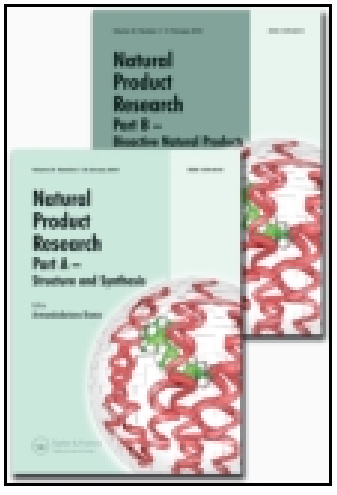

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A convenient synthesis of *p*-substituted 1-arylsulfonyl-pyrrolidin-2-ones

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A convenient and novel method of cyclisation of 4-(4-substituted-phenylsulfonamido)-butanoic acids to their corresponding *p*-substituted 1-arylsulfonyl-pyrrolidin-2-ones was achieved by using polyphosphate ester (PPE). The reaction times were considerably reduced, with an increase in yields, when PPE was used in combination with a catalytic amount of pyridine.

Keywords: *p*-substituted 1-arylsulfonyl-pyrrolidin-2-ones; polyphosphate ester; dehydrative cyclisation

1. Introduction

Pyrrolidinone derivatives, including *N*-substituted-pyrrolidin-2-ones, have been reported to have anti-HIV, antitumour, antifungal (Coutrot, Claudel, Didierjean, & Grison, 2006), antiviral (Brouillette et al., 2003), channel opening (Liang, Hsin, & Cheng, 2002), neuroprotective (Moglioni, Brousse, Larena, Moltrasio, & Ortuno, 2002) and antihypertensive (Kulig, Holzgrabe, & Malawska, 2001) activities. Substituted pyrrolidin-2-ones are of interest because of their use as intermediaries for the synthesis of γ-amino acids (Corey & Zhang, 2000) and pyrrolidines (Xia & Ganem, 2001). Though a number of methods have been reported in the literature (Brouillette et al., 2003; Coutrot et al., 2006; Domingos, Lima, Dias, Costa, 2001 and references cited therein; Kulig et al., 2001; Lesniak & Pasternak, 2005; Liang et al., 2002; Moglioni et al., 2002) for the synthesis of substituted pyrrolidin-2-ones, we want to report herewith a cost effective and convenient method for the preparation of *N*-substituted pyrrolidin-2-ones (Scheme 1).

The *p*-substituted 1-arylsulfonyl-pyrrolidin-2-ones **3a**–**e** were prepared from corresponding 4-(4-substituted-phenylsulfonamido)-butanoic acids **2a**–**e** in the presence of polyphosphate ester (PPE). The reaction provided compounds **3a**–**e** in excellent yields (65–87%) by simple stirring at room temperature (Method A).

For the second method (Method B) to synthesise compounds **3a**–**e**, PPE in the presence of catalytic amounts of dry pyridine (2–3 drops) in chloroform (2 mL) were used for the dehydrative cyclisation. It is worth noting here that the reaction time was reduced from 30 h to 17 h.

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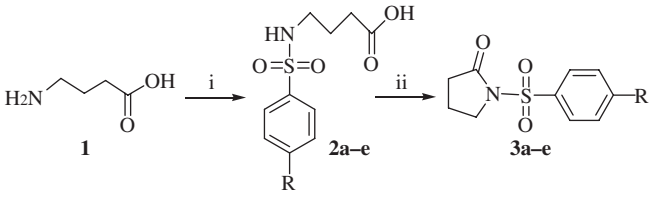

i) $RC_6H_4SO_2Cl$, aq. NaOH (5%), ether; ii) Polyphosphate (PPE) or PPE, pyridine

2a, **3a** R = CH_3, **2b**, **3b** R = Cl, **2c**, **3c** R = OCH_3, **2d**, **3d** R = NO_2, **2e**, **3e** R = $NHCOCH_3$

Scheme 1.

The PPE (F.L. Fieser & M. Fieser, 1967 and references therein) and 4-(4-substituted-phenylsulfonamido)-butanoic acids (Furniss, Hannaford, Rogers, Smith, & Tatchell) **2a**–**e** were prepared by the reported methods. The synthesised compounds were characterised by elemental/HRMS, UV, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.

In conclusion, we present a novel, efficient and cost effective method for the synthesis of *p*-substituted 1-arylsulfonyl-pyrrolidin-2-ones catalysed by PPE. It is worthwhile to note that the reaction time could be reduced when PPE was used in combination with dry pyridine (Method B), with an increase in yields.

2. Experimental

Melting points were determined on a Gallenkamp digital melting point apparatus and are uncorrected. IR spectra were recorded in KBr discs on a FT-IR model FTS 3000 MX spectrometer. Elemental analysis was performed on a Carlo Erba 1106 elemental analyser. ^{1}H NMR (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 an internal standard. EI-MS spectra were recorded on MAT 312 and MAT 311A mass spectrometers. Thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F_{254} aluminum sheets (Merck).

2.1. *General procedure for the synthesis of p-substituted 1-arylsulfonyl-pyrrolidin-2-ones (3a–e)*

Method A: A mixture of 4-(4-substitutedphenylsulfonamido)-butanoic acid (**2**) (1.00 mmol) and PPE (2.5 mL) was stirred under anhydrous conditions at room temperature for 25–30 h. After completion of the reaction, the mixture was treated with a 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 removed using a rotary evaporator. The oily product was crystallised from absolute ethanol, filtered and recrystallised from chloroform and ethanol (1 : 5) to afford compounds **3a**–**e**.

Method B: 4-(4-substitutedphenyl-sulfonamido)-butanoic acid (**2**) (1.00 mmol), PPE (2.5 mL) and catalytic amounts of dry pyridine (2–3 drops) in dry $CHCl_3$ (2 mL) were stirred at room temperature for 16–17 h. The remaining method is the same as Method A.

2.2. *p-Methylphenylsulfonyl-pyrrolidin-2-one (3a)*

Method A: yield 83%; Method B: yield 85%; m.p. = 145–146°C. UV (λ_{max}, CH_3OH, nm): 267, 246; IR (ν_{max}, KBr, cm^{-1}): 3059 (CH–Ar), 1729 (C=O), 1356, 1166 (SO_2); ^1H NMR (500 MHz, C_3H_6O-d_6): δ 2.06–2.13 (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, $J = 8.2$ Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.2, 21.7, 32.2, 47.3, 128.0, 129.7, 135.1, 145.2, 173.4; EI MS (% rel. abundance): 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.

2.3. *p-Chlorophenylsulfonyl-pyrrolidin-2-one (3b)*

Method A: yield 78%; Method B: yield 80%, m.p. = 154–156°C; UV (λ_{max}, CH_3OH, nm): 266, 242. IR (ν_{max}, KBr, cm^{-1}): 3051 (CH–Ar), 1739 (C=O), 1376, 1166 (SO_2); ^1H NMR (250 MHz, $CDCl_3$): δ 2.33–2.02 (m, 2H, CH_2), 2.40 (t, $J = 7.0$ Hz, 2H, $COCH_2$), 3.87 (t, $J = 7.0$, 2H, NCH_2), 7.88 (d, $J = 8.2$ Hz, 2H, ArH), 7.97 (d, $J = 8.2$ Hz, 2H, ArH); ^{13}C NMR (63 MHz, $CDCl_3$): δ 18.4, 32.4, 47.5, 128.4, 129.9, 135.2, 145.4, 173.5; EI MS (% rel. abundance): 260 (M^++1), 195 (62), 175 (100), 112 (15), 111 (39), 76 (16), 75 (29); HRMS: Calcd for $C_{10}H_{10}NO_3SCl$: 259.007; Found: 259.005.

2.4. *p-Methoxyphenylsulfonyl-pyrrolidin-2-one (3c)*

Method A: yield 85%; Method B: yield 87%; m.p. = 151–152°C; UV (λ_{max}, CH_3OH, nm): 291, 249; IR (ν_{max}, KBr, cm^{-1}): 3079 (CH–Ar), 1733 (C=O), 1355, 1161 (SO_2); ^1H NMR (500 MHz, acetone-d_6): δ 2.00–2.03 (m, 2H, CH_2), 2.37 (t, $J = 7.0$ Hz, 2H, CH_2CO), 3.80 (t, $J = 7.0$ Hz, 2H, CH_2), 3.86 (s, 3H, OCH_3), 7.26 (d, $J = 8.2$ Hz, 2H, ArH), 7.86 (d, $J = 8.2$ Hz, 2H, ArH); ^{13}C NMR (63 MHz, $CDCl_3$): δ 18.0, 32.6, 47.2, 57.1, 128.0, 129.2, 135.0, 145.1, 173.1. EI MS (% rel. abundance): 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, 51.61; H, 4.97; N, 5.67; S, 12.35.

2.5. *p-Nitrophenylsulfonyl-pyrrolidin-2-one (3d)*

Method A: yield 65%; Method B: yield 66%; m.p. = 162–163°C; UV (λ_{max}, CH_3OH, nm): 311, 249; IR (ν_{max}, KBr, cm^{-1}): 3068 (CH–Ar), 1739 (C=O), 1375, 1166 (SO_2); ^1H NMR (250 MHz, $CDCl_3$): δ 2.01–2.04 (m, 2H, CH_2), 2.48 (t, $J = 7.3$ Hz, 2H, $COCH_2$), 3.94 (t, $J = 7.2$, 2H, NCH_2), 7.87 (d, $J = 8.2$ Hz, 2H, ArH), 8.46 (d, $J = 8.0$ Hz, 2H, ArH); ^{13}C NMR (63 MHz, $CDCl_3$): δ 19.1, 32.5, 49.2, 128.8, 129.8, 135.7, 147.2, 176.5; HRMS Calcd for $C_{10}H_{10}NO_5S$: 270.2604; Found: 270.2646.

2.6. *p-Acetamidophenylsulfonyl-pyrrolidin-2-one (3e)*

Method A: yield 72%; Method B: yield 78%; m.p. = 153–155°C. UV (λ_{max}, CH_3OH, nm): 299, 245; IR (ν_{max}, KBr, cm^{-1}): 3286 (NH), 1725 (C=O), 1679 (C=O), 1366, 1155 (SO_2); ^1H NMR (500 MHz, acetone-d_6): δ 2.01–2.03 (m, 2H, CH_2), 2.38 (t, $J = 7.0$ Hz, 2H,

$COCH_2$), 2.46 (s, 3H, CH_3), 3.85 (t, $J = 6.8$, 2H, NCH_2), 7.73 (d, $J = 8.0$ Hz, 2H, ArH), 7.88 (d, $J = 8.2$ Hz, 2H, ArH); EI MS; *m/z* (% rel. abundance): 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, 51.26; H, 5.34; N, 9.78; S, 11.39.

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