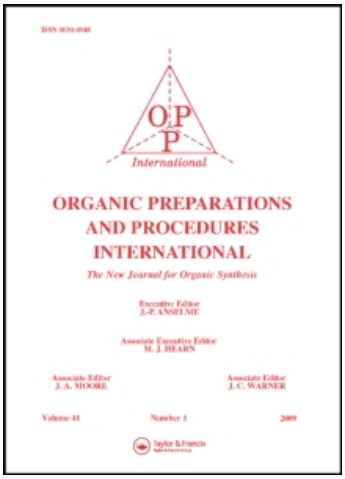

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

FACILE SYNTHESIS OF ANXIOLYTIC BUSPIRONE

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To cite this Article Mou, Jie , Zong, Zhi-Min and Wei, Xian-Yong(2008) 'FACILE SYNTHESIS OF ANXIOLYTIC BUSPIRONE', Organic Preparations and Procedures International, 40: 4, 391 — 394
To link to this Article: DOI: 10.1080/00304940809458099
URL: http://dx.doi.org/10.1080/00304940809458099

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FACILE SYNTHESIS OF ANXIOLYTIC BUSPIRONE

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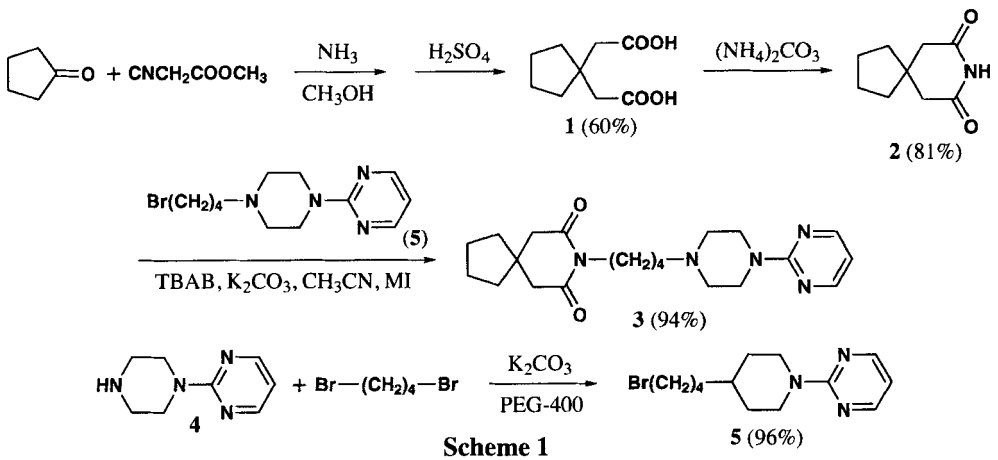
Buspirone (**3**·HCl) is an anxiolytic and antidepressant drug widely used in therapy.[1-5] Although several approaches to buspirone have been reported in the patent literatures with varying degrees of success, there are some drawbacks such as harsh reaction conditions, tedious workup, high reaction temperatures, lengthy steps, poor overall yields, and difficulties in the separation of the product from the resulting mixture.[6] Herein, we report a facile and high-yield synthesis of buspirone **3** (*Scheme 1*) under mild conditions from readily available reagents.



Scheme 1

The reaction of cyclopentanone with methyl cyanoacetate was catalyzed by ammonia in CH_3OH at –5°C for 20 h.[7,8] The resulting white crystalline powder was treated with 70% sulfuric acid aqueous solution at 170°C for 1 h. Cyclopentane-1,1-diacetic acid (**1**) was obtained as gray solid in 60% yield after recrystallization from acetone. Treatment of cyclopentane-1,1-diacetic acid **1** with ammonium carbonate at 200°C for 30 min led to 8-azaspiro[4,5]decane-7,9-dione (**2**) in 81% yield.

The conventional methods for alkylation of primary and secondary amines with alkyl halides usually produce a mixture of secondary and tertiary amines.[9] In our research, the *N*-alkylation of *N*-(2-pyrimidyl)piperazine with an excess of 1,4-dibromobutane was conducted in the presence of polyethylene glycol-400 (PEG-400)[10] as phase-transfer catalyst and sodium carbonate as a base under reflux for 7 h. The desired monoalkylation product, *N*-(ω-bromobutyl)pyrimidinylpiperazine (**5**) was obtained in 96% yield.

Organic reactions accelerated by microwave irradiation (MI) have attracted considerable attention in the past decade for the efficient synthesis of a variety of organic compounds.[11] The use of MI for the formation of several carbon-heteroatom and carbon-carbon bond forming reactions has been successfully demonstrated.[12] In our experiments, a mixture of 8-azaspiro[4,5]decane-7,9-dione (**2**) and *N*-(ω-bromobutyl)pyrimidinylpiperazine (**5**) in CH_3CN with tetrabutylammonium bromide (TBAB) and potassium carbonate was heated by MI in a sealed tube, and the product was obtained in high yield (94%). Furthermore, the work-up can be easily performed by pouring the crude product into cool water, and the product precipitated from the solution as crystalline needles. In order to establish that the reaction is not limited to a small scale synthesis, we performed the preparation of buspirone (**3**) on different scales by varying the amount of reactants from 1 to 10 mmol. The only significant change that was introduced in this process was the use of a larger reactor. Neither the time of the process nor the yield of the reaction was affected under these conditions.

In summary, we have developed a simple and practical protocol for the synthesis of (**3**) in 44% overall yield, starting from commercially available cyclopentanone, methyl cyanoacetate, *N*-(2-pyrimidyl)piperazine and 1,4-dibromobutane. The notable advantages of the present method are mild experimental conditions, simple operation, and high overall yield compared to literature procedures.

EXPERIMENTAL SECTION

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Bruker Tensor 27 spectrometer in KBr with absorptions in cm^{-1}. ^1H NMR spectra were measured on a Bruker 400 MHz spectrometer in $CDCl_3$ or DMSO-d_6 with TMS as internal standard. MIs were carried out in a CEM *Discover*™ focused microwave reactor (300 W, 2450 MHz, monomode system) which has an *in situ* magnetic stirrer. Irradiation was monitored by a computer, infrared measurement and continuous feedback temperature control (by PC). The reactions were performed under pressure in pressure-rated reaction tubes with continuous pres-

sure measurement at a constant temperature of 120°C with the power output of 100 W. Small scale reaction was carried out in a CEM 10 mL reaction vessel (5 mL working volume) with septum top. The scale-up reaction was performed in an 80 mL (50 mL working volume) microwave tube. The temperature of the reaction mixture was monitored using a fiber-optic probe inserted into the sapphire immersion well. All the solvents were purchased and used as received.

Cyclopentane-1,1-diacetic Acid (1).- To a well stirred mixture of cyclopentanone (4.2 g, 0.05 mol) and methyl cyanoacetate (6.93 g, 0.07 mol) a solution of NH_3 (2.5 g) in methanol (15 g) was added dropwise at -5°C over a period of 30 min and the reaction mixture was stirred at -5°C for a further 20 h, yielding 10.6 g white crystalline powder, which was stirred with 70% H_2SO_4 aqueous solution at 170°C for 1 h. Upon completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and then poured into water. The resulting gray solid was collected, washed with water and recrystallized from acetone to give white crystals **1** (5.08 g, 60%), mp. 177-180°C, *lit.*[13] mp. 179°C. ^{1}H NMR ($CDCl_3$): δ 1.61 (m, 8H, 4 x CH_2), 2.23 (s, 4H, 2 x CH_2), 11.2 (s, 2H, 2 x OH). IR (KBr) ν (cm^{-1}): 3287, 2990, 1670, 1455.

8-Azaspiro[4,5]decane-7,9-dione (2).- Treatment of **1** (3.72 g, 0.02 mol) with ammonium carbonate (3.96 g, 0.04 mol) in 10 mL DMF at 170°C for 30 min afforded **2**, which was crystallized from ethanol to give white crystals (2.71 g, 81%); mp. 153-154°C, *lit.*[14] mp. 153-154°C; ^{1}H NMR ($CDCl_3$): 1.51 (m, 4H, 2 x CH_2), 1.43 (t, 4H, 2 x CH_2), 2.10 (s, 4H, 2 x CH_2), 10.0 (s, 1H, N-H); IR (KBr) ν (cm^{-1}): 3211, 1734, 1674.

***N*-(ω-Bromobutyl)pyrimidinylpiperazine (5)**.- A stirred suspension of *N*-(2-pyrimidyl)piperazine (8.2 g, 0.05 mol), 1,4-dibromobutane (17.3 g, 0.075 mol), anhydrous K_2CO_3 (8.3 g, 0.05 mol) and PEG-400 (1.0 g) in 70 mL CH_3CN was heated under reflux for *ca.* 7 h. The reaction mixture was filtered and the filtrate was cooled to 0°C overnight. The crystalline powder formed was collected to give pure **5** (14.4 g, 96%), mp. 243-244°C, *lit.*[15] mp. 241-242°C; ^{1}H NMR (DMSO-d_6): 2.12 (s, 4H, 2 x CH_2), 3.54 (t, J = 5.2 Hz, 4H, 2 x CH_2), 3.66 (t, J_1 = 6.8 Hz, J_2 = 6.0 Hz, 4H, 2 x CH_2), 4.06 (s, 4H, 2 x CH_2), 6.79 (t, J = 4.8 Hz, 1H, $C^{5'}$-H), 8.47 (d, J = 4.8 Hz, 2H, $C^{4'}$,$C^{6'}$-H); IR (KBr) ν (cm^{-1}): 3374, 1596, 1131.

8-[4-[4-(2-pyrimidinyl-1-piperazine)butyl]-8-azaspiro[4,5]decane-7,9-dione (3).- A mixture of **2** (0.167 g, 1 mmol), **5** (0.298 g, 1 mmol), anhydrous K_2CO_3 (0.138 g, 1 mmol) and TBAB (2 mg) in CH_3CN (1 mL) was sealed in a 10 mL tube and irradiated at 120°C for 4 min in a monomode CEM Discover focused microwave reactor. After cooling under a stream of compressed air, the reaction mixture was poured into water and the precipitated product was collected. The crude product was recrystallized from ethanol to give pure **3** (0.376 g, 94%), mp. 104-106°C, *lit.*[16] mp. 104-106°C; ^{1}H NMR (DMSO-d_6): δ 1.40 (m, 8H, 4 x CH_2), 1.62 (m, 4H, 2 x CH_2), 2.27 (m, 2H, CH_2), 2.35 (s, 4H, 2 x CH_2), 2.61 (m, 4H, 2 x CH_2), 3.66 (m, 6H, 3 x CH_2), 6.60 (t, J = 4.8 Hz, 1H, $C^{5'}$-H), 8.34 (d, J = 4.8 Hz, 2H, $C^{4'}$,$C^{6'}$-H); IR (KBr) ν (cm^{-1}): 2951, 1723, 1677, 1588, 1484, 1383, 953, 793. The reaction carried out on a 10 mmol scall gave an identical yield under the same conditions.

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