The synthesis of novel pyrrolizidines under classical, ionic liquid and solvent-free microwave-assisted conditions

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Novel pyrrolizidines (**1**) were synthesised from 1, 3-dipolar cycloaddition of azomethine ylides and dipolarophiles (**4**). The one-pot three-component reactions were highly diastereoselective and regioselective and were carried out in classical, room temperature ionic liquid and solvent-free microwave-assisted conditions. All methods gave the products in high yields, and their structures were determined by ^{1}H and ^{13}C NMR spectral data and X-ray diffraction.

Keywords: pyrrolizidine, regioselectivity, diastereoselectivity, ionic liquid, microwave-assisted conditions

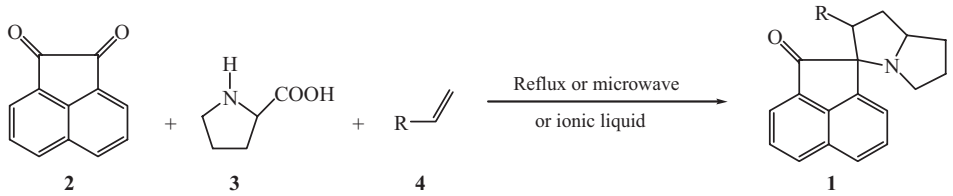
The 1,3-dipolar cycloaddition of azomethine ylides and olefins produces a variety of five-membered heterocycles such as pyrrolizidines. Because of their structural and stereochemical complexity as well as their diverse and potent biological activities, pyrrolizidines are very attractive synthetic targets. These compounds are also present in a wide variety of natural products.[1-7] A synthetic route for the preparation of a novel class of spiro-heterocycles[8,9] such as 3'-substituted pyrrolizidine-2'-spiro-2-acenaphthene-1-ones **1** was developed using environmentally friendly ionic liquids (IL) in order to increase reaction rates and product yields. Reactions in ionic liquids have different thermodynamic and kinetic behaviour and higher selectivity and or conversion have been demonstrated.[10-14] These useful materials not only dissolve many organic and inorganic substances, but they are readily recycled. Room temperature ionic liquids, especially those based on the 1-*n*-alkyl-3-methlylimidazolium cation, have shown great promise as an attractive alternative to conventional solvents.[15-17] Solvent-free microwave-assisted[18,19] conditions have been used extensively for the rapid and efficient synthesis of a variety of heterocyclic compounds. In general, products **1** were obtained by stereoselective one-pot three-component cyclocondensation of acenaphthenequinone **2,** proline **3,** and dipolarophiles **4** in under classical conditions by heating under reflux in acetonitrile, solvent free microwave-assisted and ionic liquids conditions (Scheme 1). Reaction times vary for each condition. The yields of the products and reaction conditions are summarised in Table 1.

Results and discussion

1,3-Dipolar cycloaddition of dipolarophiles **4** with non-stabilised azomethine ylides, which were generated by the decarboxylative condensation of acenaphthenequinone **2** with proline **(3)**, produced novel pyrrolizidines **1** in high yields under all three classical, ionic liquid and microwave irradiation, conditions (comparative results are given in Table 1).

The one-pot three-component reactions were first performed by refluxing an acetonitrile solution of reactants **2**, **3**, and the various dipolarophiles **4** (Scheme 1). All the addition reactions were highly diastereoselective and regioselective since they produced single products (**1**) as shown by TLC and GC-mass analysis.

The cycloaddition reactions were then carried out in solvent-free microwave-assisted conditions. As seen in Table 1, the yields at the single products remained high and comparable to



2 **3** **4** **1**

Scheme 1

Table 1 Synthesis of pyrrolizidines **1**

Entry	Product **1**	Classical heating[a]		Microwave[b]		Ionic liquid[c]	
	R	Time/min	Yield/%	Time/min	Yield/%	Time/min	Yield/%
a	–COOMe	90	91	3	95	10	89,91,86, 90[d]
b	–COOEt	120	85	3	85	5	92
c	–COOBu	150	90	3	92	15	85
d	–COO^{t}Bu	180	88	3	89	15	89
e	–Ph	300	78	5	88	40	85
f	–CN	90	80	5	85	15	87

[a]The reactions were carried out in boiling acetonitril.
[b]The reactions were carried out in methanol.
[c]The reactions were carried out in [bmim]BF_4 at 50°C.
[d][bmim]BF_4 was used for 4 runs.

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those obtained under standard heating condition but reaction times were dramatically reduced from 1.5–6.0 hours to 3–5 minutes.

Finally, a one-pot three-component cyclocondensation of acenaphthene-quinone **2,** proline **3**, and dipolarophiles **4** was carried out in small amounts of 1-butyl-3-methylimidazolium salts ([bmim]X), (X = Br, PF_6, BF_4). Interestingly the best results were obtained in [bmim]BF_4 as an IL so the reactions were run in this IL and the excellent results were summarised in Table 1. It is worthy to note that in [bmim]BF_4 the products were obtained without any impurity and so the work-up procedure was simple without using any chromatographic method. Reusability of [bmim]BF_4 was the other advantage of using these ILs.

To check the reusability of IL a model reaction of acenaphthenequinone, proline and methyl acrylate in [bmim]BF_4 was described. Reaction was run at 50°C and after completion of the reaction the mixture was washed with water. Water was evaporated and the recycled IL was washed with diethylether for further purity and reused for further reaction. As could be seen in Table 1 its activity did not show any significant decrease even after four runs.

Single products were obtained with all above methods as shown by TLC and GC–MS analysis. It is worth noting that the products **1** possess three stereogenic centres; therefore, four different diastereomers could have been produced from the cycloaddition reaction.

In order to corroborate the mechanistic hypothesis outlined in Scheme 1, optically active (d and l isomers) were used. In all cases, the same optically inactive product was isolated as a single isomer. This clearly confirmed formation of azomethine ylide after decarboxylation and concomitant loss of the stereocentres.

Finally products were then purified by column chromatography or by recrystallisation in appropriate solvents, and their structural assignments were confirmed by proton NMR spectra. In order to unequivocally determine the configuration of the stereocentres, X-ray one of the products (**1e**) was undertaken and is shown in Fig. 1.

Some selected geometrical parameters of the molecule **1e** are given in caption of Fig. 1. As can be deduced from Fig. 1, three rings of this molecule (pyrrolizidine, acenaphthenequinone and benzene rings) are almost orthogonal to each other.

Table 2 Crystal data and structure refinement for compound **1e**

CCDC NO.	604739
Empirical formula	C24 H20 N O
Formula weight	338.41
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	*a* = 8.9720(18) A alpha = 90 deg. *b* = 10.683(2) A beta = 90 deg. *c* = 18.325(4) A gamma = 90 deg.
Volume	1756.4(6) A^3
Z, Calculated density	4, 1.280 Mg/m^3
Absorption coefficient	0.078 mm^{-1}
F (000)	716
Crystal size	0.11 × 0.08 × 0.06 mm
Theta range for data collection	2.21 to 26.49 deg.
Limiting indices	–11< = *h*< = 11, –12< = *k*< = 12, –22< = *l*< = 23
Reflections collected/unique	13312/3557 [R(int) = 0.2129]
Completeness to theta = 26.49	97.5%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3557/0/235
Goodness-of-fit on F^2	0.797
Final R indices [*I*>2 sigma(I)]	R1 = 0.0750, wR2 = 0.0675
R indices (all data)	R1 = 0.2046, wR2 = 0.0938
Absolute structure parameter	0(5)
Largest diff. peak and hole	0.172 and -0.158 e A^{-3}

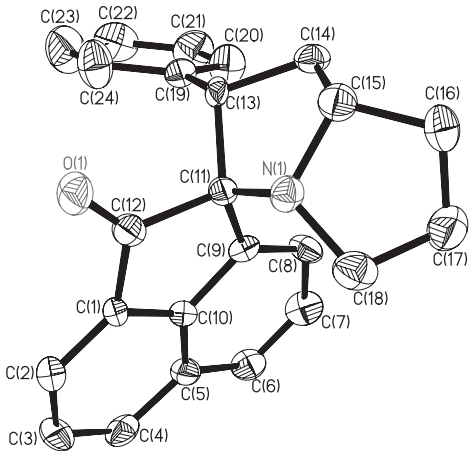

Fig. 1 Crystal structure and atom numbering of **1e**. The displacement ellipsoids are drawn at the 30% probability level. Some representative bond lengths and bond angles are: C(14)–C(15) 1.516(8); C(11)–C(13) 1.543(7); N(1)–C(18) 1.462(7); C(14)–C(13)–C(11) 101.7(4); C(18)–N(1)–C(11) 120.4(4); N(1)–C(11) C(13) 103.8(4); C15 C10 C11 C12 78.2(2); C15 C10 C11 C12 89.3(4).

The data also clearly show regiochemistry of this molecule supporting the spectroscopic data, especially the ^1H NMR.

Conclusion

We have synthesised a class of novel substituted pyrrolizidines **1** under all three classical, room temperature ILs and solvent-free irradiation-assisted conditions. In general, the latter conditions were advantageous. The reactions also proceeded in shorter time when compared to classical condition. However in ILs however, special instrumentation is required. In the presence of small amounts of environmentally friendly 1-butyl-3-methylimidazolium salts ([bmim]X), (X = Br, PF_6, BF_4), the reaction workup was simple and the ionic liquid can be easily separated from the product and reused. All reactions proceeded in a highly diastereo and regioselective manner, affording one product as a single stereoisomer, as evidenced by TLC and GC-MS analysis. The structural assignments of the products were determined by NMR spectra, analytical data, and X-ray crystallographic analysis.

Experimental

Melting points were measured on a Mettler FP5 and are uncorrected. Mass spectra were recorded on a Shimadzu QP 1100 Ex mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were obtained with Shimadzu IR-470 spectrometer (KBr film). ^1H NMR, ^{13}C NMR spectra were measured with a Bruker 500 DRX AVANCE instrument at 500 and 125 MHz respectively. Microwave irradiation was carried out in a National oven, Model 5250 at 2450 MHz. Starting materials were commercally available and were used without further purification.

X-ray crystallography

Colourless crystals of compound **1e** were obtained by slow evaporation from *n*-hexane: ethanol (1 : 4). The room temperature diffraction measurements were carried out on a yellow 0.11 × 0.08 × 0.06 mm^3 crystal on a STOE IPDS II two-circle diffractometer. The ORTEP view of compound with atomic numbering is shown in Fig. 1. The crystallographic data for the compound **1e** is listed in Table 2.

The structure was solved by using SHELXS. The structure refinement and data reduction was carried out with SHELXL of the SHELXTL suite of programs [20]. The non-hydrogen atoms were refined anisotropically and all the hydrogen atoms were located from subsequent difference Fourier maps. The structure was refined to a final R value of 0.0750 (for I > 2σ(I)) and *w*R2 value of 0.0938 (for all data).

General procedure

(1) Classical condition: A stirred mixture of acenaphthenequinone, (10 mmol), proline (l0 mmol) and dipolarophile (15 mmol) in acetonitrile (30 ml) were heated under reflux for 2–4 h. The solvent was then evaporated under reduced pressure, and the resultant residue was either purified by column chromatography eluting with hexane/ethyl acetate or recrystallisation from ether–petroleum ether (1 : 4). The yields of the products are shown in Table 1, and spectral data of the products are given below.

(2) Microwave-assisted condition: A mixture of acenaphthenequinone (10 mmol), proline (l0 mmol), dipolarophile (15 mmol) were placed in a beaker (covered with a watch glass) and was irradiated at 600W at 90°C for 3–5 min in a domestic microwave oven. After the mixture was cooled, the residue was either purified by column chromatography eluting with hexane/ethyl acetate (3/1) or recrystallisation from ether–petroleum ether (1 : 4). The yields of the products are shown in Table 1, and spectral data of the products are given below.

(3) Ionic liquid: Acenaphthenequinone (1 mmol), proline (l mmol), dipolarophile (1.5 mmol) and the IL (0.3 g) were placed in a test tube and heated at 50°C for the appropriate time (Table 1). After completion of the reaction was determined by TLC analysis, the reaction mixture was cooled to room temperature followed by addition of water. The precipitated residue was filtered and for further purification was recrystallised from ether : petroleum ether (1 : 4). The yields of the products are given in Table 1, and spectral data are given below.

1a: Yellow crystals; m.p. = 144–148°C; IR (KBr): 560, 793, 832, 1011, 1120, 1193, 1427, 1450, 1485, 1606, 1734 (CO), 2964, 3042 $cm^{-1;}$ ^1H NMR (500 MHz, $CDCl_3$) δ: 1.57 (m, 1H), 1.84 (m, 2H), 2.06 (m, 1H), 2.29 (m, 2H), 2.46 (m, 2H), 2.73 (S, 3H), 3.94 (dd, 1H, *J* = 6.67 Hz, *J* = 12.7 Hz), 4.08 (m, 1H), 7.41 (d, 1H, *J* = 6.9 Hz), 7.58 (t, 1H, *J* = 7.6 Hz), 7.69 (t, 1H, *J* = 7.5 Hz), 7.83 (d, 1H, *J* = 8.3 Hz), 7.96 (d, 1H, *J* = 6.9 Hz), 8.06 (d, 1H, *J* = 8.1 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 28.62, 32.69, 34.02, 47.41, 50.82, 56.01, 65.30, 76.54 (spiro carbon), 121.55–142.0 (10 signals arom), 171.02 (CO), 206.36 (CO); MS (*m/z*,%) 321 (M^+, 75), 292 (M–CO, 25), 262 (M–CO–OMe, 100), 235 (M–CO–Ome–CO, 100). (Found: C, 75.1; H, 5.8; N, 4.4. $C_{20}H_{19}NO_3$ requires C, 74.75; H, 5.96; N, 4.36).

1b: Yellow crystals; m.p. = 93–95°C; IR (KBr): 781, 1011, 1077, 1166, 1190, 1256, 1369, 1485, 1598, 1618, 1727 (CO), 2859, 2894, 2957, 3046 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: –0.11 (t, 3H, *J* = 10 Hz), 1.52 (m,1H), 1.77 (m, 2H), 2.00 (m, 1H), 2.22 (m, 2H), 2.40 (m, 2H), 3.21 (m, 2H), 3.87 (dd, 1H, *J* = 7 Hz, *J* = 11.52 Hz), 4.12 (m, 1H), 7.36 (d, 1H, *J* = 6.8 Hz), 7.52 (t, 1H, *J* = 7.6 Hz), 7.64 (t, 1H, *J* = 7.5 Hz), 7.77 (d, 1H, *J* = 8.2 Hz), 7.91 (d, 1H, *J* = 6.9 Hz), 8.01 (d, 1H, *J* = 8.1 Hz); ^{13}C NMR (125.7 MHz, DMSO-d6) δ: 10.84, 27.05, 31.15, 32.19, 45.67, 54.30, 58.1, 63.6, 74.79 (spiro carbon), 119.8–140.5 (10 signal arom), 168.7 (CO), 205.1 (CO); MS (*m/z*,%) 335 (M^+, 50), 307 (M–CO, 25), 278 (M–$COCH_2CH_3$, 25), 262 (M–$COOCH_2CH_3$, 100), 235 (M–$COOCH_2CH_3$ – CO, 100). (Found: C, 75.3; H, 6.2; N, 4.3. $C_{21}H_{21}NO_3$ requires C, 75.20; H, 6.31; N, 4.18).

1c: Yellow crystals; m.p. 95°C, IR (KBr): 789, 1166, 1193, 1260, 1345, 1485, 1590, 1723 (CO), 2330, 2357, 2848, 2949 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.37 (m, 7H), 1.58 (m, 1H), 1.83 (m, 2H), 2.07 (m, 1H), 2.29 (m, 2H), 2.5 (m, 2H), 3.17 (m, 1H), 3.3 (m, 1H), 3.96 (dd, 1H, *J* = 6.7 Hz, *J* = 12.7 Hz), 4.1 (m, 1H), 7.43 (d, 1H, *J* = 6.5 Hz), 7.6 (t, 1H, *J* = 7.75 Hz), 7.72 (t, 1H, *J* = 7.5 Hz), 7.85 (d, 1H, *J* = 8.5 Hz), 7.99 (d, 1H, *J* = 7 Hz), 8.09 (d, 1H, *J* = 8.5 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 14.08, 18.35, 28.57, 29.49, 31.54, 32.72, 34.11, 47.46, 55.76, 63.94, 65.32, 76.32, (spiro carbon) 121.68-142.28 (10 signals arom) 170.66 (CO), 206.2 (CO); MS (*m/z*,%), 363 (M^+, 100) 307 (M–CO, 25), 262 (M–CO–C_4H_9, 100), 235 (M–CO–C_4H_9 –CO–O, 100). (Found: C, 75.9; H, 7.1; N, 3.7. $C_{23}H_{25}NO_3$ requires C, 76.01; H, 6.93; N, 3.85).

1d: Yellow crystals; m.p. = 175–177°C; IR (KBr): 481, 532, 781, 832, 979, 995, 1081, 1120, 1205, 1252, 1283, 1365, 1427, 1462, 1598, 1614, 1723 (CO), 2330, 2357, 2844, 2902, 2941, 3042 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.4 (S, 9H), 1.55 (m, 1H), 1.83 (m, 2H), 2.01–2.07 (m, 1H), 2.24 (m, 2H), 2.46 (m, 2H), 3.87 (dd, 1H, *J* = 6.6 Hz, *J* = 12.96 Hz), 4.08 (m, 1H), 7.42 (d, 1H, *J* = 6.9 Hz), 7.59 (t, 1H, *J* = 7.6 Hz), 7.71 (t, 1H, *J* = 7.6 Hz), 7.85 (d, 1H, *J* = 8.3 Hz), 7.97 (d, 1H, *J* = 7 Hz), 8.1 (d, 1H, *J* = 8.2 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ: 26.81, 28.8, 33.02, 34.00, 47.48, 56.78, 65.35, 76.42 (spiro carbon), 80.56, 121.7–136.8 (10 signals arom), 169.7 (CO), 207.1 (CO); MS (*m/z*,%) 363 (M^+, 25), 307 (M–C_4H_9, 75), 278 (M–C_4H_9 . CO, 25), 262(M–C_4H_9–COO, 75), 235 (M–$COOC_4H_9$–CO, 100). (Found: C, 76.1; H, 7.01; N, 3.9. $C_{23}H_{25}NO_3$ requires C, 76.01; H, 6.93; N, 3.85).

1e: Yellow crystals; m.p. = 197–199°C; IR (KBr): 524, 699, 762, 1116, 1209, 1248, 1337, 1361, 1450, 1403, 1594, 1618, 1707, 2361, 2840, 2890, 2949, 3027, 3054 cm^{-1}; ^1H NMR (500 MHz, CDCl3) δ: 1.59 (m, 1H), 1.94 (m, 2H), 2.14 (m, 1H), 2.41 (m, 2H), 2.55 (m, 2H), 4.25 (m, 2H), 6.71 (m, 5H), 7.39–7.53 (m, 3H), 7.6 (d, 1H, *J* = 13.6 Hz), 7.81 (d, 1H, *J* = 6.4 Hz), 7.83 (1H, d, *J* = 8.1 Hz); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ: 31.47, 35.4, 38.47, 49.55, 60.09, 67.27, 82.89 (spiro carbon), 123.11–144.01 (14 signal arom), 211.08 (CO); MS (*m/z*,%), 339 (M^+, 100), 235 (M–C_6H_5–CO, 100). (Found: C, 84.1; H, 6.3; N, 4.0. $C_{24}H_{21}NO$ requires C, 84.92; H, 6.24; N, 4.13).

1f: Yellow crystals; m.p. 114–116°C; IR (KBr): 781, 1014, 1108, 1197, 1244, 1427, 1443, 1485, 1549, 1723 (CO), 2236 (CN), 2334, 2349, 2851, 2956 cm^{-1}; ^1H NMR (500 MHz, CDCl3) δ: 1.66 (m, 1H), 1.92 (m, 2H), 2.11 (m, 1H), 2.19 (m, 1H), 2.6 (m, 2H), 2.8 (m,1H), 3.78 (dd, 1H, *J* = 7 Hz, *J* = 11.52 Hz), 4.12 (m,1H), 7.67 (d, 1H, *J* = 7 Hz), 7.71 (t, 1H, *J* = 7.6 Hz), 7.77 (t, 1H, *J* = 7.5 Hz), 7.97 (d,1H, *J* = 8.3 Hz), 8.02 (d, 1H, *J* = 7 Hz), 8.17 (d, 1H, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ: 28.5, 32.5, 37.0, 39.5, 48.4, 65.3, 76.3 (spiro carbon), 118.5 (CN), 127.7-142.3 (10 signals arom), 207.6 (CO); MS (*m/z*,%), 288 (M^+, 25), 259 (M–CO, 25), 235 (M–CN–CO, 100). (Found: C, 78.3; H, 5.6; N, 9.6. $C_{19}H_{16}N_2O$ requires C, 79.14; H, 5.59; N, 9.72).

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