One-pot highly diastereoselective synthesis of some novel spiro pyrrolizidines via 1,3-dipolar cycloaddition reaction of azomethine ylide

Javad Azizian*, Ali Reza Karimi, R. Dastkhan, Ali A. Mohammadi and Mohammad R. Mohammadizadeh

Department of Chemistry, Faculty of Science, Shahid Beheshti University, PO Box 19395-4716, Tehran, Iran

Indenoquinoxaline-11-one derivatives react with proline and *N*-aryl maleimides via decarboxylative azomethine ylide formation and subsequent 1,3-dipolar cycloaddition involving an exo- transition state to give new heterocyclic adducts in 71–94% yields.

Keywords: spiro pyrrolizidine, indenoquinoxaline-11-one, azomethine ylide

1,3-dipolar cycloaddition employing azomethine ylides is an important process in organic synthesis, acquiring a prominent place of synthesis strategy for a varity of targets, including natural products such as azasugars and alkaloids.[1]

Pyrrolizidine alkaloids occur naturally in various plant species and in insects. Their structural and stereochemical complexity, coupled with their diverse and potent biological activities,[2] make pyrrolizidine alkaloids as well as structurally related unnatural compounds very attractive synthetic targets.[3] Quinoxaline derivatives are an important class of nitrogen-containing heterocycles and they constitute useful intermediates in organic synthesis.[4] They have been utilised in dyes,[5] pharmaceuticals[6,7] and have also been used as building blocks for the synthesis of organic semiconductors.[8,9]

Thus introduction of a spiro pyrrolizidine ring to the 11-position of the indenoquinoxaline system is expected to influence the biological activities significantly. Hence, it was thought desirable to synthesise a system having both ring system, in order to evaluate the biological activities of spiro products.

As a part of our ongoing research programme in the area of cycloaddition reactions,[10] we report here the facile synthesis of some novel spiro pyrrolizidine derivatives from indenoquinoxaline-11-one, proline and *N*-aryl maleimides in a 1,3-dipolar cycloaddition reaction.

The three-component diversity elements are introduced by simple addition of 1 equiv. of indenoquinoxaline-11-one to 1 equiv. of proline in DMSO (2–3 ml) as a solvent and this is then followed by addition of the *N*-aryl maleimides (1 equiv.), and the reactants are further exposed to MW to afford the corresponding spiro pyrrolizidines that were characterised as **4** (Scheme 1). These were characterised on the basis of their elemental analyses and IR, ^{1}H NMR, ^{13}C NMR and mass spectra data.

High diastereomeric excess of reaction was deduced on the basis of ^{1}H NMR spectra which no or trace endo-isomer could be detected. Note that the adduct (**4**) have four chiral centres, but their synthesis affords only one diastereomer, due to the dipole configuration (**6**) and exo-transition state structure, that has been mentioned by Grigg and his co-workers, in later extensive studies.[11-15] The stereochemistry of the cycloadducts (**4a–f**) was deduced on the basis of the ^{1}H NOEDSY and coupling constants of **3a**, **3b** and **8a** protons and comparison with related systems.[9c, 12, 15]

Table 1 Synthesis of **4(a–f)** under M.W. or reflux conditions

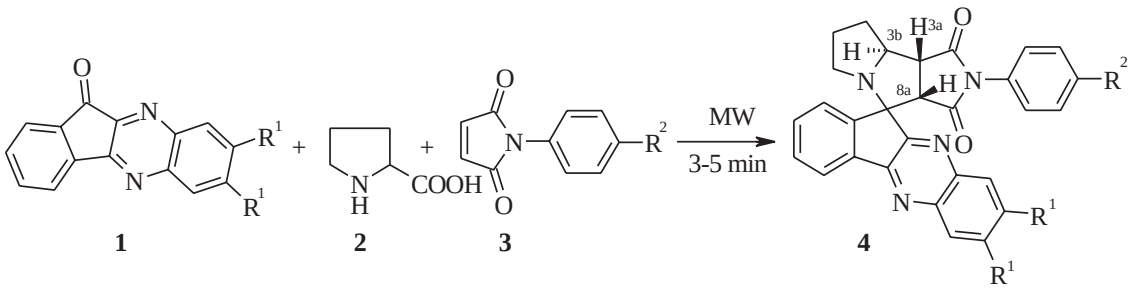
4	R_1	R_2	M.W.		Reflux	
			Time/min	Yield/%	Time/h	Yield/%
a	CH_3	Cl	5	88	3.5	80
b	CH_3	CH_3	3	93	2	83
c	H	Cl	5	85	3.5	77
d	H	H	4	92	3	82
e	H	CH_3	3	91	2.5	80
f	CH_3	H	3	89	2.5	80

On the other hand, heating the same reaction mixture in DMSO under reflux conditions afforded the products in longer reaction times and lower yields as shown in Table 1.

These results showed the utility of the microwave irradiation in organic synthesis and its advantages in comparison with classical heating, specially in processes that need strong heating and/or vigorous reaction conditions.

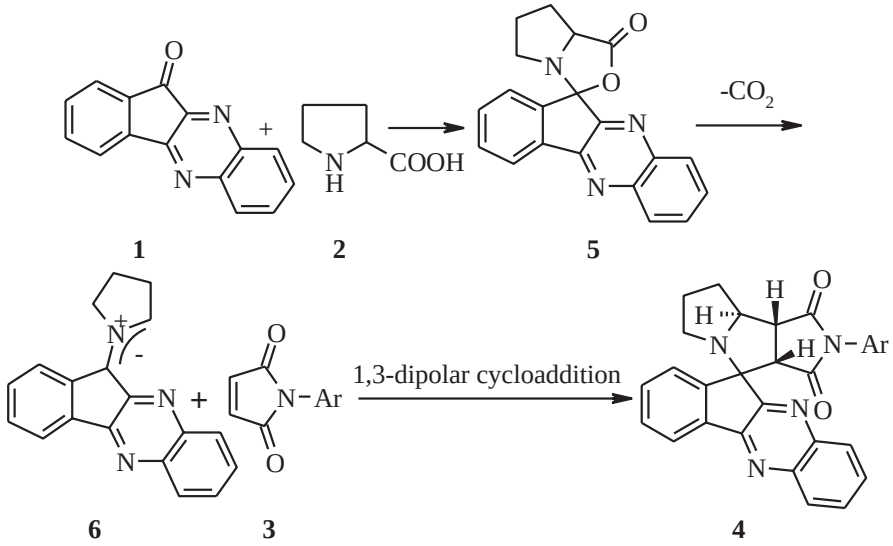
Presumably, the reaction proceeds through formation of azomethine ylide by thermal decarboxylation of mixtures of L-proline and indenoquinoxaline-11-one. The formed 1,3-dipole (**6**) subsequently undergoes cycloaddition reaction with *N*-aryl maleimide as dipolarophile, to produce stereoselective new adduct (Scheme 2).

In conclusion, 1,3-dipolar cycloaddition of indeno-quinoxaline-11-one derivatives (**1**), proline (**2**) and *N*-aryl maleimide (**3**) promoted by microwave irradiation, was a facile, high yield, high diastereomeric excess and rapid reaction, with easy recrystallisation that could be used as a path for synthesis of new pyrrolizidine alkaloids resemble spiro compounds.



Scheme 1

* Correspondence. E-mail: J-Azizian@cc.sbu.ac.ir



Scheme 2

Experimental

IR spectra were measured on a Bomen MB 100 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-500 Avance spectrometer at 500.1 and 125.8 MHz using TMS as internal standard. Mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer.

General procedure

Typical experimental procedure **A**: To 0.232 g of indenoquinoxaline-11-one (**1**) (1 mmol) was added 0.115 g of L-proline (**2**) (1 mmol) in 2–3 ml DMSO. To this solution was then added 0.173 g of *N*-phenyl maleimide (**3**) (1 mmol). The contents were taken in a pyrex test tube, placed in an alumina bath inside the microwave oven and irradiated for 3–5 min with a power of 600 W. After cooling, water added to the mixture and the separated solid was filtered off and recrystallised in ethanol to give a pure solid.

Typical experimental procedure **B**: To 0.232 g of indenoquinoxaline-11-one (**1**) (1 mmol) was added 0.115 g of L-proline (**2**) (1 mmol) in 10 ml DMSO. To this solution was then added 0.173g of *N*-phenyl maleimide (**3**) (1 mmol) and refluxing at 100 °C was continued for a further 3.5 h. After cooling, water added to the mixture and the separated solid was filtered off and recrystallised in ethanol to give a pure solid.

Compound **4a:** IR (KBr) (ν_{max}, cm^{-1}): 1710 (C=O); ^{1}H NMR($CDCl_3$, 500 MHz) δ_H: 1.88, 2.13, 2.45 (4H, m, $2CH_2$), 2.47 (3H, s, CH_3), 2.50 (3H, s, CH_3), 2.80, 3.01 (2H, m, $H_{6a, 6b}$), 3.72 (1H, dd, $H_{3a\alpha}$, *J*=9.8 Hz, *J*=6.5 Hz), 4.36 (1H, d, $H_{8a\alpha}$, *J*= 9.8 Hz), 5.04 (1H, m, $H_{3b\beta}$), 7.02-8.23 (10H, m, arom); ^{13}C NMR($CDCl_3$, 125 MHz) δ_C: 20.56, 20.73 ($2CH_3$), 25.92, 31.02, 50.24 ($3CH_2$), 53.96, 54.84, 67.25 (3CH Aliphatic), 74.29 (C_{spiro}, s), 123.02, 126.23, 128.13, 129.00, 129.05, 129.38, 130.72, 130.74, 131.54, 134.43, 139.28, 139.87, 140.09, 140.68, 141.93, 144.71, 152.44, 161.08 (Aromatic), 174.32, 177.28 (2C=O); MS (*m/z*, %): 520 (M^+, 60), 366 (100), 285 (60), 246 (75), 170 (15), 110 (60), 77 (20), 41 (35). ^{1}H NOEDSY (%): irradiation of H_{3a} caused enhancement of H_{8a} (9.2), H_{3b} (1.5) and H_{6a} (1.8). $C_{31}H_{25}N_4O_2Cl$.

Compound **4b:** IR (KBr) (ν_{max}, cm^{-1}): 1705 (C=O), 1605 (C=C); ^{1}H NMR($CDCl_3$, 500 MHz) δ_H: 1.88, 2.14, 2.45 (4H, m, $2CH_2$), 2.47 (3H, s, CH_3), 2.50 (3H, s, CH_3), 2.57 (3H, s, CH_3), 2.80, 3.04 (2H, m, $H_{6a, 6b}$), 3.73 (1H, dd, $H_{3a\alpha}$, *J*=9.9 Hz, *J*=6.5 Hz), 4.39 (1H, d, $H_{8a\alpha}$, *J*= 9.9 Hz), 5.06 (1H, m, $H_{3b\beta}$), 6.96–8.22 (10H, m, arom); ^{13}C NMR($CDCl_3$, 125 MHz) δ_C: 20.52, 20.73, 21.56 ($3CH_3$), 25.90, 30.94, 50.18 ($3CH_2$), 54.10, 54.77, 67.21 (3CH Aliphatic), 74.15 (C_{spiro}, s), 122.98, 126.24, 126.74, 128.94, 129.25, 129.66, 129.86, 130.62, 131.48, 138.71, 139.30, 139.88, 139.98, 140.49, 141.92, 144.92, 152.44, 161.20 (Aromatic), 174.64, 177.65 (2C=O); MS (*m/z*, %): 500 (M^+, 35), 366 (75), 285 (80), 246 (100), 187 (15), 110 (65), 77 (25), 44 (45). ^{1}H NOEDSY (%): irradiation of H_{3a} caused enhancement of H_{8a} (8.5), H_{3b} (1.2) and H_{6a} (2).$C_{32}H_{28}N_4O_2$.

Compound **4c:** IR (KBr) (ν_{max}, cm^{-1}): 1710 (C=O); ^{1}H NMR($CDCl_3$, 500 MHz) δ_H: 1.88, 2.12, 2.48 (4H, m, $2CH_2$), 2.79, 3.04 (2H, m, $H_{6a, 6b}$), 3.75 (1H, dd, $H_{3a\alpha}$, *J*=9.9 Hz, J=6.5 Hz), 4.39 (1H, d, $H_{8a\alpha}$, *J*= 9.9 Hz), 5.03 (1H, m, $H_{3b\beta}$), 7.01–8.26 (12H, m, arom); ^{13}C NMR($CDCl_3$, 125 MHz) δ_C: 25.95, 31.03, 50.17 ($3CH_2$), 54.10, 54.77, 67.34 (3CH Aliphatic), 74.26 (C_{spiro}, s), 123.36, 126.31, 127.98, 129.45, 129.62, 129.75, 130.32, 130.66, 130.85, 132.06, 134.47, 138.92, 141.01, 143.15, 145.01, 153.39, 162.06 (Aromatic), 174.32, 177.10 (2C=O); MS (*m/z*, %): 492 (M^+, 90), 338 (100), 257 (30), 218 (40), 110 (30), 41 (20). ^{1}H NOEDSY (%): irradiation of H_{3a} caused enhancement of H_{8a} (9), H_{3b} (1) and H_{6a} (1.5) .$C_{29}H_{21}N_4O_2Cl$.

Compound **4d:** IR (KBr) (ν_{max}, cm^{-1}): 1711 (C=O); ^{1}H NMR($CDCl_3$, 500 MHz) δ_H: 1.87, 2.13, 2.46 (4H, m, $2CH_2$), 2.78, 3.04 (2H, m, $H_{6a, 6b}$), 3.75 (1H, t, $H_{3a\alpha}$, *J*=9.5 Hz), 4.40 (1H, d, $H_{8a\alpha}$, *J*= 9.5 Hz), 5.06 (1H, m, $H_{3b\beta}$), 7.08–8.26 (13H, m, arom); ^{13}C NMR($CDCl_3$, 125MHz) δ_C: 25.94, 30.97, 50.14 ($3CH_2$), 54.24, 54.73, 67.35 (3CH Aliphatic), 74.18 (C_{spiro}, s), 123.31, 126.35, 126.79, 128.73, 129.25, 129.50, 129.68, 129.94, 130.24, 130.78, 132.02, 139.23, 138.93, 141.12, 143.14, 145.18, 153.38, 162.15 (Aromatic), 174.56, 177.36 (2C=O); MS (*m/z*, %): 458 (M^+, 90), 338 (100), 257 (45), 218 (60), 110 (70), 41 (40). ^{1}H NOEDSY (%): irradiation of H_{3a} caused enhancement of H_{8a} (8.5), H_{3b} (1) and H_{6a} (2) .$C_{29}H_{22}N_4O_2$.

Compound **4e:** IR (KBr) (ν_{max}, cm^{-1}): 1707 (C=O); ^{1}H NMR($CDCl_3$, 500 MHz) δ_H: 1.88, 2.12, 2.46 (4H, m, $2CH_2$), 2.30 (3H, s, CH_3), 2.80, 3.04 (2H, m, $H_{6a, 6b}$), 3.74 (1H, t, $H_{3a\alpha}$, *J*=9.5 Hz), 4.39 (1H, d, $H_{8a\alpha}$, *J*= 9.5 Hz), 5.06 (1H, m, $H_{3b\beta}$), 6.95-8.26 (12H, m, arom); ^{13}C NMR($CDCl_3$, 125 MHz) δ_C: 21.55 (CH_3), 25.94, 30.96, 50.13 ($3CH_2$), 54.25, 54.71, 67.31 (3CH Aliphatic), 74.13 (C_{spiro}, s), 123.30, 126.35, 126.60, 129.48, 129.48, 129.59, 129.67, 129.92, 129.96, 130.20, 130.75, 132.00, 138.93, 141.13, 143.14, 145.24, 153.39, 162.19 (Aromatic), 174.66, 177.48 (2C=O); MS (*m/z*, %): 473 (M^+, 95), 338 (100), 257 (35), 218 (30), 110 (30), 77 (10), 41 (10). ^{1}H NOEDSY (%): irradiation of H_{3a} caused enhancement of H_{8a} (9), H_{3b} (1.2) and H_{6a} (1.6). $C_{30}H_{24}N_4O_2$.

Compound **4f:** IR (KBr) (ν_{max}, cm^{-1}): 1708 (C=O); ^{1}H NMR($CDCl_3$, 500 MHz) δ_H: 1.88, 2.13, 2.45 (4H, m, $2CH_2$), 2.46 (3H, s, CH_3), 2.50 (3H, s, CH_3), 2.82, 3.05 (2H, m, $H_{6a, 6b}$), 3.87 (1H, dd, $H_{3a\alpha}$, *J*=9.8 Hz, *J*=6.5 Hz), 4.77 (1H, d, $H_{8a\alpha}$, *J*= 9.8 Hz), 5.14 (1H, m, $H_{3b\beta}$), 7.01–8.18 (11H, m, arom); ^{13}C NMR($CDCl_3$, 125 MHz) δ_C: 20.50, 20.72 ($2CH_3$), 25.90, 30.95, 50.20 ($3CH_2$), 54.07, 54.79, 67.26 (3CH Aliphatic), 74.22 (C_{spiro}, s), 122.34, 126.25, 128.93, 129.03, 129.16, 129.67, 130.77, 130.80, 131.64, 134.53, 139.38, 139.97, 140.20, 140.75, 141.95, 144.81, 152.54, 161.28 (Aromatic), 174.56, 177.53 (2C=O); MS (*m/z*, %): 486 (M^+, 75), 366 (100), 285(35), 246 (40), 110 (20), 77(10), 41 (10). ^{1}H NOEDSY (%): irradiation of H_{3a} caused enhancement of H_{8a} (9.4), H_{3b} (1.5) and H_{6a} (2.2) .$C_{31}H_{26}N_4O_2$.

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