An Efficient Synthesis of Buspirone and its Analogues

Eine leistungsfähige Synthese von Buspiron und Buspiron-ähnlichen Verbindungen

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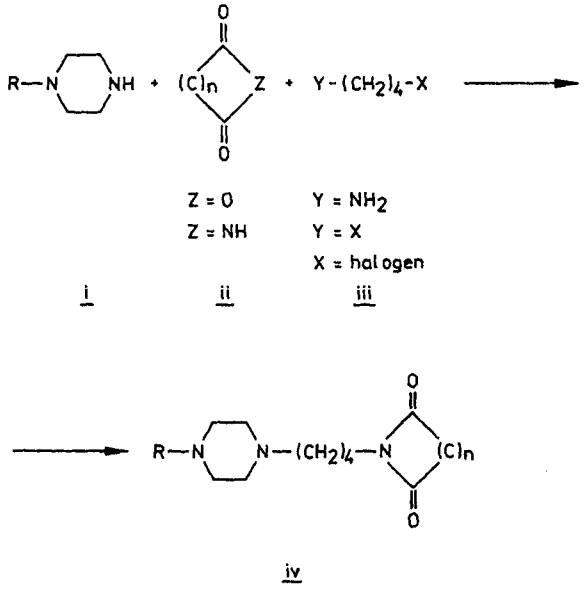
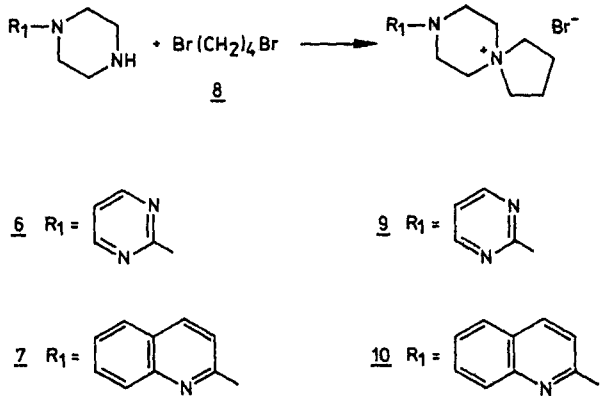
Benzodiazepines at clinically effective doses often produce side effects like drowsiness, ataxia, or sedation[1]. Thus, some interest has recently been put to non-diazepine anxiolytic compounds. That resulted in the development of such compounds like buspirone (**1**), gepirone (**2**), SM-3997 (**3**)[2] or ipsopirone with the possibility of selective activation of the 5-HT_{1A} receptor[3]. This is a new class of anxiolytics with so-called anxioselective properties[1,2]. Several syntheses of the compounds were described[4-8]. In general, all syntheses are based on three fragments: *N*-derivative of piperazine **i**, substituted imide or anhydride **ii**, four-carbon aliphatic chain **iii** (Scheme 1). That type of synthesis is mainly done in two steps: coupling of the four carbon chain **iii** with one of the fragments **i** or **ii** followed by attachment of the second unit **ii** or **i**, respectively. In each of the two steps basic catalysis is used. We tried to employ heterogenous basic catalysis to these reactions using phase-transfer method.



Scheme 1

It appeared that preparation of compounds **1-5** can be done in one pot with high yields. We used anhydrous K_2CO_3 as a solid phase and such catalysts as 18-crown-6, tricaprylylmethylammonium chloride (Aliquat 336), and triethylbenzylammonium bromide (TEBA) (Table 1). The synthesis of buspirone and its analogues was done in one or two step reactions. In two step reactions 1-(2-pyrimidyl)-piperazine (**6**)[9] or 1-(2-quinoline)-piperazine (**7**)[10] were reacted with 1,4-dibromobutane (**8**) to give quaternary ammonium salts **9**[5] or **10**, respectively (Scheme 2). The employed method allowed to obtain relatively good yields (65% to 99%). The best results were achieved with xylene as a solvent. In the case of ethanol only Aliquat 336 gave reasonable results. The yields obtained in these cases were higher than reported[4]. The ammonium salts **9** and **10** were subjected to the reaction with 3,3-tetramethyleneglutarimide (**11**), 3,3-dimethylglutarimide (**12**), 3,6-methylenehexahydrophthalimide (**13**), and compounds **1-5** were prepared (Scheme 3). Compounds **4** and **5** are new analogues of buspirone with potent pharmacological properties.



Scheme 2

Compounds **1-5** were prepared in xylene using anhydrous K_2CO_3 in the presence of 18-crown-6 (these reactions give very poor yields in protic solvents). Therefore, we tried to cumulate the two steps using aromatic hydrocarbons as solvents. In one pot reactions compounds **6** or **7** were treated with 1,4-dibromobutane followed by the addition of the corresponding imide **11**, **12**, or **13** (Table 1). In such a procedure compounds **1-5** were prepared with very high yields. We did not find any striking difference between employed solvents and catalysts. The biggest difference in yield (xylene-TEBA: xylene-Aliquat 336) was 11% and can be assigned to the difference in substrates as well.

Thus, the employment of the phase-transfer catalysis may be used as a general method for the short synthesis of that type of compound. Because compounds **1-3** are already of commercial importance the shortening of their synthesis may be significant.

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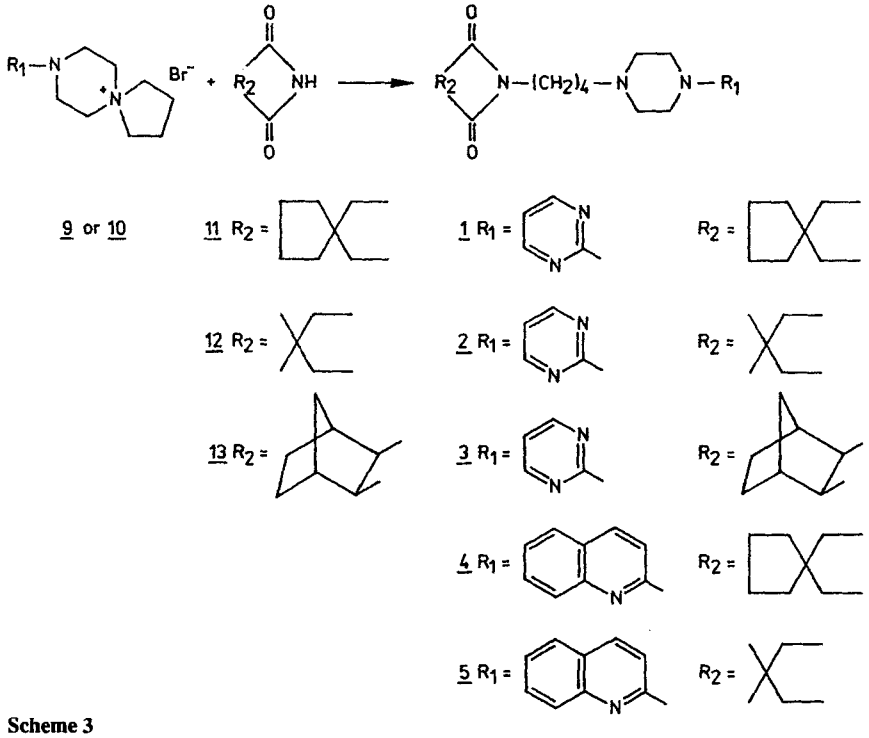

Scheme 3

Table 1: Preparation of buspirone and its analogues

Entry	NHP[1]	Imide	Solvent	Catalyst	Time 1[2] [h]	Time 2[3] [h]	Product	Yield [%][4]
1	6	11	a	Aliquat 336	3	4	1	90
2	6	11	b	TEBA	4	6	1	96
3	6	11	a	TEBA	3	5	1	97
4	6	11	a	18-crown-6	4	3	1	95
5	6	12	b	TEBA	4	5	2	89
6	6	13	b	TEBA	4	5	3	86
7	7	11	a	Aliquat 336	6	6	4	87
8	7	12	a	Aliquat 336	6	6	5	86
9	7	12	a	18-crown-6	4	4	5	90

1. NHP: *N*-heterocyclic piperazine.
2. Time 1: time of reaction with 1,4-dibromobutane.
3. Time 2: time of reaction with imide.
4. HPLC yields.

a: xylene
b: toluene

Experimental Part

M.p.'s: Boetius apparatus (Carl Zeiss, Jena), uncorrected.- IR spectra: UR-20 spectrophotometer.- The ^{1}H-NMR and ^{13}C-NMR spectra: Bruker WP-100SY spectrometer; δ values (ppm), internal standard $(CH_3)_4Si$.- Temp. in °C.

8-(2-Quinolinyl)-8-aza-5-azoniospiro[4,5]decane bromide (**10**)

The mixture of 1-(2-quinolinyl)piperazine (**7**) (3.5 g, 0.016 mole), 1,4-dibromobutane (**8**) (3.67 g, 0.017 mole), finely powdered K_2CO_3 (4.58 g, 0.033 mole) and Aliquat 336 (300 mg) in 80 ml of 95% ethanol was stirred and refluxed for 6 h. The hot reaction mixture was filtered and the filter cake washed with 20 ml of hot 95% ethanol. The combined filtrates were concentrated under reduced pressure to about 1/3 of the initial volume, filtered again and the filtrate evaporated to dryness. The residue was crystallized from 99.8% ethanol to yield 5.04 g (90.5%) of **10**, m.p. 241-243°.- IR (KBr): 3060; 2990; 2860; 1630; 1610; 1570; 1510; 1480; 1440; 1340; 1280 cm^{-1}.- ^{1}H-NMR (D_6-DMSO, 100 MHz): δ (ppm) = 2.38 (m, 4H), 3.08 (m, 4H), 4.15 (m, 8H), 7.28-8.10 (m, 6H).- ^{13}C-NMR (D_6-DMSO): δ (ppm) = 156.30 (s), 146.80 (s), 137.90 (d), 129.68 (d), 127.51 (d), 126.23 (d), 123.19 (s), 122.85 (d), 110.28 (d), 61.49 (t), 57.88 (t), 20.88 (t).

General procedure for the preparation of N-heterocyclic derivatives of piperazine from quaternary ammonium salts.

The mixture of corresponding imide (0.0167 mole), quaternary ammonium salt **9** or **10** (0.0167 mole), K_2CO_3 (5.54 g, 0.040 mole) and 18-crown-6 (10 mg) in 50 ml of xylene was refluxed for 6 h, filtered and the filter cake washed with 20 ml of hot xylene. The combined filtrate was evaporated and the residue was crystallized from ethyl acetate.

Free bases were converted into hydrochlorides by suspending the corresponding base in ethanol (5 ml/g) and treating with an equi-molar amount of ethanolic HCl. After the addition of HCl the suspension dissolved, and after a while started to precipitate. The precipitate was filtered off and washed with ethanol.

8-[4-[4-(2-Quinolinyl)-1-piperazinyl]butyl]-8-azaspirol[4.5]decane-7,9-dione (**4**)

Imide: 3,3-tetramethyleneglutarimide (**11**) (2.79 g).- Quaternary ammonium salt: 8-(2-quinolinyl)-8-aza-5-azoniaspiro[4.5]decane bromide (**10**) (5.81 g). Yield: 6.45 g (89%), m.p. 116-118°.- $C_{26}H_{34}N_4O_2$.- IR (KBr): 2970; 1720; 1680; 1590; 1555; 1500; 1450; 1360; 1260; 1140 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.58 (m, 12 H), 2.51 (m, 6H), 2.56 (s, 4H), 3.75 (m, 6H), 6.91-7.82 (m, 6H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 172.10 (s), 157.41 (s), 147.90 (s), 137.34 (d), 129.44 (d), 127.16 (d), 126.65 (d), 123.06 (s) 122.30 (d), 109.50 (d), 58.23 (t), 53.11 (t), 45.06 (t), 44.91 (t), 39.45 (s), 39.22 (t), 37.55 (t), 26.04 (t), 24.18 (t).

4a-*Hydrochloride*

Yield: 96%, m.p. 220-223°.- $C_{26}H_{34}N_4O_2$·HCl.- IR (KBr): 2940; 2880; 2400; 1720; 1670; 1610; 1510; 1440; 1370; 1230; 1120 cm^{-1}.- ^{1}H-NMR (D_6-DMSO): δ (ppm) = 1.54 (m, 12 H), 2.62 (s, 4H), 3.40 (m, 10 H), 4.00 (d, 2H, J = 12 Hz), 7.26-8.12 (m, 6H), 11.92 (bs, 1H).- ^{13}C-NMR (D_6-DMSO): δ (ppm) = 172.02 (s), 156.29 (s), 147.31 (s), 137.88 (d), 129.68 (d), 127.89 (d), 126.54 (d), 123.00 (s), 122.86 (d), 110.28 (d), 55.00 (t), 50.10 (t), 43.72 (t), 40.00 (s), 38.98 (t), 37.86 (t), 36.92 (t), 24.58 (t), 23.80 (t), 20.42 (t).

4,4-Dimethyl-1-[4-[4-(2-quinolinyl)-1-piperazinyl]butyl]-2,6-piperidinedione (**5**)

Imide: 3,3-dimethylglutarimide (**12**) (2.36 g). Quaternary ammonium salt: 8-(2-quinolinyl)-8-aza-5-azonia-spiro[4.5]decane bromide (**10**) (5.81 g). Yield: 6.14 g (90.1%), m.p. 111-113°.- $C_{24}H_{32}N_4O_2$.- IR (KBr): 2970; 1715; 1675; 1590; 1560; 1500; 1460; 1260; 1130 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.06 (s, 6H), 1.55 (m, 4H), 2.41 (s, 4H), 2.61 (m, 6H), 3.75 (m, 6H), 6.92-7.93 (m, 6H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 171.86 (s), 157.43 (s), 147.93 (s), 137.36 (d), 129.45 (d), 127.17 (d), 126.69 (d), 123.10 (s), 122.32 (d), 109.52 (d), 58.24 (t), 53.13 (t), 46.47 (t), 45.08 (t), 39.33 (t), 29.10 (s), 27.68 (q), 26.04 (t), 24.26 (t).

5a-*Hydrochloride*

Yield: 98%, m.p. 224-227°.- $C_{24}H_{32}N_4O_2$·HCl.- IR (KBr): 2980; 2900; 2450; 1720; 1670; 1610; 1510; 1440; 1250; 1200; 1120 cm^{-1}.- ^{1}H-NMR (D_6-DMSO): δ (ppm) = 0.99 (s, 6H), 1.52 (m, 4H), 3.49 (bm, 14H) 4.64 (bd, 2H), 7.28-8.10 (m, 6H), 11.74 (bs, 1H).- ^{13}C-NMR (D_6-DMSO): δ (ppm) = 171.96 (s), 156.19 (s), 147.52 (s), 137.87 (d), 129.61 (d), 127.44 (d), 126.82 (d), 123.04 (s), 122.75 (d), 110.24 (d), 55.00 (t), 50.35 (t), 45.27 (t), 41.70 (t), 37.83 (t), 28.69 (s), 26.99 (q), 24.73 (t), 20.53 (t).

General procedure for the one step reaction (Table 1)

The mixture of *N*-heterocyclic piperazine (0.013 mole), 1,4-dibromobutane (3.11 g, 0.0144 mole), K_2CO_3 (4.42 g, 0.032 mole), and quaternary ammonium salt (0.0013 mole) or 25 mg of 18-crown-6 in 100 ml of the corresponding solvent was refluxed as indicated. After that time 0.013 mole of an imide was added and the mixture was refluxed again. The hot reaction mixture was filtered and washed with 20 ml of hot solvent. The combined filtrates were evaporated under reduced pressure. The crude product was crystallized from ethyl acetate.

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