PD(0)-CATALYSED SYNTHESIS OF BUSPIRONE AND GEPIRONE

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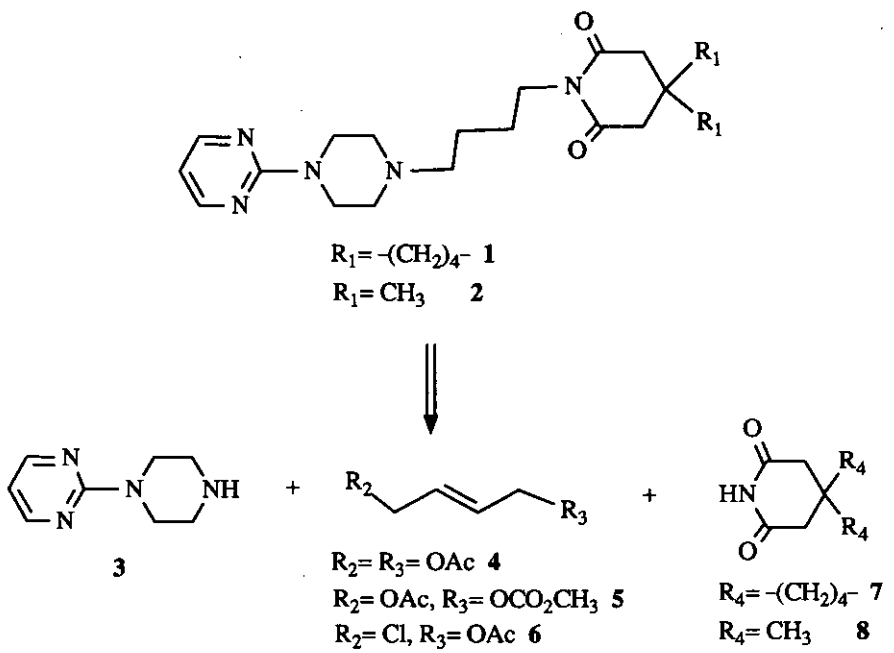
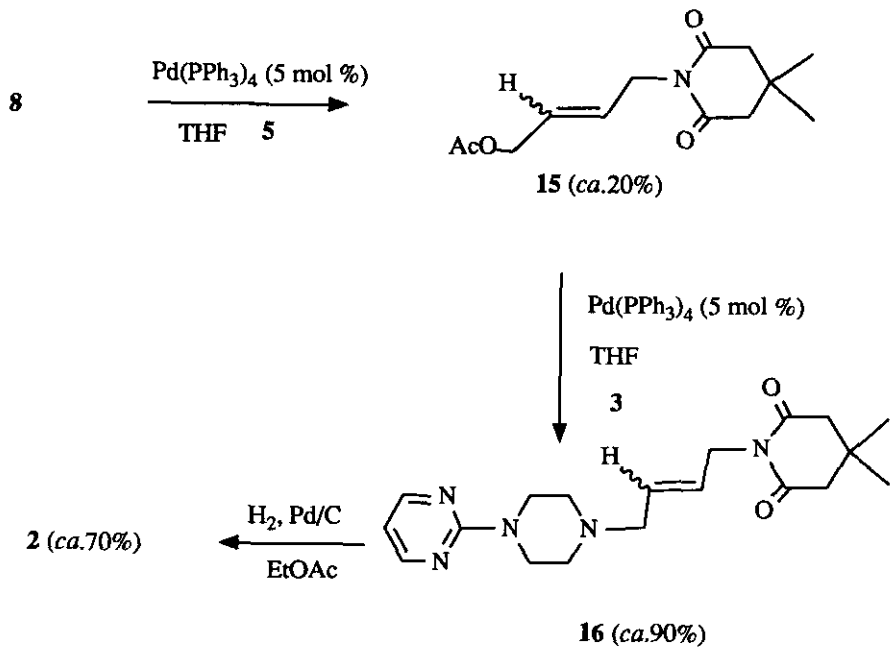
Abstract - A novel synthetic approach to buspirone and its anologue (gepirone) is described, in which 3 subunits, namely 2-(1-piperazinyl)pyrimidine, a bifunctional allylderivative, and an imide were efficiently assembled *via* a Pd(0)-catalysed amination-imidation sequence followed by a hydrogenation.

The search for effective anxiolytic drugs has received considerable attention in recent years as a result of the prevalence of various forms of anxiety disorder. This continuing effort has led to the discovery of a number of novel compounds including buspirone (**1**) and gepirone (**2**), which have been shown to alleviate symptoms of anxiety in man.[1] There has been considerable interest in the synthesis[2] of (**1**) and (**2**) over the last few decades. Unlike others, we envisioned buspirone (or gepirone) as a linear assembly of three readily disconnected building blocks, namely 2-(1-piperazinyl)pyrimidine (**3**), a bifunctional allyl derivative (**4, 5** or **6**), and 8-azaspiro[4.5]decane-7,9-dione (**7**) (or 4,4-dimethylpiperidine-2,6-dione (**8**)) as retro-synthetically analysed in Scheme 1. Prompted by the continuing interest of these drugs on the market we now wish to report an efficient assembly of the building blocks (**3**), (**6**)(or **4**, **5**) and (**7**)(or **8**) *via* a novel palladium(0)-catalysed sequential amination-imidation[3] sequence.



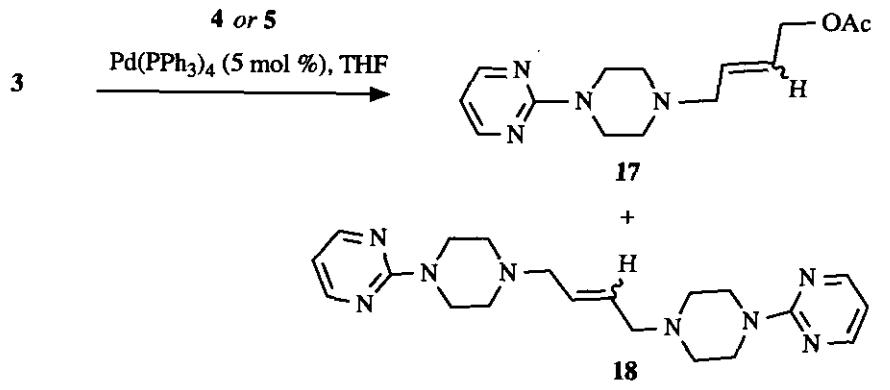
Scheme 1

4-Methoxycarbonyloxybut-2(Z)-enyl acetate (**5**) was prepared from (Z)-but-2-ene-1,4-diol[4] and was treated with **8** in the presence of $Pd(PPh_3)_4$[5] (5 mol %) in THF to give the desired 4-(4,4-dimethyl-2,6-dioxopiperidin-1-yl)but-2-enyl acetate (**15**)[6] as a mixture of geometric isomers (E/Z : *ca.* 9/1) in 23 % yield. This low yield could be due to the inert nature of **8** toward the allylpalladium complex.[7] Treatment of **15** with 2-(1-piperazinyl)pyrimidine (**3**)[8] and $Pd(PPh_3)_4$ (5 mol %) gave 4,4-dimethyl-1-[4-(4-pyrimidin-2-yl-piperazin-1-yl)but-2-en-1-yl]-piperidine-2,6-dione (**16**)[9] (E/Z : *ca.* 9:1) in over 90% yield. Hydrogenation of **16** (Pd/C, EtOAc, 1 atm) furnished gepirone (**2**)[10] in *ca.* 70% yield as outlined in Scheme 2.



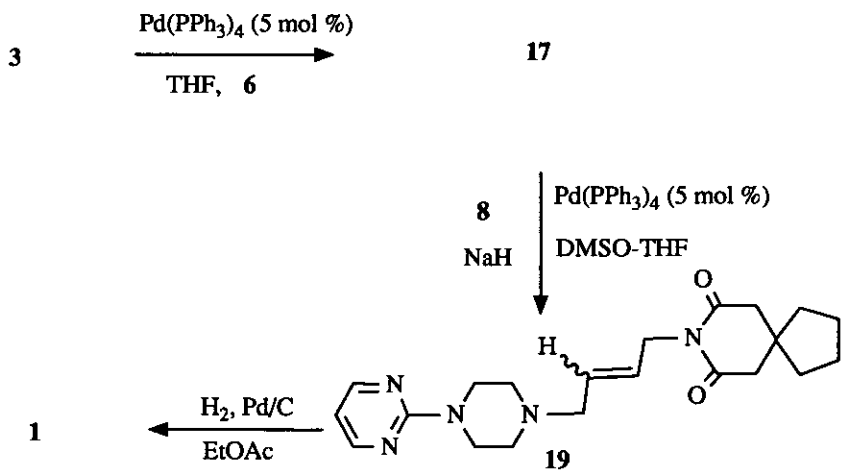
Scheme 2

An alternative, more efficient sequence involved treatment of **3** with **5** in the presence of $Pd(PPh_3)_4$ (5 mol %) in THF to give the desired 4-(4-pyrimidin-2-yl-piperazin-1-yl)but-2-enyl acetate (**17**)[11] (E/Z: *ca.* 9:1) in 56% yield accompanied by the undesired dimer (**18**) (*ca.* 21%) as shown in Scheme 3. A similar result (**17**, *ca.* 50% yield) was obtained when **5** was replaced by 4-acetoxybut-2(Z)-enyl acetate (**4**).[12]



Scheme 3

Replacement of **5** with 4-chlorobut-2-enyl acetate (**6**)[13] brought about considerable improvement in the selectivity and allowed formation of the required **17** in *ca.* 80% yield (E/Z : *ca.* 9:1). Treatment of **17** with **8** and $Pd(PPh_3)_4$ (5 mol %) in THF-DMSO[7b] provided 8-[4-(4-pyrimidin-2-yl-piperazin-1-yl)but-2-enyl]-8-aza-spiro[4.5]decane-7,9-dione (**19**)[14] in *ca.* 70% yield. A subsequent hydrogenation of **19** furnished buspirone (**1**)[15] in *ca.* 70% yield (Scheme 4).



Scheme 4

In conclusion, we have developed novel syntheses of buspirone (**1**)[16] and gepirone (**2**)[17] in which the 3 subunits, namely the 2-(1-piperazinyl)pyrimidine (**3**), a bifunctional allylderivative (**4**, **5** or **6**), and (**7**) (or **8**) were efficiently assembled *via* a novel Pd(0)-catalysed amination-imidation sequence,[18] followed by hydrogenation. It should be noted that this method empolys mild reaction conditions, exhibits high chemoselectivity and has the potential for use as a general method for the preparation of analogues of **1** and **2**.

ACKNOWLEDGEMENTS

I thank Mr. Edwin Vogel for his excellent assistance in the laboratory, Drs. M. Hauck and M. Bokel for their analytical services, and Lonza Ltd. for the permission to publish this work.

REFERENCES AND NOTES

1. (a) M. Abou-Gharbia, J.A. Moyer, U. Patel, M. Webb, G. Schiehser, T. Andree, and J. Haskins, *J. Med. Chem.*, 1989, **31**, 1024; (b) J.A. Cipollina, E.H. Ruediger, J.S. New, M.E. Wire, T.A. Shepherd, D.W. Smith, and J. P. Yevich, *ibid.*, 1991, **34**, 3316; (c) J.P. Yevich, J.S. New, D.W. Smith, W.G. Lobeck, J.D. Catt, J.L. Minielli, M.S. Eison, D.P. Taylor, L.A. Riblet, and D.L. Temple, Jr., *ibid.*, 1986, **29**, 359. (d) R.E. Newton, J.D. Marunycz, M.T. Alderdice, and M.J. Napoliello, *Am. J. Med.*, 1986, **80**, 17; (e) D.P. Taylor, *Faseb J.*, 1988, **2**, 2445; (f) D.W. Robertson and R.W. Fuller, *Annu. Rep. Med. Chem.*, 1988, **23**, 49.

2. (a) Y.H. Wu and J.W. Rayburn, *US Patent 3717634*, 1973; (b) W.M. Welch and D.M. Viverios, *J. Labelled Compounds and Radiopharma.*, 1988, **27**, 701; (c) J. Cybulski, Z. Chilmonczyk, W. Szelejewski, K. Wojtasiewicz, and J.T. Wrobel, *Arch. Pharm.*, 1992, **325**, 313.

3. For sequential π-allylpalladium alkylation-amination reaction: (a) Y. Tanigawa, K. Nishimura, A. Kawasaki, and S.-I. Murahashi, *Tetrahedron Lett.*, 1982, **23**, 5549; (b) S.-I. Murahashi, Y. Tanigawa, Y. Imada, and Y. Taniguchi, *ibid.*, 1986, **27**, 227. For sequential π-allylpalladium alkylations reaction: (c) R.S. Valpey, D.J. Miller, J.M. Estes, and S.A. Godleski, *J. Org. Chem.*, 1982, **47**, 4717.

4. W. Oppolzer and J.-M. Gaudin, *Helv. Chim. Acta*, 1987, **70**, 1477.

5. R.F. Heck, 'Palladium Reagents in Organic Syntheses', Academic Press, Inc., New York, 1985, pp. 2.

6. Ir (thin film) υ_{max} 2958, 2874, 1738, 1674, 1468 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 1.10 (s, 6H), 2.07 (s, 3H), 2.52 (s, 4H), 4.40 (d, 2H, J= 5 Hz), 5.72 (m, 2H); ^{13}C nmr (75 MHz, $CDCl_3$) δ 20.887 (q), 27.694 (q), 29.212 (s), 36.465 (s), 40.252 (t), 60.212 (s), 63.996 (t),

127.887 (d), 128.124 (d), 171.479 (s); GCms (m/z) 253 (M^+).

7. (a) R.D. Connell, T. Rein, B. Akermark, and P. Helquist, *J. Org. Chem.*, 1988, **53**, 3845; (b) M. Takagi and K. Yamamoto, *Chem. Lett.*, 1989, 2123. (c) L.S. Hegedus, *J. Am. Chem. Soc.*, 1987, **109**, 4335. (d) Y. Inoue, M. Taguchi, M. Toyofuku, and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 3021.

8. (a) D.L. Kuo, *EP 491328*, 1992. (Chem. Abstr.,1992, 117, 151018 x) (b) D.L. Kuo and R: Voeffray, *EP 491329*, 1992 (Chem. Abstr.,1992, 117, 151019 x)

7. Ir (thin film) υ_{max} 2958, 1726, 1675, 1548 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 1.10 (s, 6H), 2.50 (t, 4H, J= 6 Hz), 2.51 (s, 4H), 3.03 (d, 2H, J= 6 Hz), 3.84 (t, 4H, J= 6 Hz), 4.40 (d, 2H, J 6 Hz), 5.64-5.77 (m, 2H), 6.50 (t, 1H, J= 6 Hz), 8.30 (d, 2H, J= 6 Hz); GCms (m/z) 357 (M^+).

10. mp 106.5-107.5 °C (lit.,[2b] 105-106 °C); ^1H nmr (300 MHz, $CDCl_3$) δ 1.05 (s, 6H), 1.52 (m, 4H), 2.35 (m, 2H), 2.48 (s, 8H), 3.73-3.84 (m, 6H), 6.44 (t, 1H, J= 5 Hz), 8.27 (d, 2H, J= 5 Hz); ^{13}C nmr (75 MHz, $CDCl_3$) δ 24.253 (t), 26.017 (t), 27.678 (q), 29.118 (s), 39.313 (t), 43.604 (t), 46.436 (t), 53.036 (t), 58.036 (t), 58.275 (t), 109.705 (d), 157.616 (d), 171.814 (s); GC-MS (m/z) 359 (M^+).

11. Ir (thin film) υ_{max} 3456, 2995, 1739, 1678, 1450 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 2.09 (s, 3H), 2.55 (t, 4H, J= 5 Hz), 3.18 (d, 2H, J= 5 Hz), 3.85 (t, 4H, J= 5 Hz), 4.59 (d, 2H, J= 5 Hz), 5.70-5.90 (m, 2H), (irradiation at 4.59 δ gives a coupling constant of 15.5 Hz), 6.50 (t, 1H, J= 5 Hz), 8.31 (d, 1H, J= 5 Hz); ^{13}C nmr (75 MHz, $CDCl_3$) δ 20.907 (q), 43.346 (t), 52.707 (t), 60.020 (t), 64.281 (t), 109.855 (d), 128.006 (d), 130.461 (d), 157.607 (d), 161.493 (s), 170.583 (s); GC-MS (m/z) 276 (M^+).

12. J.P. Genet, M. Balabane, J.E. Bäckvall, and J.E. Nyström, *Tetrahedron Lett.*, 1983, **24**, 2745.

13. J.-E. Bäckvall, J.-E. Nyström, and R.E. Nordberg, *J. Am. Chem. Soc.*, 1985, **107**, 3676.

14. ^{1}H Nmr (300 MHz, $CDCl_3$) δ 1.45-1.57 (m, 4H), 1.63-1.79 (m, 4H), 2.47 (t, 4H, J= 5 Hz), 3.82 (t, 4H, J= 5 Hz), 4.39 (d, 2H, J= 5 Hz), 5.55-5.80 (m, 2H), 6.47 (t, 1H, J= 5 Hz), 8.30 (d, 2H, J= 5 Hz); ^{13}C nmr (75 MHz, $CDCl_3$) δ 24.085 (t), 37.445 (t), 39.418 (s), 40.419 (t), 43.419 (t), 44.674 (t), 52.706 (t), 60.182 (t), 109.627 (d), 127.683 (t), 129.801 (t), 157.488 (d), 161.464 (s), 171.636 (s).

15. mp 102-105 °C; ir (thin film) υ_{max} 3439, 2960, 1674, 1357 cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.42-1.63 (m, 8H), 1.65-1.80 (m, 4H), 2.39-2.44 (m, 2H), 2.81 (t, 4H, J= 5 Hz), 2.62 (s, 4H), 3.72-3.95 (m, 6H), 6.48 (t, 1H, J= 5 Hz), 8.30 (d, 2H, J= 5 Hz); ^{13}C nmr (75 MHz, $CDCl_3$) δ 23.990 (t), 25.824 (d), 37.346 (t), 39.112 (t), 39.267 (t), 43.365 (t), 44.680 (t), 52.829 (t), 58.068 (t), 60.12 (s), 109.548 (d), 157.425 (d), 161.356 (s), 171.895 (s); GCms (m/z) 385 (M^+).

16. D.L. Kuo, *Switzerland Patent Application 2334*, 1991.

17. D.L. Kuo, *Switzerland Patent Application 2411*, 1991.

18. A one pot operation of this amination-imidation sequence resulted in > 20% yield (not optimised) of (**19**).

Received, 25th January, 1993