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A novel synthesis and antimicrobial activity of 1-[(Substituted-phenyl) sulfonyl]pyrrolidin-2-ones

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Abstract
Novel cyclization of 4-(substituted-phenylsulfonamido)butanoic acids to their corresponding 1-[(substituted-phenyl)sulfonyl]pyrrolidin-2-ones was successfully achieved by using polyphosphate ester (PPE). The reaction time was considerably reduced with corresponding increase in the yields, when polyphosphate ester (PPE) was used in combination with 4-(N,N-dimethylamino)pyridine (DMAP). All the synthesized compounds were screened for their antimicrobial activity. Minimum Inhibitory Concentration (MIC) values of synthesized compounds were also determined, and were found to be in the range of 0.09–1.0 mg.

Keywords: *1-[(4-Substitutedphenyl)sulfonyl]pyrrolidin-2-ones, polyphosphate ester, dehydrative cyclization, antimicrobial activity*

Introduction

The N-substitutedpyrrolidin-2-ones and the pyrrolidinone moiety in the structures of several bioactive compounds have been reported as anti-HIV, anti-tumor and antifungal agents [1]. They have also been reported for other promising therapeutic applications such as; inhibitors of influenza virus [2], potent and selective potassium channel openers [3], neuroprotective [4] and anti-hypertensive [5] agents. Substituted pyrrolidin-2-ones are also important because of their use as intermediates for the synthesis of γ- amino acids [6] and pyrrolidines [7].

A number of methods have been reported in the literature [1–5,8,9] for the synthesis of substituted pyrrolidin-2-ones. Herein, we report an interesting, cost effective and synthetically useful method for the preparation of N-substitutedpyrrolidin-2-ones (Scheme 1).

The synthesized compounds were screened for their antimicrobial activity (Tables I– III).

Materials and methods

General

Melting points were determined on a Gallenkamp digital melting point apparatus and are uncorrected. IR spectra were recorded in KBr disc on a FT-IR model FTS 3000 MX spectrometer. Elemental analysis was performed on a Carlo Erba 1106 elemental analyzer. ^{1}H NMR (300, 400 and 500 MHz) spectra were recorded on a Bruker NMR spectrophotometer. The chemical shifts of proton signals are in parts per million (ppm) downfield from tetramethylsilane (TMS) as internal standard. EI-MS spectra were recorded on MAT 312 and MAT 311A mass spectrometer. Thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F_{254} aluminum sheets (Merck).

General procedure for the synthesis of 1-[(substituted-phenyl)sulfonyl]pyrrolidin-2-ones ***(3a–g)***

Method A**:** In this method polyphosphate ester (PPE) was used for the dehydrative cyclization of

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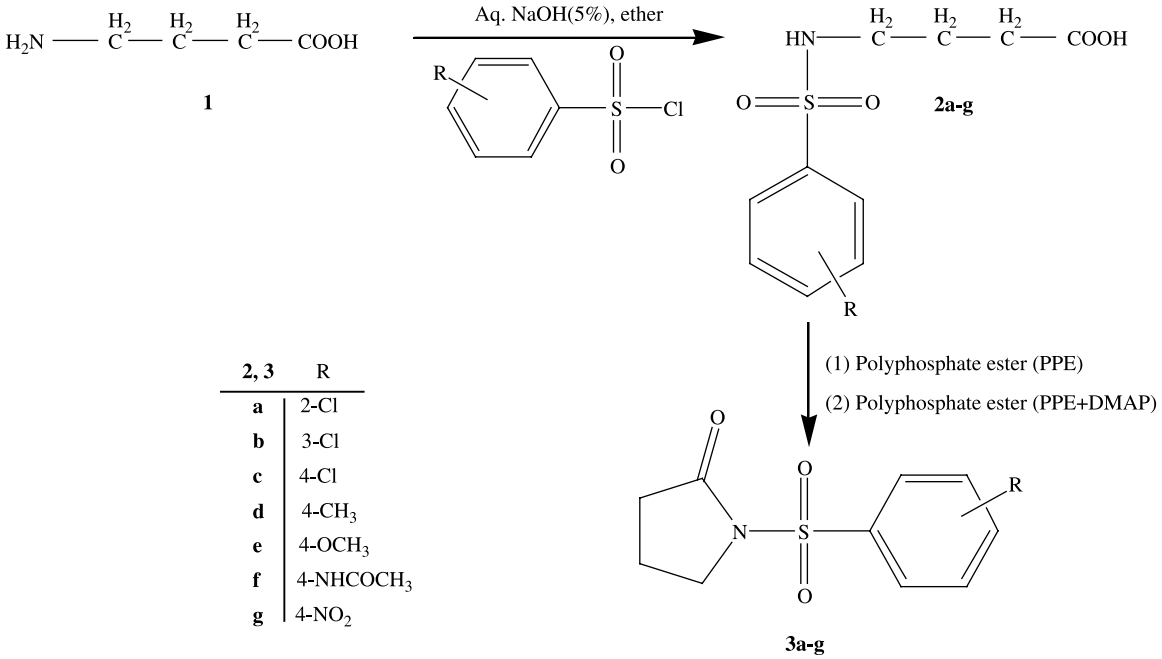

Scheme 1. Synthesis of the 1-[(substituted-phenyl) sulfonyl] pyrrolidin-2-ones

4-(substituted-phenylsulfonamido)butanoic acids **2a–g** to 1-substituted-pyrrolidin-2-ones **3a–g** (Scheme 1). A mixture of 4-(substituted-phenylsulfonamido)butanoic acid **(2)** (1.0 mmol) and polyphosphate ester (2.5 mL) was stirred, under anhydrous conditions, at room temperature for 25–30 h. After completion of the reaction the mixture was a treated with saturated solution of aqueous sodium bicarbonate (25 mL), and extracted with chloroform (3 × 15 mL). The combined extract was washed with brine, water and dried over sodium sulfate (anhydrous). The solvent was distilled off using a rotary evaporator. The oily product was crystallized with absolute ethanol, filtered and recrystallized from chloroform and ethanol (1:5). The compounds **3a–g** were purified by preparative TLC on silica plates, using pet. ether: ethylacetate (4:1) as eluent.

Method B: In this method 4-(4-substituted-phenylsulfonamido)butanoic acid **(2)** (1.0 mmol), polyphosphate ester (PPE)(2.5 mL) and a catalytic amount of DMAP (25 mg) in dry $CHCl_3$ (2 mL), were stirred at room temperature for 15–20 h. The remaining procedure for the synthesis of 1-[(substituted-phenyl)sulfonyl]pyrrolidin-2-ones **(3a–g)**, followed that described in method A. The reaction time was reduced with a corresponding increase in yield, as indicated with each case.

1-[(2-Chlorophenyl)sulfonyl]pyrrolidin-2-one (3a). Reaction time (method A) 27 h, yield 81%; (method B) 16 h, yield = 89%, m.p = 149°–151°C, UV (λ_{max}, CH_3OH, nm): 269, 247. IR (ν_{max}, KBr, cm^{-1}): 3089 (CH(Ar), 1739 (C = O), 1376, 1163

Table I. Antibacterial Activity of the Synthesized Compounds **3a–g**.

Compd. No.	Escherichia coli	Pseudomonas aeruginosa	Bacillus subtillus	Staphylococcus aureus	Micrococcus luteus
3a	17.60 ± 0.76	11.26 ± 0.56	16.15 ± 0.037	–	–
3b	12.10 ± 0.031	10.66 ± 0.22	10.11 ± 0.078	–	–
3c	11.86 ± 0.035	–	–	10.95 ± 0.21	–
3d	11.42 ± 0.24	–	–	–	–
3e	11.27 ± 0.34	–	10.09 ± 0.71	–	–
3f	14.20 ± 0.49	–	–	–	–
3 g	13.35 ± 0.21	–	–	10.85 ± 0.07	–
Chlorampenicol	17.00	19.60	18.80	16.45	17.20
Cefixime (Standard)	30.00	17.78	28.70	36.12	34.11

Zone diameter of growth inhibition (mm) after 24 h, < 10 mm (−), Concentration 1 mg/mL in DMSO.
- ± represents standard deviation
- The data represents the mean values of two replicates
- Inhibition zone diameter including diameter of borer (8 mm).

Table II. Minimum Inhibitory Concentrations (MIC) of the Synthesized Compounds **3a–g** in mg/mL.

Compd. No.	Escherichia coli	Pseudomonas aeruginosa	Bacillus subtillus	Staphylococcus aureus	Micrococcus luteus
3a	0.09	0.2	0.1	–	–
3b	0.4	–	–	–	–
3c	0.5	–	–	–	–
3d	0.6	–	–	0.8	–
3e	0.8	–	1.0	–	–
3f	0.4	–	–	–	–
3 g	0.5	–	–	–	–

(SO_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm): 2.36–2.12 (m, 2H, CH_2), 2.46 (t, $J = 7.0$ Hz, 2H, $COCH_2$), 3.88 (t, $J = 7.0$, 2H, NCH_2), 7.63–7.69 (m, 2H, ArH), 7.74 (d, 1H, ArH, $J = 7.2$ Hz), 7.95 (d, 1H, ArH, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): (19.1, 32.6, 48.5, 129.3, 129.9, 136.3, 145.8, 173.4. EI(MS; *m/z* (rel. int. %): 260 ($M^+ + 1$), 195 (69), 175 (100), 112 (14), 111 (45), 76 (26), 75 (9). HRMS (EI, 80 eV): *m/z* calculated for $C_{10}H_{10}NO_3SCl$: 259.007 Found: 259.009.

1-[(3-Chlorophenyl)sulfonyl]pyrrolidin-2-one (3b). Reaction time (method A) 29 h, yield 79%; (method B) 18 h, yield = 92%, m.p = 141°–142°C, UV (λ_{max}, CH_3OH, nm): 268, 255. IR (ν_{max}, KBr, cm^{-1}): 3069 (CH(Ar), 1736 (C = O), 1375, 1163 (SO_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm): 2.33–2.08 (m, 2H, CH_2), 2.51 (t, $J = 7.0$ Hz, 2H, $COCH_2$), 3.89 (t, $J = 7.0$, 2H, NCH_2), 7.69 (d, 1H, ArH, $J = 6.0$ Hz), 7.79 (bs, 1H, ArH), 7.91 (s, 1H, ArH), 7.93–7.96 (m, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): (18.7, 35.6, 49.5, 129.3, 130.3, 137.1, 145.0, 173.0. EI(MS; *m/z* (rel. int. %): 260 ($M^+ + 1$), 195 (49), 175 (100), 112 (20), 111 (40), 76 (21), 75 (28). HRMS (EI, 80 eV): *m/z* calculated for $C_{10}H_{10}NO_3SCl$: 259.007 Found: 259.003.

1-[(4-Chlorophenyl)sulfonyl]pyrrolidin-2-one (3c). Reaction time (method A) 28 h, yield 78%; (method B) 17 h, yield = 86%, m.p = 153°–155°C, UV (λ_{max}, CH_3OH, nm): 266, 242. IR (ν_{max}, KBr, cm^{-1}): 3055 (CH(Ar), 1735 (C = O), 1375, 1166 (SO_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ(ppm): 2.34–2.02 (m, 2H, CH_2), 2.40 (t, $J = 7.0$ Hz, 2H, $COCH_2$), 3.87 (t, $J = 7.0$, 2H, NCH_2), 7.89 (d, $J = 8.2$ Hz, 2H, ArH), 7.96 (d, $J = 8.2$ Hz, 2H, ArH). ^{13}C NMR (63 MHz, $CDCl_3$): (18.4, 32.4, 47.5, 128.3, 129.9, 135.3, 145.4, 173.6. EI(MS; *m/z* (rel. int. %): 260 ($M^+ + 1$), 195 (62), 175 (100), 112 (15), 111 (39), 76 (16), 75 (29). HRMS (EI, 80 eV): *m/z* calculated for $C_{10}H_{10}NO_3SCl$: 259.007 Found: 259.004.

1-[(4-Methylphenyl)sulfonyl]pyrrolidin-2-one (3d). Reaction time (method A) 27 h, yield 81%; (method B) 17 h, yield 85%; m.p 145°–147°C. UV (λ_{max}, CH_3OH, nm): 261, 244. IR (ν_{max}, KBr, cm^{-1}): 3057 (CH(Ar), 1728 (C = O), 1352, 1166 (SO_2). ^{1}H NMR (500 MHz, Acetone-d_6): δ(ppm): 2.05–2.12 (m, 2H, CH_2), 2.38 (t, $J = 8.0$ Hz, 2H, $COCH_2$), 2.43 (s, 3H, CH_3), 3.90 (t, $J = 7.0$, 2H, NCH_2), 7.42 (d, $J = 8.2$ Hz, 2H, ArH), 7.88 (d, $J = 8.3$ Hz, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): (18.2, 21.7, 32.2, 47.3, 128.0, 129.7, 135.1, 145.2, 173.4. EI(MS; *m/z* (rel. int. %): 241 ($M^+ + 2$), 240 ($M^+ + 1$), 177 (3), 176 (39), 175 (90), 174 (90), 157 (3), 156 (6), 155 (62), 139 (16), 121 (29), 120 (89), 119 (4), 118 (4), 93 (2), 92 (29), 91 (100), 89 (17), 65 (54). Anal. Calcd for $C_{11}H_{13}NO_3S$: (239.2899) C, 55.21; H, 5.48; N, 5.85; S, 13.41. Found: C, 55.54; H, 5.29; N, 5.66; S, 13.70%.

1-[(4-Methoxyphenyl)sulfonyl]pyrrolidin-2-one (3e). Reaction time (method A) 25 h, yield 85%; (method B) 15 h, yield 91%; m.p 151–152°C. UV (λ_{max}, CH_3OH, nm): 291, 247. IR (ν_{max}, KBr, cm^{-1}): 3069

Table III. Antifungal Activity of **3a–d** and **3f** and Inhibition Zones (%).

	Compd. No.					
Name of Fungi	**3a**	**3b**	**3c**	**3d**	**3f**	Standard drug
Trichphyton longifusus	40	50	30	60	0	Miconazole
Candida albicans	0	0	40	0	**90**	Miconazole
Aspergillus flavus	**90**	60	0	0	0	Amphotericin
Microsporum canis	40	0	0	0	0	Miconazole
Fusarium solani	40	0	0	50	40	Miconazole
Candida glabrata	0	0	0	0	0	Miconazole

Conc. of sample 200 μg/mL in DMSO at 27°C, Incubation period 7 days.

(CH(Ar), 1731 (C = O), 1355, 1161 (SO_2). ^{1}H NMR (500 MHz, Acetone-d_6): δ(ppm): 2.00–2.03 (m, 2H, CH_2), 2.37 (t, $\mathcal{J}$ = 7.0 Hz, 2H, CH_2CO), 3.80 (t, $\mathcal{J}$ = 7.0 Hz, 2H, CH_2), 3.86 (s, 3H, OCH_3), 7.26 (d, $\mathcal{J}$ = 8.2 Hz, 2H, ArH), 7.86 (d, $\mathcal{J}$ = 8.2 Hz, 2H, ArH). ^{13}C NMR (63 MHz, $CDCl_3$): δ(ppm): 18.0, 32.6, 47.2, 57.1, 128.0, 129.2, 135.0, 145.1, 173.1. EI(MS; *m/z* (rel. int. %): 256 ($M^+ + 1$), 192 (54), 172 (16), 171 (100), 109 (4), 108 (4), 107 (39), 76 (29), 65 (54). Anal. Calcd for $C_{11}H_{13}NO_4S$: (255.2993) C, 51.75; H, 5.13; N, 5.49; S, 12.56. Found: C, 51.60; H, 4.98; N, 5.68; S, 12.33%.

1-[(4-Acetamidophenyl)sulfonyl]pyrrolidin-2-one (3f). Reaction time (method A) 27 hours, yield = 72%; (method B) 19 hours, yield 77%; m.p 155°–156°C. UV (λ_{m*ax}, CH_3OH, nm): 299, 245. IR (ν_{max}, KBr, cm^{-1}): 3286 (NH), 1725 (C = O), 1678 (C = O), 1362, 1155 (SO_2). ^{1}H NMR (500 MHz, Acetone-d_6): δ(ppm): 2.01–2.03 (m, 2H, CH_2), 2.38 (t, $\mathcal{J}$ = 7.0 Hz, 2H, $COCH_2$), 2.48 (s, 3H, CH_3), 3.83 (t, $\mathcal{J}$ = 6.8, 2H, NCH_2), 7.73 (d, $\mathcal{J}$ = 8.0 Hz, 2H, ArH), 7.86 (d, $\mathcal{J}$ = 8.2 Hz, 2H, ArH). EI(MS; *m/z* (rel. int. %): 284 ($M^+ + 2$), 220 (62), 198 (39), 183 (100), 155 (29), 75 (4), 65 (16). Anal. Calcd for $C_{12}H_{14}N_2O_4S$: (282.315) C, 51.05; H, 5.10; N, 9.92; S, 11.36. Found: C, 51.36; H, 5.37; N, 9.70; S, 11.29.

1-[(4-Nitrophenyl)sulfonyl]pyrrolidin-2-one (3g). Reaction time (method A): 30 h, yield 65%; (method B) 20 h, yield 72%; m.p 161°–163°C. UV (λ_{max}, CH_3OH, nm): 309, 246. IR (ν_{max}, KBr, cm^{-1}): 3066 (CH(Ar), 1739 (C = O), 1375, 1166 (SO_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ(ppm): 2.01–2.04 (m, 2H, CH_2), 2.48 (t, $\mathcal{J}$ = 7.3 Hz, 2H, $COCH_2$), 3.92 (t, $\mathcal{J}$ = 7.2, 2H, NCH_2), 7.88 (d, $\mathcal{J}$ = 8.2 Hz, 2H, ArH), 8.48 (d, $\mathcal{J}$ = 8.0 Hz, 2H, ArH). ^{13}C NMR (63 MHz, $CDCl_3$): (19.1, 32.5, 49.2, 128.8, 129.8, 135.7, 147.2, 176.5. HRMS (EI, 80 eV): *m/z* calculated for $C_{10}H_{10}NO_5S$: 270.2604. Found: 270.2648.

Results and discussion

Chemistry

In the present work, 1-[(substitutedphenyl)sulfonyl]-pyrrolidin-2-ones **3a–g** were prepared from 4-(substitutedphenylsulfonamido)butanoic acids **2a–g** in the presence of polyphosphate ester (PPE). The reaction provided 1-[(substituted-phenyl)sulfonyl]pyrrolidin-2-ones **3a–g** in excellent yield (65–85%) by simple stirring at room temperature (method A).A second method (method B) was also employed for the synthesis of 1-[(substituted-phenyl)sulfonyl]pyrrolidin-2-ones **3a–g** in 72–92% yields. In this method polyphosphate ester (PPE) and 4-(N, N-dimethylamino)pyridine (DMAP) in chloroform (2 mL), were used for the dehydrative cyclization of 4-(Substitutedphenylsulfonamido)butanoic acids **2a–g** to the corresponding 1-[(Substituted-phenyl)sulfonyl]pyrrolidin-2-ones **3a–g**. It is worth noting here that the reaction time was reduced from 30 to 15 hours. Polyphosphate ester (PPE) and 4-(substitutedphenylsulfonamido)butanoic acids **2a–g** were prepared by reported methods [10,11]. The synthesized compounds were characterized by elemental / HRMS, UV, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.

Antimicrobial activity

The synthesized compounds were tested *in vitro* for their antibacterial activity against *Staphylococcus aureus*, *Bacillus subtillus, Escherichia coli, Pseudomonas aeruginosa* and *Micrococcus luteus* bacteria by the agar well diffusion method [12]. DMSO was used as a control solvent and, chloramphenicol and cefixime as standard drugs. After 24 h incubation at 37°C, the zone of inhibition was measured in mm. The results are listed in Table I**.** The results showed that all compounds were active against *E. coli*. It is worth noting here that compound **3a** exhibited significant activity against *E. coli* (17.6 mm) and *B. subtillus* (16.15 mm). The other compounds showed moderate to low activity. The structure-activity relationship (SAR) shows that the presence of the chloro group at the 2-position (ortho) of the phenyl substituent enhanced the antibacterial action of the compounds. The minimum Inhibitory Concentration (MIC) values for **3a–g** were also determined by the agar well diffusion method [12], and the results are shown in Table II. Five selected compounds **3a–d** and **3f** were screened *in vitro* for their antifungal activity against six species using the agar plate technique [13]. The linear growth of the fungus was obtained by measuring the diameter of the fungal colony after seven days. The amount of growth inhibition in each case was calculated as percentage inhibition. The results shown in Table III, indicated that compounds **3a** and **3f** exhibited significant activity (90%) against *Aspergillus flavus and Candida albicans*. respectively. It is worth noting that compound **3a** exhibited significant (maximum) antibacterial and antifungal activities, possibly due to the presence of chloro group at the 2-position (ortho) of the phenyl substituent, in addition to the sulfonamido moiety.

Conclusions

We have developed an efficient, simple and cost effective method for the synthesis of 1-[(substituted-phenyl)sulfonyl]pyrrolidin-2-ones by using polyphosphate ester (PPE). It is worth noting that reaction times have been reduced with a corresponding increase in the yields, when PPE was used in combination with DMAP (method B). To the best of our knowledge from the existing literature, the

reported method for the synthesis of substituted pyrrolidin-2-ones is novel.. The antimicrobial studies showed that compound **3a** exhibited significant (maximum) antibacterial and antifungal activities.

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