

PD(0)-CATALYSED SYNTHESIS OF BUSPIRONE AND GEPIRONE

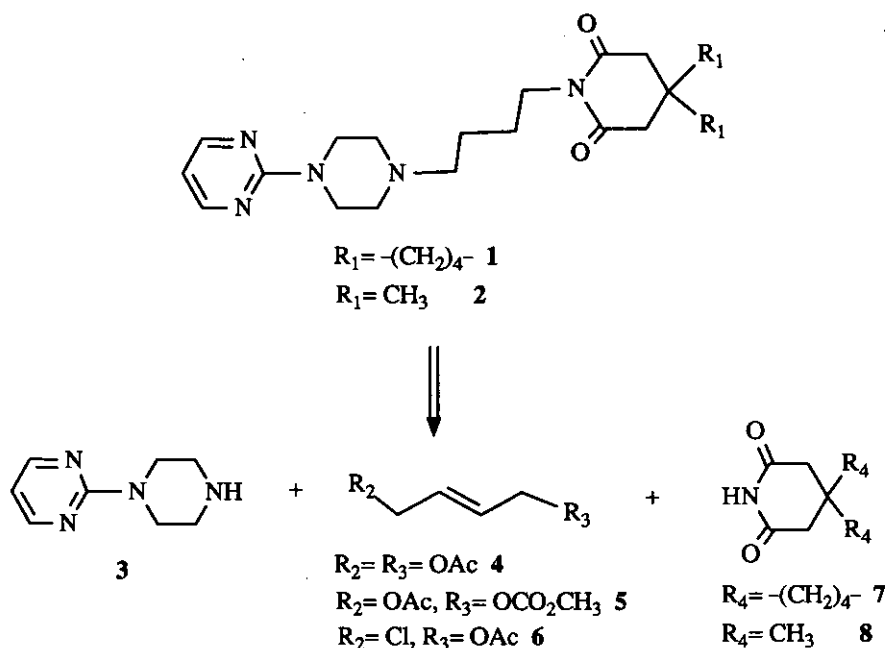
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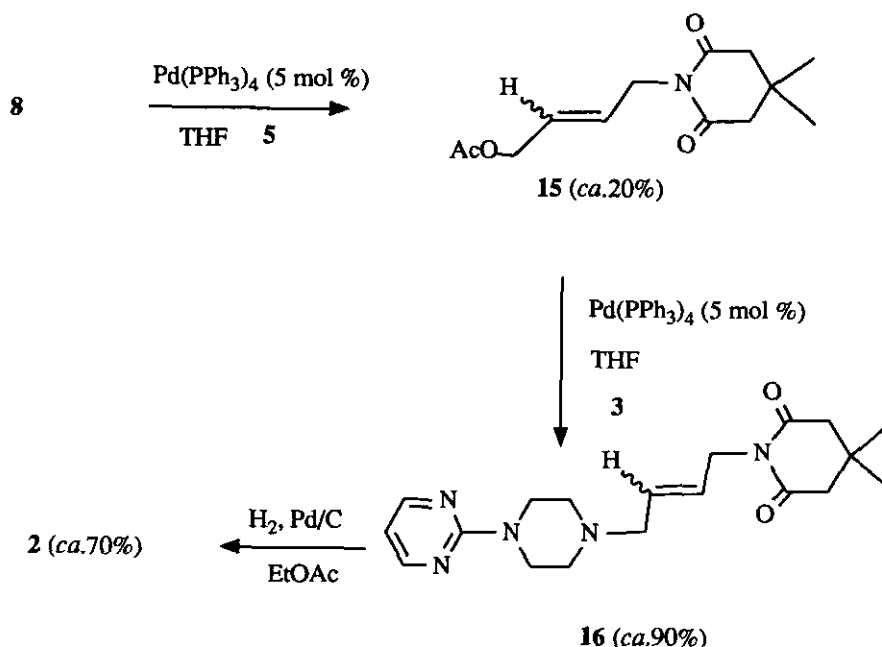
Abstract - A novel synthetic approach to buspirone and its analogue (gepirone) is described, in which 3 subunits, namely 2-(1-piperazinyl)pyrimidine, a bifunctional allyl derivative, and an imide were efficiently assembled *via* a Pd(0)-catalysed amination-imidation sequence followed by a hydrogenation.

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 synthesis² 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-imidation³ sequence.



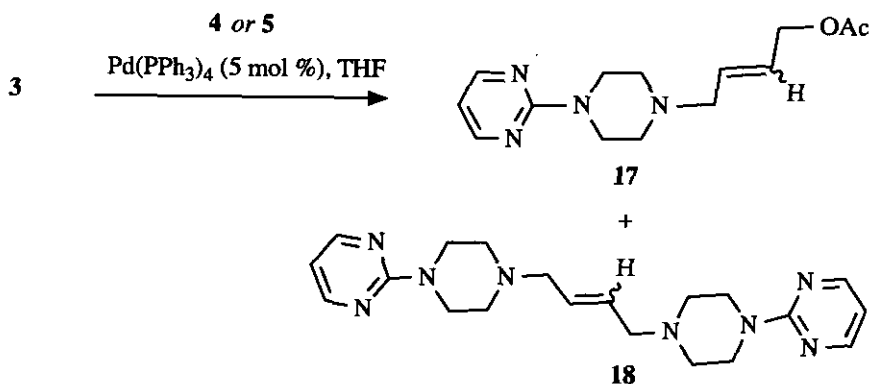
Scheme 1

4-Methoxycarbonyloxybut-2(Z)-enyl acetate (**5**) was prepared from (Z)-but-2-ene-1,4-diol⁴ 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.



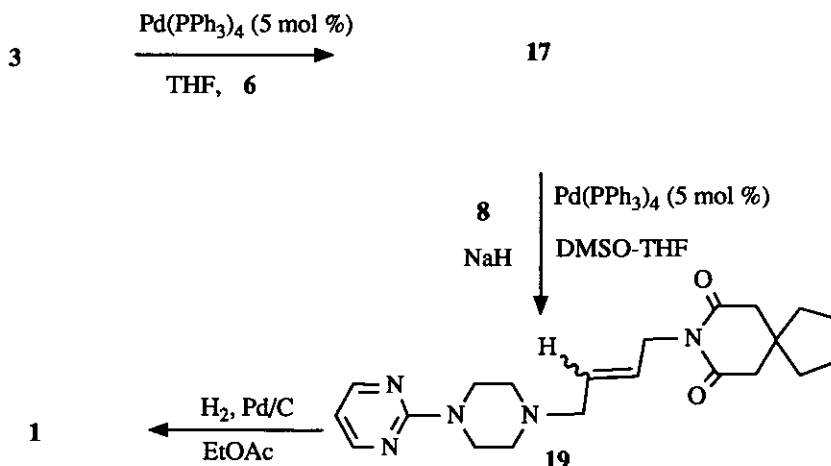
Scheme 2

An alternative, more efficient sequence involved treatment of **3** with **5** in the presence of $\text{Pd}(\text{PPh}_3)_4$ (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(PPh₃)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 allyl derivative (**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 employs 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

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6. Ir (thin film) $\nu_{\max}$ 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^+).
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8. (a) D.L. Kuo, *EP 491328*, 1992. (Chem. Abstr., 1992, 117, 151018 x) (b) D.L. Kuo and R. Voefrày, *EP 491329*, 1992 (Chem. Abstr., 1992, 117, 151019 x)
7. Ir (thin film) $\nu_{\max}$ 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 $^\circ\text{C}$ (lit.,^{2b} 105-106 $^\circ\text{C}$); ^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) $\nu_{\max}$ 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^+).
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14. ^1H 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) ν_{max} 3439, 2960, 1674, 1357 cm^{-1} ; ^1H 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^+).
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18. A one pot operation of this amination-imidation sequence resulted in > 20% yield (not optimised) of (19).

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