

Note

Microwave-induced synthesis of nitrogen-mustard derivatives

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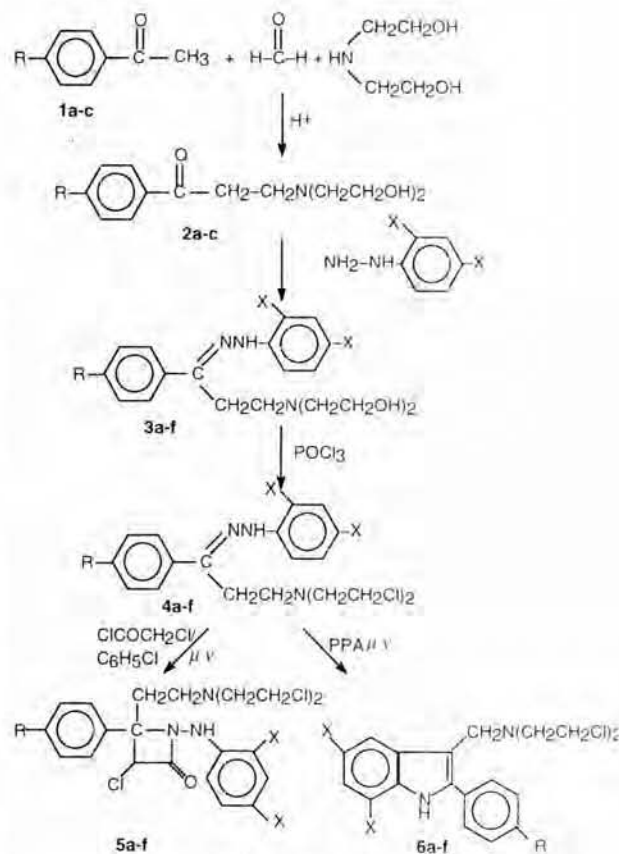
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N,N-Bis (2-hydroxyethyl) amino substituted propiophenones **2a-c** have been prepared using Mannich reaction from substituted acetophenones **1a-c**. **2a-c** on hydrazinolysis yield **3a-f** which on chlorination give nitrogen mustards **4a-f**. **4a-f** on reaction with chloroacetyl chloride, *N*-methylmorpholine and chlorobenzene under microwave activation (MWI) afford β -lactams **5a-f** while cyclisation of **4a-f** with polyphosphoric acid under MWI give the indoles **6a-f**.

Nowadays there is considerable interest in rapid chemical synthesis under microwave irradiation using unaltered domestic microwave ovens^{1,2} owing to substantial reduction in the reaction period. In continuation of our work on microwave assisted synthesis³⁻⁸ we report herein the synthesis of some new nitrogen mustards. Compounds containing β , β -bis(2-chloroethyl) amino grouping otherwise known as nitrogen mustards have frequently displayed selective action against neoplastic cells as compared to normal cells. Nitrogen mustards have been associated with cancer chemotherapy. Keeping in view the potential of microwave irradiation and the biological importance⁹⁻¹² of nitrogen mustard we synthesized some novel nitrogen mustard derivatives incorporating β -lactam ring and indole moiety.

Mannich reaction on substituted acetophenones **1a-c** with formaldehyde and diethanolamine in the presence of HCl gave *N,N*-bis (2-hydroxyethyl) amino substituted propiophenone **2a-c**. IR spectrum of **2a-c** showed absorption bands at 1680 (C=O), 3300 (OH) cm^{-1} . Hydrazinolysis of **2a-c** yielded [*N,N* bis (2-hydroxyethyl) amino substituted propiophenone] arylhydrazones **3a-f** which exhibited absorption bands in the region 3100-3200 cm^{-1} due to NH and at 1650-1665 cm^{-1} for C=N. The disappearance of C=O stretching vibration confirms the formation of product. In ^1H NMR spectrum a broad singlet appeared at δ 9.7 due to NH. Chlorination of **3a-f** with POCl_3 gave [*N,N*-bis (2-chloroethyl) amino substituted propiophenone] aryl hydrazones **4a-f**. In IR



Scheme I

spectrum of **4a-f** the peak in the region of 3300-3320 cm^{-1} due to OH disappeared. **4a-f** when irradiated with chloroacetyl chloride in the presence of *N*-methylmorpholine and chlorobenzene gave corresponding β -lactams **5a-f** which showed a characteristic peak at 1730 cm^{-1} (C=O, β -lactam ring). Cyclisation of **4a-f** with polyphosphoric acid gave 2-aryl-3-[*N,N*-bis(2-chloroethyl) aminomethyl] indoles **6a-c** and 2-aryl-5,7-dinitro-3-*N,N*-bis(2-chloroethyl) aminomethyl indoles **6d-f** (Scheme I). In IR spectrum the absence of peak in the region of 1520-1620 cm^{-1} due to C=N confirmed the formation of product.

Experimental Section

Physical and spectral data for the new compounds are listed in Table I. Mps were taken on electrothermal melting point apparatus and are uncorrected. IR (KBr) were recorded on a model 599 Perkin-Elmer spectrophotometer. ^1H NMR spectra on

a Hitachi R-600 FT spectrophotometer using Me_4Si as internal standard (chemical shifts in δ , ppm) and mass spectra on a JEOL-JMS-DX 303 mass spectrophotometer. The purities of compounds were checked on silica-coated Al plates (merck). Irradiations were carried out in Padmini essentia microwave oven model Brownie (2450 MHz).

Synthesis of *N,N*-bis (2-hydroxyethyl) amino substituted propiophenone 2a-c. A mixture of substituted acetophenones **1a-c** (0.01 mole), formaldehyde (0.013 mole), diethanolamine (0.013 mole), ethanol (20 mL) and a few drops of conc. HCl

was refluxed for 5hr. The excess solvent was distilled under reduced pressure and a product separated as coloured oil. The physical and spectral data of compounds **2a-c** are given in Table I.

General procedure for the synthesis of [*N,N*-bis(2-hydroxyethyl) amino substituted propiophenone] arylhydrazones 3a-f. A mixture of **2a-c** (0.01 mole) and phenylhydrazine or 2,4-dinitrophenylhydrazine (0.011 mole) was refluxed in ethanol (20 mL) for 8-10 hr. The excess solvent was removed *in vacuo* and the solid obtained on concentration was filtered, washed with water and

Table I—Analytical and spectral data of compounds **2a-c**, **3a-f**, **4a-f**, **5a-f**, **6a-f**.

Compd	mp °C	Yield (%)	Found % (Calcd)			¹ H NMR(δ , ppm)
			C	H	N	
2a	Oil	88	65.68	8.20	6.01	3.68 (m, 12 H, CH_2N , CH_2O), 4.74 (br, 2 H, OH), 7.2-7.5 (m, 5 H, Ar-H)
			(65.82)	8.01	5.90)	
2b	Oil	85	57.50	6.68	5.20	3.50 (m, 12 H, CH_2N , CH_2O), 4.90 (brs, 2 H, OH), 7.22-7.6 (m, 4 H, Ar-H)
			(57.45)	6.62	5.15)	
2c	Oil	82	66.98	8.40	5.60	2.13 (s, 3H, Ar- CH_3), 3.70 (m, 12 H, CH_2N , CH_2O), 5.00 (brs, 2 H, OH), 7.21-7.53 (m, 4 H, Ar-H)
			(66.93)	8.36	5.57)	
3a	107-8	79	69.80	7.70	12.88	3.70 (m, 12 H, CH_2N , CH_2O), 5.02 (brs, 2 H, OH), 7.2-7.6 (m, 10 H, Ar-H), 9.60 (brs, 1 H, NH)
			(69.72)	7.64	12.84)	
3b	117-18	80	63.10	6.68	11.69	3.80 (m, 12 H, CH_2N , CH_2O), 5.02 (brs, 2 H, OH), 7.2-7.5 (m, 9 H, Ar-H), 9.70 (brs, 1 H, NH)
			(63.07)	6.63	11.61)	
3c	123-25	83	70.40	7.97	12.39	2.10 (s, 3 H, Ar- CH_3), 3.60 (m, 12 H, CH_2N , CH_2O), 5.00 (brs, 2 H, OH), 7.22-7.6 (m, 9 H, Ar-H), 9.80 (brs, 1 H, NH)
			(70.38)	7.91	12.31)	
3d	160	70	54.70	5.57	16.80	3.68 (m, 12 H, CH_2N , CH_2O), 4.90 (brs, 2 H, OH), 7.2-7.5 (m, 8 H, Ar-H), 9.8 (brs, 1 H, NH)
			(54.67)	5.51	16.78)	
3e	81-82	75	50.53	4.91	15.58	3.70 (m, 12 H, CH_2N , CH_2O), 4.80 (brs, 2 H, OH), 7.3 (m, 7 H, Ar-H), 9.6 (brs, 1 H, NH)
			(50.49)	4.87	15.50)	
3f	90	72	55.70	5.85	16.30	2.12 (s, 3 H, Ar- CH_3), 3.68 (m, 12 H, CH_2N , CH_2O), 5.00 (brs, 2 H, OH), 7.2-7.5 (m, 7 H, Ar-H), 9.70 (brs, 1 H, NH)
			(55.68)	5.80	16.24)	
4a	95	80	66.68	6.35	11.59	3.80 (m, 12 H, CH_2N , CH_2Cl), 7.2-7.6 (m, 10 H, Ar-H), 9.80 (brs, 1 H, NH)
			(66.63)	6.31	11.53)	
4b	97	81	57.28	5.58	10.60	(m, 12 H, CH_2N , CH_2Cl), 7.2-7.6 (m, 9 H, Ar-H), 9.60 (brs, 1 H, NH)
			(57.21)	5.52	10.53)	
4c	88	76	63.53	6.68	11.17	2.10 (s, 3H, Ar- CH_3), 3.60 (m, 12 H, CH_2N , CH_2Cl), 7.2-7.6 (m, 9 H, Ar-H), 9.80 (br, 1 H, NH)
			(63.49)	6.61	11.11)	
4d	92	68	50.29	4.70	15.53	3.68 (m, 12 H, CH_2N , CH_2Cl), 7.2-7.6 (m, 8 H, Ar-H), 9.80 (brs, 1 H, NH)
			(50.22)	4.62	15.41)	
4e	85	65	46.70	4.15	14.40	(m, 12 H, CH_2N , CH_2Cl), 7.3-7.7 (m, 7 H, Ar-H), 9.6 (brs, 1 H, NH)
			(46.67)	4.09	14.32)	
4f	83	62	51.30	4.98	14.99	(s, 3 H, Ar- CH_3), 3.64 (m, 12 H, CH_2N , CH_2Cl), 7.1-7.6 (m, 7 H, Ar-H), 9.70 (brs, 1 H, NH)
			(51.28)	4.91	14.95)	

Contd.

Contd.

Table I—Analytical and spectral data of compounds 2a-c, 3a-f, 4a-f, 5a-f, 6a-f

Compd	mp °C	Yield (%)	Found % (Calcd)			¹ H NMR(δ, ppm)
			C	H	N	
5a	120	65	57.22 (57.20)	5.49 5.44	9.60 9.53	3.70(m, 12 H, CH ₂ N, CH ₂ Cl), 4.30 (s, 1 H, CH ring), 7.2-7.60 (m, 10 H, Ar-H) 9.80 (brs, 1 H, NH)
5b	109	68	53.09 (53.05)	4.89 4.84	8.90 8.84	3.60 (m, 12 H, CH ₂ N, CH ₂ Cl), 4.40 (s, 1H, CH ring), 7.3-7.9 (m, 9 H, Ar-H) 9.60 (brs, 1 H, NH)
5c	115	62	58.12 (58.08)	5.80 5.72	9.30 9.24	2.20 (s, 3 H, Ar-CH ₃), 3.50 (m, 12 H, CH ₂ N, CH ₂ Cl), 7.21-7.53 (m, 9 H, Ar-H), 9.70 (brs, 1 H, NH)
5d	150	66	47.56 (47.50)	4.19 4.14	13.22 13.19	3.70 (m, 12 H, CH ₂ N, CH ₂ Cl), 4.30 (s, 1 H, CH ring) 7.2-7.60 (m, 8 H, Ar-H), 9.80 (brs, 1 H, NH)
5e	180	69	44.68 (44.60)	3.76 3.71	12.41 12.38	3.80 (m, 12 H, CH ₂ N, CH ₂ Cl), 4.45 (s, 1 H, CH ring), 7.3-7.9 (m, 7 H, Ar-H), 9.60 (brs, 1 H, NH)
5f	172	65	48.50 (48.48)	4.46 4.40	12.90 12.85	2.10 (s, 3 H, Ar-CH ₃), 3.68 (m, 12 H, CH ₂ N, CH ₂ Cl) 4.25 (s, 1 H, CH ring) 7.20-7.70 (m, 7 H, Ar-H), 9.70 (brs, 1 H, NH)
6a	108	70	65.75 (65.70)	5.80 5.76	8.09 8.06	3.50 (m, 10 H, CH ₂ N, CH ₂ Cl), 9.57 (br, 1 H, NH), 7.21-7.85 (m, 9 H, Ar-H), 9.70 (brs, 1 H, NH)
6b	165	80	59.80 (59.76)	4.99 4.98	7.36 7.33	3.68 (m, 10 H, CH ₂ N, CH ₂ Cl), 7.20-7.45 (m, 8 H, Ar-H), 9.6 (br, 1 H, NH)
6c	85	76	66.50 (66.48)	6.15 6.09	7.80 7.75	2.10 (s, 3 H, Ar-CH ₃), 3.70 (m, 10 H, CH ₂ N, CH ₂ Cl), 7.4-7.95 (m, 8 H, Ar-H), 9.70(br, 1 H, NH)
6d	95	65	52.38 (52.17)	4.50 4.11	12.98 12.81	3.80 (m, 10 H, CH ₂ N, CH ₂ Cl), 7.45-7.77 (m, 7 H, Ar-H), 9.6 (br, 1 H, NH)
6e	90	68	48.38 (48.35)	3.62 3.60	11.85 11.87	2.14 (s, 3 H, Ar-CH ₃), 3.65 (m, 10 H, CH ₂ N, CH ₂ Cl), 7.1-7.57 (m, 6 H, Ar-H), 9.70(br, 1 H, NH)
6f	112	60	53.28 (53.21)	4.48 4.43	12.45 12.41	2.14 (s, 3 H, Ar-CH ₃), 3.65 (m, 10 H, CH ₂ N, CH ₂ Cl), 7.1-7.75 (m, 6 H, Ar-H), 9.70 (br, 1 H, NH)

recrystallised from ethanol. The physical and spectral IR data of compounds 3a-f are given in Table I.

General procedure for the synthesis of [N,N-bis(2-chloroethyl) amino substituted propiophenone] arylhydrazones 4a-f. To a chilled solution of POCl₃ (0.02 mole) was added 3a-f (0.01 mole) slowly and refluxed on a steam-bath. The progress of reaction was monitored on TLC. On completion of reaction, the reaction mixture was neutralised with NaHCO₃. The solid obtained was filtered, washed with water and recrystallised from petrol-ethyl acetate (1:1). The physical and spectral data of compounds 4a-f are given in Table I.

General procedure for the synthesis of N-(2-arylethyl)-3-chloro-4-aryl-4-[N,N-bis(2-chloroethyl) aminoethyl] azetidin-2-ones 5a-f. A mixture of hydrazones 4a-f (0.01 mole), chloroacetyl chloride (0.015 mole) and N-methylmorpholine (0.03 mole) in chlorobenzene (20 mL) was taken in a conical flask

fitted with a trap. The reaction mixture was irradiated for 6-8 min. A 500 mL beaker containing 200 mL of water was placed in an oven next to the reaction flask to serve as a heat sink. The inorganic salt formed was filtered and the filtrate was concentrated to yield the product. The physical and spectral data of compounds 5a-f are given in Table I.

General procedure for the synthesis of 2-aryl - 3-[N,N-bis(2-chloroethyl) aminomethyl] indoles 6a-c and 2-aryl-5,7- dinitro-3-[N,N-bis(2-chloroethyl)aminomethyl] indoles 6d-f. A mixture of hydrazones 4a-f (0.01 mole) and polyphosphoric acid (10 mL) was taken in an 100mL conical flask and subjected to microwave irradiation for 3-4 min at 2450 MHz. After completion of the reaction, it was neutralised with NaHCO₃. The solid thus separated was filtered off, thoroughly washed with water to give the product. The physical and spectral data of compounds 6a-f are given in Table I.

References

- 1 Caddick S, Tetrahedron, 51, 1995, 10403.
- 2 Galema S A, Chemical Soc Rev, 26, 1997, 233.
- 3 Kidwai M, Kumar P & Kohli S, J Chem Res (S), 1997, 24.
- 4 Kidwai M, Kumar R & Goel Y, Main Gp Met Chem, 20, 1997, 367.
- 5 Kidwai M & Kumar R, Gazz Chem Ital, 127, 1997, 263.
- 6 Kidwai M, Kohli S & Kumar P, J Chem Res (S), 1998, 52.
- 7 Kidwai M, Kohli S & Kumar P, J Chem Res (S), 1998, 586.
- 8 (a) Kidwai M, Kohli S, Saxena R K, Gupta R & Bradoo S, Indian J Chem, 37B, 1998, 963.
- 9 (b) Kidwai M, Kohli S, Goel A K & Dubey M P, Indian J Chem, 37B, 1998, 1063.
- 10 Palmer B D, Wilson W R & Cliffe S, Denny W A, J Med Chem, 35, 1992, 3214.
- 11 Denny W A & Wilson W R, J Med Chem, 29, 1986, 879.
- 12 Rodriguez M, Imbach J-L & Martinez J, J Med Chem, 27, 1984, 1222.
- 13 Palmer B D, Wilson W R, Atwell G J, Schultz D, Xu X Z & Denny W A, J Med Chem, 37, 1994, 2175.