An Efficient Synthesis of Highly Substituted Pyrrole and Bis Pyrrole Derivatives

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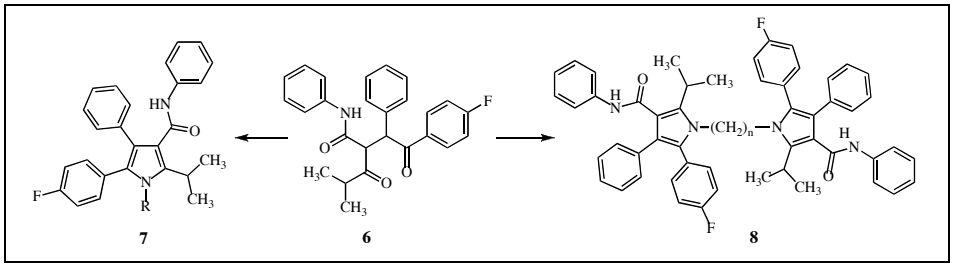

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INTRODUCTION

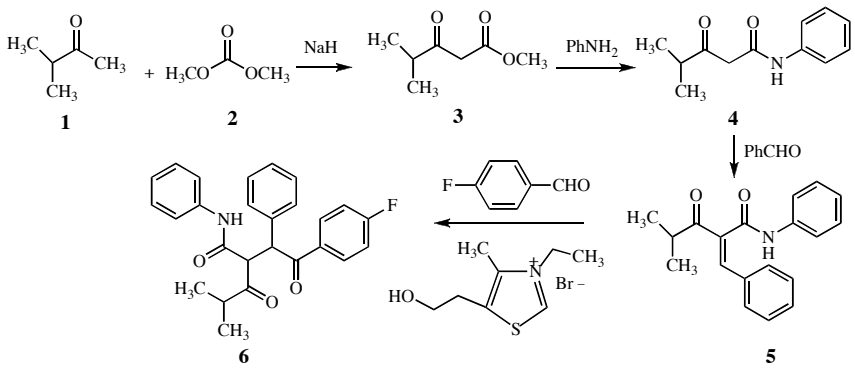
Pyrrole heterocycle is an important structural attribute in many bioactive natural products, [1,2] therapeutic compounds [3] and new organic materials [4]. Consequently, the efficient assembly of this class of molecules is a significant objective in synthetic chemistry. The construction of the pyrrole ring system typically involves condensation of preformed intermediates with amines [5]. More contemporary transition-metal-based strategies include the addition of chromium carbenes to dipolarophiles [6], the copper(I)-catalyzed cycloisomeri- zation of alkynyl imines [7] and rhodium-catalysed reactions, either N-H insertions [8] or the combination of isonitriles and 1,3-diketones [9]. Herein, we report the realization of an efficient assembly of highly substituted pyrroles (**7**) and bis pyrroles (**8**) by utilizing a Paal-Knorr sequence between 1,4-diketo compound (**6**) and amines catalysed by an organic acid.

RESULTS AND DISCUSSION

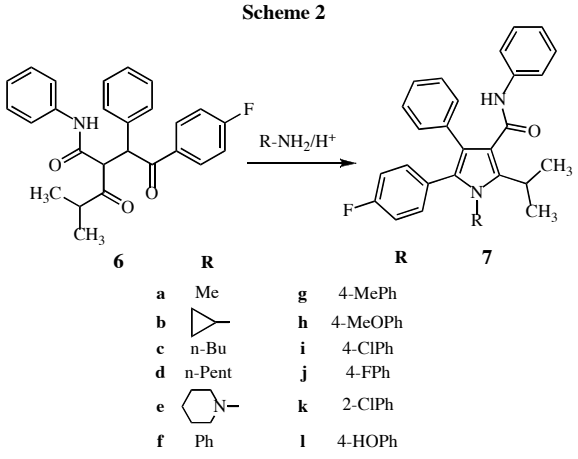
The required key 1,4-diketo intermediate, 2-[2-(4-fluorophenyl)-2-oxo-1-phenylethyl]-4-methyl-3-oxo-*N*-phenylpentanamide (**6**) was accessed by a synthetic sequence starting from commercially available 3-methyl-2-butanone (**1**). Reaction of ketone **1** with carbonic acid dimethyl ester (**2**) in the presence of sodium hydride afforded 4-methyl-3-oxo-pentanoic acid methyl ester (**3**), which on reaction with aniline gave 4-methyl-3-oxo-pentanoic acid phenylamide (**4**). Condensation of **4** with benzaldehyde resulted in 2-benzylidine-4-methyl-3-oxo-pentanoic acid phenylamide (**5**) and subsequent condensation with 4-fluorobenzaldehyde yielded the desired highly substituted key intermediate **6** (Scheme 1). The structural assignment of **6** was in agreement with the reported literature [10].

1,4-Diketo derivative **6** reacted readily with various aliphatic and aromatic amines in cyclohexane/*p*-TSA

Scheme 1



Scheme 2



medium to yield highly substituted pyrroles **7a-l** in 64-92% yields (Scheme 2). For example, the product formed in the reaction of **6** and 4-methoxyaniline was assigned 5-(4-fluorophenyl)-2-isopropyl-1-(4-methoxyphenyl)-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (**7h**) structure, based on its spectral data. In the mass spectrum of **7h**, the highest ion peak was observed at m/z 488(M^+). The IR spectrum of the product **7h** showed the presence of amide NH (3388 cm^{-1}) and C=O (1663 cm^{-1}) functions. The ^{1}H-NMR spectrum of **7h** was characterized by the presence of signals at δ ppm, due to isopropyl group (d, 1.21, 6H; m, 2.8, 1H), methoxy group (s, 3.75, 3H), aromatic protons (m, 6.9-7.55, 18H) and the amide protons (br s, 9.95, deuterium exchangeable). δ 1.05 (d, 6H, 2 x CH_3), 1.82 (m, 1H, CH), 3.74 (s, 2H, N-CH_2), 6.96-7.48 (m, 14H, Ar-H), 9.79 (s, 1H, NH, deuterium exchangeable).

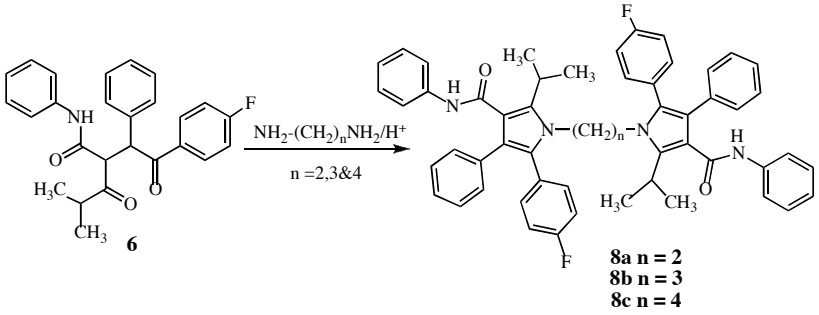
In conclusion we have demonstrated an efficient synthesis of highly substituted pyrrole and bis pyrrole derivatives is provided.

EXPERIMENTAL

The ^{1}H-NMR spectra were recorded in DMSO-d_6 using 400 and 200 MHz, respectively on a Varian Gemini 2000 FT NMR spectrometer. Chemical shifts were reported in δ ppm relative to TMS. FT-IR spectra were recorded in the solid state as KBr dispersion using Perkin-Elmer 1650 FT-IR spectrometer. Mass spectra (70 eV) were recorded on HP-5989 A LC-MS spectrometer. Melting points were determined by using the capillary method on POLMON (Model MP-96) melting point apparatus. Solvents and reagents were used without further purification.

4-Methyl-3-oxo-pentanoic acid methyl ester (3). To a mixture of 60% sodium hydride (10.25 g, 0.256 mole) in tetrahydro furan (150 mL) was added 3-methyl-2-butanone (**1**, 10 g, 0.116 mole) slowly drop wise below 15°C, after 20 minutes maintenance, slowly added dimethyl carbonate (**2**, 15.7 g, 0.174 mole) dropwise below 20°C. Then the temperature was slowly increased to 30°C and maintained for 18-20 hours. The excess sodium hydride was quenched with acetic acid till the pH reaches to 6, followed by added water (300 mL) below 10°C. The resultant reaction mass was extracted with dichloromethane (2 x 100 mL) and the combined organic layers washed with water. The separated organic layer was concentrated under vacuum. The compound **3** was collected at 75-85°C under vacuum (~10 mbar) in 85% yield, bp 147°C-149°C, mass (m/z): 144, ir (KBr, cm^{-1}): 1721(C=O), ^{1}H nmr (DMSO-d_6, δ ppm): 0.9 (d, 3H, CH_3), 1.21 (d, 3H, CH_3), 2.9 (m, 1H, CH), 3.92 (s, 2H, CH_2), 4.6 (s, 3H, -OCH_3).

Scheme 3



Reaction of **6** with different α,ω-diamines afforded the corresponding bis pyrrole derivatives **8a-c** in 80-85 % yield (Scheme 3). For example, the product formed the reaction of **6** with 1,2-diaminoethane in a mixture of toluene and cyclohexane in the presence of acetic acid at reflux temperature was characterized as 1,1'-ethane-1,2-diylbis[5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide] (**8a**) based on IR, ^{1}H-NMR and mass spectral data. In mass spectrum of **8a**, molecular ion peak appeared at 822 (M^+) and IR spectrum showed amide NH (3410 cm^{-1}) and carbonyl (1670 cm^{-1}) absorptions. ^{1}H-NMR Spectrum of **8a** displayed signals at

4-Methyl-3-oxo-pentanoic acid phenylamide (4). To a mixture of **3** (10 g, 0.07 mole) and ethylene diamine (4.55 g, 0.076 mole) in toluene (80 mL) was added aniline (16.3 g, 0.175 mole) slowly drop wise, then the temperature was maintained at reflux for 18-20 hours (*vide* TLC), then the reaction mass was cooled to room temperature and the unreacted aniline washed away with 5% hydrochloric acid (25 mL) followed by water (2 x 100 mL). The organic layer was concentrated under reduced pressure to obtain compound **4** as viscous liquid in 80 % yield, bp 261°C-264°C, mass (m/z):205, ir (KBr, cm^{-1}): 3299 (NH),

Table 1

CHN Analysis Data for Compounds **7a-l** and **8a-c**

Compd No.	Mol. Formula	Calculated			Found		
		C	H	N	C	H	N
7a	$C_{27}H_{25}FN_2O$	78.62	6.11	6.79	78.71	6.02	6.68
7b	$C_{29}H_{27}FN_2O$	79.43	6.21	6.39	79.27	6.35	6.40
7c	$C_{30}H_{31}FN_2O$	79.26	6.87	6.16	79.30	6.92	6.22
7d	$C_{31}H_{33}FN_2O$	79.46	7.10	5.98	79.12	7.16	6.11
7e	$C_{31}H_{32}FN_3O$	77.31	6.71	8.73	77.56	6.72	8.71
7f	$C_{32}H_{27}FN_2O$	80.99	5.73	5.90	80.90	5.75	5.58
7g	$C_{33}H_{29}FN_2O$	81.12	5.98	5.73	81.03	6.12	5.50
7h	$C_{33}H_{29}FN_2O_2$	78.55	5.79	5.55	78.81	5.71	5.66
7i	$C_{32}H_{26}ClFN_2O$	75.51	5.15	5.50	75.30	5.20	5.83
7j	$C_{32}H_{26}F_2N_2O$	78.03	5.32	5.69	78.30	5.40	5.55
7k	$C_{32}H_{26}ClFN_2O$	75.51	5.15	5.50	75.25	5.25	5.30
7l	$C_{32}H_{27}FN_2O_2$	78.35	5.55	5.71	78.02	5.70	5.92
8a	$C_{54}H_{48}F_2N_4O_2$	78.81	5.88	6.81	78.63	6.01	6.97
8b	$C_{55}H_{50}F_2N_4O_2$	78.92	6.02	6.69	78.61	6.22	6.63
8c	$C_{56}H_{52}F_2N_4O_2$	79.03	6.16	6.58	78.30	6.30	6.71

Table 2

Characterization Data of Compounds **7a-7l** and **8a-c**

Compd No.	MR °C	Reaction Time (hrs)	Yield (%)	M^+ (m/z)	IR NH	(cm^{-1}) amide C=O	^{1}H-NMR (δ-ppm)
7a	185-187	12	90[#]	412[d]	3391,	1669	1.35 (d, 6H), 3.42 (s, 3H, N-CH_3), 6.9-7.55 (m, 14H, Ar-H), 9.75 (s, 1H, NH)
7b	189-192	10	92[#]	438[c]	3367,	1644	1.05 (m, 1H), 1.4 (d, 6H), 3.5-3.7 (m, 1H, N-CH), 6.9-7.55 (m, 14H, Ar-H), 9.75 (s, 1H, NH)
7c	148-150	10	89[#]	454[e]	3396,	1657	0.75 (t, 3H), 0.9-1.5 (m, 11H), 3.8 (t, 2H, N-CH_2), 6.9-7.55 (m, 14H, Ar-H), 9.75 (s, 1H, NH)
7d	102-104	8	88[#]	468[a]	3407,	1663	0.78 (t, 3H, CH_3), 0.8-1.6 (m, 13H), 3.75 (t, 2H, N-CH_2), 6.9-7.55 (m, 14H, Ar-H), 9.75 (s, 1H, NH)
7e	99-101	5	81[#]	481[a]	3412,	1664	0.6-1.75 (m, 14H), 3.4 (m, 4H, N-CH_2), 6.9-7.55 (m, 14H, Ar-H), 9.65 (s, 1H, NH)
7f	134-136	9	86[#]	474[b]	3411,	1664	1.22 (d, 6H, 2 x CH_3), 2.8 (m, 1H, CH), 6.75-7.6 (m, 19H, Ar-H), 9.95 (s, 1H, NH)
7g	211-214	16	85[#]	488[a]	3409,	1664	1.22 (d, 6H, 2 x CH_3), 2.3 (s, 3H, CH_3), 2.8 (m, 1H, CH), 6.9-7.6 (m, 18H, Ar-H), 9.95 (s, 1H, NH)
7h	105-106	8	85[#]	504[e]	3388,	1663	1.21 (d, 6H, 2 x CH_3), 2.8 (m, 1H, CH), 3.75 (s, 3H, OCH_3) 6.9-7.55 (m, 18H, Ar-H), 9.95 (s, 1H, NH)
7i	200-203	18	64[@]	508[a]	3406,	1671	1.20 (d, 6H 2 x CH_3), 2.8 (m, 1H, CH), 6.9-7.55 (m, 18H, Ar-H), 9.98 (s, 1H, NH)
7j	189-191	18	66[@]	492[a]	3405,	1667	1.20 (d, 6H, 2 x CH_3), 2.8 (m, 1H, CH), 6.9-7.6 (m, 18H, Ar-H), 9.98 (s, 1H, NH)
7k	210-214	20	71[@]	508[a]	3410,	1670	1.20 (d, 6H, 2 x CH_3), 6.9-7.55 (m, 18H, Ar-H), 9.85 (s, 1H, NH)
7l	232-235	12	83[@]	490[a]	3300(br), 1667		1.21 (d, 6H, 2 x CH_3), 2.85 (m, 1H, CH), 4.35 (s, 1H, OH), 6.75-7.55 (m, 18H, Ar-H), 9.98 (s, 1H, NH)
8a	301-304	10	85	822[f]	3410,	1670	1.05 (d, 6H, 2 x CH_3), 1.82 (m, 1H, CH), 3.74 (s, 2H, N-CH_2), 6.96-7.48 (m, 14H, Ar-H), 9.79 (s, 1H, NH)
8b	312-314	12	83	836[f]	3411,	1672	1.10 (d, 6H, 2 x CH_3), 1.9 (m, 1H, CH), 2.12 (t, 2H,N-CH_2-CH_2) 3.34 (t, 2H, N-CH_2), 6.96-7.58 (m, 14H, Ar-H), 9.75 (s, 1H, NH)
8c	327-331	14	90	850[f]	3407,	1668	1.08 (d, 6H, 2 x CH_3), 1.63 (m, 2H,N-CH_2-CH_2), 2.05 (m, 1H, CH), 3.31 (t, 2H, N-CH_2), 6.96-7.6 (m, 14H, Ar-H), 9.82 (s, 1H, NH)

[a] ^{1}H-NMR Spectra of **7a, 7b, 7c, 7d, 7e, 7f, 7g, 7h, 7i, 7j, 7k** and **7l** were recorded in DMSO-d_6 at 400 MHz except **7k** (200 MHz); [b] ^{13}C-NMR of **7g** (DMSO-d_6):δ 20.6, 21.98, 26.17,38.24, 40.75, 114.5, 114.96, 117.7, 119.4, 120.7, 123, 125.7, 127.7, 128.4, 129, 129.3, 129.5, 132.9, 133.1, 134.5, 134.8, 137.5, 137.9, 139.3, 165.68; [c] Recrystallised from (a) Pet ether (b) Cyclohexane (c) Ethanol: H_2O (1:1) (d) Pet ether: Isopropyl alcohol (1:1) (e) Pet ether: Isopropyl alcohol (8:2) (f) Ethyl acetate: Pet ether (1:1) Isopropyl alcohol (8:2) (f) Ethyl acetate: Pet ether (1:1); # Prepared in method A; @ Prepared in method B.

3045(CH) 1729 (C=O), 1652 (amide C=O), ^{1}H nmr (DMSO-d_6, δ ppm): 0.92 (d, 3H, CH_3), 1.20 (d, 3H, CH_3), 2.85 (m, 1H, CH), 3.95 (s, 2H, CH_2), 6.63-7.00 (m, 5H, Ar-H), 9.8 (s, 1H, NH).

2-Benzylidine-4-methyl-3-oxo-pentanoic acid phenylamide (5). A mixture of **4** (10 g, 0.048 mole), β-alanine (2.2 g, 0.024 mole), benzaldehyde (9.3 g, 0.087 mole) and acetic acid (0.3 g, 0.005 mole) in *n*-hexane (120 mL) were maintained at reflux temperature and water was collected azetropically for 8-12 hours (*vide* TLC). The obtained solid was collected by filtered at 10-15°C and washed with *n*-hexane followed by drying, yielded compound **5** in 90% yield as cream solid, mp 190-193°C, mass (m/z): 293, ir (KBr, cm^{-1}): 3312 (NH), 3049 (CH) 1729 (C=O),

1663 (amide C=O), ^{1}H nmr (DMSO-d_6, δ ppm): 1.01 (d, 3H, CH_3), 1.23 (d, 3H, CH_3), 2.88 (m, 1H, CH) 5.53 (s, 1H, CH), 6.8-7.2 (m, 10H, Ar-H), 10.2 (s, 1H, NH).

2-[2-(4-Fluorophenyl)-2-oxo-1-phenylethyl]-4-methyl-3-oxo-*N*-phenylpentanamide (6). A mixture of **5** (10 g, 0.034 mole), 3-ethyl-5-(2-hydroxyethyl)-4-methyl-3-thiazolium bromide (8.3 g, 0.033 mole), 4-fluoro benzaldehyde (5.6 g, 0.045 mole) and triethyl amine (7.6 g, 0.075 mole) were maintained at 65-70°C for 10-14 hours (*vide* TLC) under neat reaction conditions. Isopropyl alcohol was added (25 mL) and the reaction mixtures was cooled to room temperature and maintained for 3-4 hours. The obtained solid was collected by filtration, washed with isopropyl alcohol (10 mL), and dried to give compound **6** in 84% yield as white solid, mp 206-209°C; ir (cm^{-1}): 3295 (NH), 1721, 1683(C=O), 1652, 1598 (amide C=O). ^{1}H nmr (DMSO-d_6, δ ppm): 0.94 (d, 3H, CH_3), 1.17 (d, 3H, CH_3), 2.91 (m, 1H, CH), 4.88 (d, 1H, CH), 5.43 (d, 1H, CH), 6.98-7.39 (m, 12H, Ar-H), 8.10-8.17(d, 2H, Ar-H), 10.19 (s, 1H, NH); ^{13}C nmr (DMSO-d_6, δ ppm): 17.88, 18.81, 38.92, 51.82, 63.07, 115.71, 119.64, 123.87, 127.47, 128.58, 128.81, 131.70, 132.18, 135.08, 138.10, 164.93,164.97, 196.38, 207.99.

General procedure for the preparation of compounds (7a-7l).

Method A. A mixture of 2-[2-(4-fluorophenyl)-2-oxo-1-phenylethyl]-4-methyl-3-oxo-*N*-phenylpentanamide (**6**, 1.0 g, 0.0024 mole), the appropriate amine (0.0029 mole) and *p*-toluenesulfonic acid (0.2 g, 0.0011 mole) in cyclohexane (20 mL) was maintained at reflux until completion of the reaction (*vide* TLC). The reaction mixture was then cooled to 30 °C, dissolved in ethyl acetate (5 mL) and the resulting solution washed with 10 % sodium bicarbonate solution (2 x 10 mL) followed by water (10 mL). The organic layer was separated and concentrated under vacuum and the resulting residue was triturated with the appropriate solvent (10-15 mL) and recrystallised (Table-2).

Method B. To a solution of 2-[2-(4-fluorophenyl)-2-oxo-1-phenylethyl]-4-methyl-3-oxo-*N*-phenylpentanamide (**6**, 1.0 g, 0.0024 mole), ethanol (5 mL) and acetic acid (5 mL), the appropriate amine (0.0029 mole) was added and the mixture was refluxed on oil-bath till the completion of the reaction (*vide* TLC). The reaction mixture was cooled to 30 °C, dissolved in ethyl acetate (20 mL) and washed with 10% sodium bicarbonate solution (2 x 10 mL) followed by water (10 mL). The organic layer was separated, concentrated under vacuum and the obtained residue was triturated with appropriate solvent and recrystallised (Table-2).

General procedure for the preparation of bis pyrrole derivatives (8a-8c). A mixture of 2-[2-(4-fluorophenyl)-2-oxo-1-phenylethyl]-4-methyl-3-oxo-*N*-phenylpentanamide (**6**, 1.0 g, 0.0024 mole), appropriate diamine (0.006 mole) and acetic acid (3 mL) in toluene and cyclohexane (30 mL, 1:1 mixture) was maintained at reflux for 10-15 hours (*vide* TLC). The reaction mixture was cooled to 30 °C, dissolved in ethyl acetate (20 mL) and washed with 10% sodium bicarbonate solution (2 x 15 mL) followed by water (10 mL). The organic layer was separated and concentrated under vacuum, the resulting solid was recrystallised from ethyl acetate and diethyl ether (1:1).

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