against the negative symptoms of schizophrenia.[2] Therapeutic advantages may be offered by compounds with affinities for multiple receptors. Clozapine, which binds to both dopamine and serotonin receptors, is the most noteworthy of these drugs due to its efficacy and its lack of EPS. However, clozapine causes a low but significant incidence of agranulocytosis, and requires periodic blood monitoring during continued therapy.[3] Since the currently available agents thus have serious limitations, there is a major medical need for better therapies.

* Corresponding author. Fax: +34 981 594912; e-mail: qofara@usc.es

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01780-9

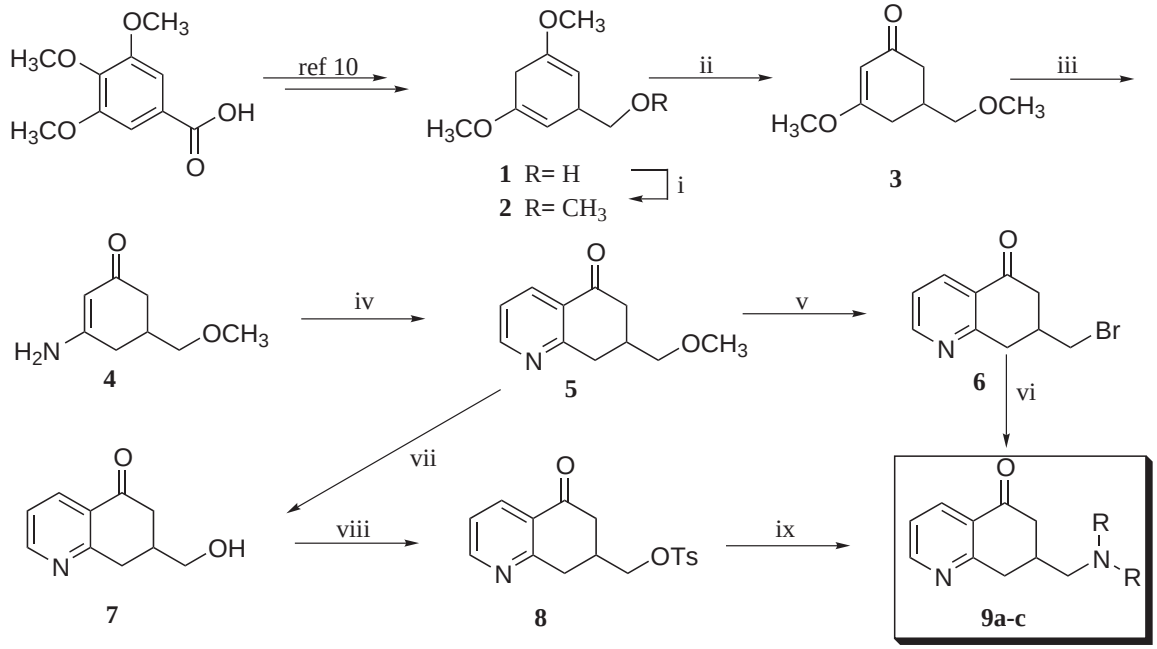


Haloperidol



Clozapine

In previous papers we have reported the synthesis and neuroleptic activity of aminoalkylbenzocycloalkanones,[4] which are conformationally restricted butyrophenone analogues of haloperidol with the aminobutyl side chain partially incorporated in a semirigid framework. We have also prepared and studied the CNS activity of several cyclic butyrophenone derivatives of pyrrole,[5] furan,[6] thiophene,[7] and indole.[8] We report here an efficient, convenient method for the preparation of a series of butyrophenone quinoline derivatives, the 7-aminomethyl-7,8-dihydro-6*H*-quinolin-5-ones. The proposed method includes the preparation of 3-amino-5-methoxymethyl-2-cyclohexen-1-one (**4**, Scheme 1), a potentially useful synthon for the synthesis of other β-substituted cycloalkanones with fused heterocycles containing N (as practical ambident nucleophiles, enaminones are frequently employed as building blocks for the preparation of a variety of bicyclic compounds of biological interest).[9] Because of this great synthetic potential of enaminone **4**, we optimized its preparation before using it as the basis of a convenient synthesis of the target 7-aminomethyl-dihydroquinolinones **9**.



Scheme 1. (i) CH_3I, NaH 60%, THF, rt. (ii) Dowex 50W-X4, MeOH, rt. (iii) NH_3(g)/MeOH, −20°C to rt. (iv) Method A: (a) CH_2=CH–CHO, MeOH/AcOH (b) $Pd(PPh_3)_4$, 10% Pd/C, K_2CO_3, DMF, reflux. Method B: Pd/C, CH_2=CH–CHO, 4 Å molecular sieves, toluene, reflux. Method C: (a) CH_2=CH–CHO, MeOH/AcOH (b) DBU/MIK, 110°C (c) DDQ, rt. (v) BBr_3 (2 equiv.)/DCM, −78°C to rt. (vi) NRR, K_2CO_3, KI, MIK, reflux. (vii) BBr_3 (1 equiv.)/DCM, −78°C to rt. (viii) TsCl/py; (ix) NRR, Hünig's base, THF, reflux.

1,4-Dihydro-3,5-dimethoxybenzyl alcohol (**1**) was readily prepared from inexpensive 3,4,5-trimethoxybenzoic acid in 85% yield, as previously described.[10] Methylation of its hydroxyl group (ICH_3, 95%), followed by mild acidic hydrolysis of the resulting enolether **2** (Dowex 50W-X4 resin) provided the β-methoxyenone **3** in 63% yield. Ammonolysis of **3** in methanol afforded the desired enamine **4** in good yield.[11]

The key step in the synthesis of compounds **9** was the cyclization of the enaminone **4** to obtain the quinolinone system. 7,8-Dihydro-6*H*-quinolin-5-ones, which are versatile intermediates in organic synthesis and medicinal chemistry,[12] are usually prepared in low yield from propynal and the corresponding enaminone.[13] These low yields and the difficulty in preparing propynal prompted us to seek alternative methods. We found that palladium-catalyzed reaction of enaminone **4** with acrolein in methanol overnight, followed by removal of the solvent, addition of DMF and refluxing in the presence of $Pd(PPh_3)_4$, 10% Pd/C and potassium carbonate, gave the corresponding dihydroquinolinone **5** in good yield (70%, Method A).[14] Alternatively, reaction of the enaminone with acrolein in toluene in the presence of molecular sieves and a catalytic amount of Pd as dehydrogenating agent also afforded **5** in 70% yield (Method B). Finally, a 65% overall yield of **5** (Method C) was obtained more onerously by reaction of **4** with acrolein in methanol and acetic acid, followed by treatment with DBU at 110°C in methyl isobutyl ketone and oxidation with DDQ.[15]

All three methods proved to be regioselective when a substituted acrolein was used. Thus, reaction between 3-amino-2-cyclohexen-1-one and crotonaldehyde under the conditions of the above methods afforded 7,8-dihydro-4-methyl-6*H*-quinolin-5-one without any NMR evidence of the 2-methyl regioisomer.

Demethylation of **5** using 1 equiv. of BBr_3 at −70°C to +20°C gave the alcohol **7** (70%; mp 92–94°C) as a white crystalline solid. Tosylation of **7** using *p*-toluenesulfonyl chloride in pyridine afforded the corresponding sulfonate ester **8** (85%; mp 119.5–120.5°C). The aminomethyldihydroquinolinones **9** were then obtained cleanly and in good yield from **8** by nucleophilic reaction with 1-(2-methoxyphenyl)piperazine (**10**), 4-(4-fluorobenzoyl)piperidine (**11**) or 4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine (**12**) (Table 1).[16,17] The amino substituents **10**–**12** were chosen because of the known CNS activity of related compounds containing them.[7]

Table 1
7-Aminomethyl-7,8-dihydro-6*H*-quinolin-5-ones **9a**–**c**

Compound	NRR	Mp (°C)	Yield from **7** (%)
9a	10	129–130	45
9b	11	149–150	55
9c	12	150–151	35

Alternatively, demethylation and bromination of **5** were achieved in a one-pot reaction by treating the substrate with 2 equiv. of BBr_3 in CH_2Cl_2 at −70°C and bringing the mixture slowly up to room temperature, which yielded the bromoderivative **6** in 50% yield. Subsequent nucleophilic displacement of the bromine atom from **6** by refluxing with the corresponding amine in methyl isobutyl ketone in the presence of K_2CO_3 and a catalytic amount of KI afforded 7-aminomethyl-7,8-dihydro-6*H*-quinolin-5-ones (**9a**–**c**) in moderate yield.[18]

In conclusion, we have developed an efficient, convenient strategy for the regioselective synthesis of new conformationally restricted butyrophenones in the quinoline series. The

hexahydroquinolinones **9** were obtained from protected alcohol **5** either via the corresponding tosylate or in a one-pot reaction via the bromo derivative. This methodology provides a new approach to potential CNS-active agents. Work in progress in our laboratory will be reported in due course.

Acknowledgements

This work was supported by the *Xunta de Galicia* under grant XUGA20319B97. B.P. was aided by grants from the *Xunta de Galicia* and the University of Santiago de Compostela, and wishes to thank the programme Ciencia y Tecnología para el Desarrollo (CYTED).

References

1. Davis, K. L.; Kahn, R. S.; Ko, G.; Davidson, M. *Am. J. Psychiatry* **1991**, *148*, 474–486.
2. Simpson, G. M.; Pi, E. H.; Sramek, J. J. *Drugs* **1981**, *21*, 138–151.
3. West, S. A.; Nemeroff, C. B. *Drugs Today* **1993**, *29*, 183–188.
4. (a) Cortizo, L.; Santana, L.; Raviña, E.; Orallo, F.; Fontenla, J. A.; Castro, E.; Calleja, J. M.; Ceballos, M. L. *J. Med. Chem.* **1991**, *34*, 2242–2247. (b) Fontenla, J. A.; Osuna, J. A.; Rosa, E.; Castro, E.; Loza, M. I.; G.-Ferreiro, T.; Calleja, J. M.; Sanz, F.; Rodriguez, J.; Fueyo, J.; Raviña, E.; Masaguer, C. F.; Vidal, A.; de Ceballos, M. *J. Med. Chem.* **1994**, *37*, 2564–2573.
5. (a) Masaguer, C. F.; Raviña, E. *Tetrahedron Lett.* **1996**, *37*, 5171–5174. (b) Masaguer, C. F.; Casariego, I.; Raviña, E. *Chem. Pharm. Bull.* **1999**, *47*, 621–632.
6. Casariego, I.; Masaguer, C. F.; Raviña, E. *Tetrahedron Lett.* **1997**, *38*, 5555–5558.
7. Raviña, E.; Negreira, J.; Cid, J.; Masaguer, C. F.; Rosa, E.; Rivas, M. E.; Fontenla, J. A.; Loza, M. I.; Tristan, H.; Cadavid, M. I.; Sanz, F.; Lozota, E.; Carotti, A.; Carrieri, A. *J. Med. Chem.* **1999**, *42*, 2774–2779.
8. Masaguer, C. F.; Raviña, E.; Fontenla, J. A.; Brea, J.; Tristan, H.; Loza, M. I. *Eur. J. Med. Chem.* **2000**, *35*, 83–95 and references cited therein.
9. (a) Singh, H.; Chimni, S.; Kumar, S. *Tetrahedron* **1995**, *51*, 12775–12780. (b) Pitts, W.; Jetter, J.; Pinto, D.; Orwat, M.; Batt, D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 307–312. (c) Foster, J.; Nicholson, J.; Butcher, R.; Stables, J.; Edafiogho, I.; Goodwin, A.; Henson, M.; Smith, C.; Scott, K. *Bioorg. Med. Chem.* **1999**, *7*, 2415–2425.
10. Chapman, O. L.; Fitton, P. *J. Am. Chem. Soc.* **1963**, *85*, 41–47.
11. Compound **4**: 85%; cream-coloured crystals, mp = 110–111°C (EtOAc); IR (KBr) 3101, 1689, 1256, 1122 cm^{-1}; MS (EI) 155 (M^+), 140, 110, 83; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.22 (s, 1H, CH), 5.02 (brs, 1H, NH), 3.33 (s, 2H, CH_2), 3.32 (s, 3H, OCH_3), 2.33 (m, 4H, CH_2), 2.11 (m, 1H, CH).
12. (a) Caprathe, B. W.; Jaen, J. C.; Wise, L. D. *J. Med. Chem.* **1991**, *34*, 2736–2746. (b) Hartmann, R. W.; Frotscher, M. *Arch. Pharm.* **1999**, *332*, 358–362.
13. (a) Zymalkowski, F.; Rimek, H. *Arch. Pharm.* **1961**, *294*, 759–765. (b) Albright, J. D.; Du, X. *J. Heterocycl. Chem.* **2000**, *37*, 41–46. (c) Bell, I. M.; Erb, J.; Freidinger, R.; Gallicchio, S.; Guare, J. P.; Guidotti, M. T.; Halpin, R. A.; Hobbs, D. W.; Homnick, C. F.; Kuo, M. S. and colleagues. *J. Med. Chem.* **1998**, *41*, 2146–2163.
14. Compound **5**: IR (KBr) 2894, 1688, 1583; MS (EI) 191 (M^+), 159, 146; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.66 (dd, 1H, J = 4.7, 1.8 Hz, H-2), 8.23 (dd, 1H, J = 7.8, 1.8 Hz, H-4), 7.27 (dd, 1H, J = 4.7, 7.8 Hz, H-3), 3.43 (d, 2H, J = 5.1 Hz, CH_2O), 3.35 (s, 3H, CH_3O) 3.3–2.4 (m, 5H, aliphatics).
15. A similar procedure starting from commercially available 3-amino-5,5-dimethylcyclohexen-2-one has been described for the synthesis of 7,7-dimethyl-7,8-dihydro-6*H*-quinolin-5-one; Curran, A. C. W. *J. Chem. Soc., Perkin Trans. 1* **1976**, 975–977. See also Jaen, J. C.; Kropko, M. L.; Theiss, J. C. *Eur. J. Med. Chem.* **1993**, *28*, 547–553.
16. Compound **9b**: mp = 149–150°C (*iso*-PrOH); IR (KBr) 3101, 1689, 1256, 1122 cm^{-1}; MS (EI) 366.0 (M+), 331, 220, 146; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.68 (dd, 1H, J = 4.8, 1.8 Hz, H-2), 8.26 (dd, 1H, J = 7.8, 1.8 Hz, H-4), 7.95 (m, 2H, Ar), 7.30 (dd, 1H, J = 7.8, 4.8 Hz, H-3), 7.14 (m, 2H, Ar), 4.05 (d, 2H, J = 5.2 Hz, CH_2–N), 3.4–1.2 (m, 14H, aliphatics).

17. Complete details of the synthesis, spectral characteristics and biological evaluation of compounds **9** will be published elsewhere in a full paper. All compounds gave satisfactory microanalyses (C, H, N±0.4%) and spectral data (^{1}H and ^{13}C NMR, FTIR, MS). Yields given correspond to isolated pure compounds.
18. The cyclopropylquinolinone 1,1a,2,7a-tetrahydro-3-azacyclopropa[*b*]naphthalen-7-one was isolated as an elimination by-product (30% yield). A similar elimination has been observed in the tetralone series: see Ref 4(a).