The Facile Synthesis of N-Aryl Isoxazolones as DNA Intercalators Under Solvent-free Conditions Using Microwave Irradiation

Ali Reza Molla Ebrahimlo*
Chemistry Department, Islamic Azad University, Khoy Branch, Khoy, Iran.

Received 9 December 2011, revised 20 February 2012, accepted 20 March 2012.

ABSTRACT
The reaction of chloroheterocycles with some isoxazolones under microwave irradiation and under solvent-free conditions to give the corresponding mono isoxazolinyl derivatives is reported. The main advantages of this method are: (i) elimination of the nitrogen gas (N₂), (ii) solvent-free conditions, (iii) microwave irradiation, (iv) avoiding the use of silica gel for purification of the products, and (v) higher and shorter reaction times. These compounds have potential applications as DNA intercalators.

KEYWORDS
Isoxazolones, N-aryl isoxazolones, solvent-free, 2-chlorobenzoxazole, 2-chlorobenzothiazole.

1. Introduction
Isoxazolones derivatives are important heterocyclic compounds with a wide range of reported biological activities. Recently, several N-substituted isoxazol-5(2H)-ones such as the N-(cyanoethyl) derivative have been isolated from root exudates of sweet pea seedlings, and they were shown to effect protection against infection. In addition, isoxazol-5(2H)-ones exhibit herbicidal, bactericidal and anticholestermic and hypolipemic properties.

Khalafy and co-workers have reported the synthesis of new N-substituted derivatives of 3-arylaminoisoxazol-5(2H)-ones 1a–c with benzoxazole and benzothiazole at nitrogen in chloroform under reflux conditions to produce the corresponding N-benzoxazole and N-benzothiazole derivatives 2a–c and 3a–c (Scheme 1). We have also reported the reaction of 2-chloro-5-nitropyridine and 2,3-dichloroquinoxaline with isoxazolone in the absence of solvent by heating the required regents in a sealed tube at 130 °C for an hour to give N-substituted derivatives 4 and 5 (Scheme 2). Here we describe the synthesis of N-aryl isoxazolones in solid phase under microwave irradiation in higher yields and shorter reaction times.

2. Results and Discussion
The isoxazolones 1a–c were prepared from the reaction of the corresponding thiocarbamates 6a–c with hydroxylamine by the general method of Worrall (Scheme 3). The synthesis of the starting material generally involves the displacement of an activated halide in a heterocyclic system by a 2H-isoxazolone. Thus, reaction of isoxazolones 1a–c with 2-chlorobenzoxazole, 2-chlorobenzothiazole, 2-chloro-5-nitropyridine and 2-chloropyrimidine in solid phase under microwave irradiation afforded the corresponding N-benzoxazole, N-benzothiazole, N-pyridine and N-pyrimidine derivatives 2a–c, 3a–c, 4b,c and 7b,c (Scheme 4). The base-catalyzed rearrangements of N-substituted derivatives of 3-arylaminoisoxazol-5(2H)-ones 1 appears to be generally applicable to the synthesis of new planar polycyclic heterocycles.

Experimental
General
Freshly distilled solvents were used and anhydrous solvents were dried according to Perrin and Armarego. Melting points were determined on a Philip Harris C495471 apparatus and are uncorrected. Infrared spectra were recorded on a Thermonicolet
Nexus 670) FT-infrared spectrometer, using sodium chloride cells and measured as Nujol mulls or KBr. $^1$H (300 MHz) and $^{13}$C (75.5 MHz) NMR measurements were recorded on a Bruker 300 spectrometer in DMSO-$d_6$ or CDCl$_3$ using TMS as the internal reference. High-resolution mass spectra were recorded on a Varian Matt 311 spectrometer. Mass spectra were recorded on a HP 5973 MSD instrument connected to a HP 6890 GC. Relative abundances of fragments are quoted in brackets after the m/z values. The reactions were performed in a microwave oven (DeLonghi, model number CE290DN).

Typical Procedure
A mixture of isoxazolone 1 (2 mmol) and chloroheterocycle (2 mmol) was mixed and ground in a mortar and pestle until a fine homogeneous powder was obtained (5 min). The mixture was then irradiated under microwave irradiation for 5 min at 130 °C. The resulting product was recrystallized from ethanol to give the corresponding N-aryl isoxazolone.

Ethyl 2-(benzoxazol-2-yl)-3-phenylamino-5-oxo-2,5-dihydroisoxazole-4-carboxylate (2a)
As white needles (66 mg, 90 %), mp 113–114 °C (lit.$^6$ 114–116 °C) $^1$H NMR (CDCl$_3$) $\delta$ 1.40 (t, J = 7.0 Hz, 3H), 4.41 (q, J = 7.0 Hz, 2H), 6.94 (t, J = 7.1 Hz, 1H, Ar), 7.11 (t, J = 7.4 Hz, 2H, Ar), 7.17 (d, J = 7.5 Hz, 2H, Ar), 7.27 (t, J = 7.6 Hz, 1H, Ar), 7.34 (t, J = 7.1 Hz, 1H, Ar), 7.42 (d, J = 8.0 Hz, 1H, Ar), 7.46 (d, J = 7.7 Hz, 1H, Ar), 9.96 (s, exchanged by D$_2$O addition, 1H, NH). $^{13}$C NMR (CDCl$_3$) $\delta$ 14.78, 61.54, 79.11, 111.26, 120.98, 122.85, 125.83, 127.26, 129.76, 135.63, 139.71, 150.04, 140.58, 164.55, 165.21. FT-IR (KBr) $\nu_{max}$ cm$^{-1}$: 3270, 2990, 1784, 1668, 1628, 1489, 1201, 1030, 761, 704. GC-MS (EI, 70ev): m/z (%) 365 (M$^+$, 13), 321 [(M-CO$_2$), 14], 276 (32), 275(100), 236 (32), 217 (11), 216 (62), 145 (23), 144 (82), 78(17), 77(76), 44 (42), 29 (58).

Ethyl 2-(benzoxazol-2-yl)-3-(4-bromophenylamino)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (2b)
As white needles (0.82g, 92 %), mp 151–152 °C (lit.$^6$ 151–153 °C). $^1$H NMR(CDCl$_3$) $\delta$ 1.45 (t, J = 7.1 Hz, 3H), 4.44 (q, J = 7.1 Hz, 2H), 7.11 (d, J = 8.7 Hz, 2H, Ar), 7.30 (d, J = 8.7 Hz, 2H, Ar), 7.36 (t, J = 7.7 Hz, 1H, Ar), 7.42 (t, J = 7.4 Hz, 1H, Ar), 7.51 (d, J = 8.2 Hz, 1H, Ar), 7.54 (d, J = 8.0 Hz, 1H, Ar), 9.99 (s, exchanged by D$_2$O addition, 1H, NH). $^{13}$C NMR (CDCl$_3$) $\delta$ 14.76, 61.70, 79.68, 111.35, 120.60, 121.06, 124.30, 126.02, 127.35, 132.92, 134.97, 139.72, 150.12, 151.60, 151.60, 163.61, 164.38, 165.24. FT-IR (KBr) $\nu_{max}$ cm$^{-1}$: 3238, 2978, 1786, 1672, 1627, 1204, 786, 746. GC-MS (EI,70ev): m/z (%) 443 [(M$^+$ + 2), 3], 441 (M$^+$, 3), 399 [(M-CO$_2$), 26], 397 [(M-CO$_2$), 26],

![Scheme 2](image_url)

![Scheme 3](image_url)
Ethyl 2-(benzoxazol-2-yl)-3-(4-methylphenylamino)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (2c)

As white needles (0.68 g, 90 %), mp 130–132 °C (lit. 6 129–131 °C).

$^1$H NMR (CDCl$_3$) $\delta$ 1.45 (t, J = 7.1 Hz, 3H), 2.12 (s, 3H), 4.45 (q, J = 7.1 Hz, 2H), 6.92 (d, J = 7.9 Hz, 2H, Ar), 7.08 (d, J = 7.9 Hz, 2H, Ar), 7.33 (t, J = 7.7 Hz, 1H, Ar), 7.40 (t, J = 8.2 Hz, 1H, Ar), 7.47 (d, J = 8.2 Hz, 1H, Ar), 9.90 (s, exchanged by D$_2$O addition, 1H, NH).

$^{13}$C NMR (CDCl$_3$) $\delta$ 14.81, 21.11, 61.50, 78.91, 111.27, 121.08, 122.94, 125.74, 127.13, 130.29, 132.99, 137.44, 139.91, 150.15, 151.76, 164.01, 164.85, 165.38.

FT-IR (KBr) $\nu$ max cm$^{-1}$: 3267, 1790, 1683, 1667, 1632, 1561, 1536, 1293, 1201, 1030, 985, 791.

GC-MS (EI, 70 ev): m/z (%) 379 (M+, 7), 335 [(M-CO$_2$), 34], 290 (23), 289 (100), 251 (11), 250 (46), 230 (57), 158 (60), 117 (55), 91 (100), 77 (44), 65 (50), 44 (9), 29 (66).

Ethyl 2-(benzothiazol-2-yl)-3-phenylamino-5-oxo-2,5-dihydroisoxazole-4-carboxylate (3a)

As white prisms (0.7 g, 92 %), mp 140–143 °C (lit. 5 141–142 °C).

$^1$H NMR (CDCl$_3$) $\delta$ 1.29 (t, J = 7.1 Hz, 3H), 4.27 (q, J = 7.1 Hz, 2H), 7.04–7.08 (m, 1H), 7.18–7.23 (m, 4H), 7.35 (td, J = 7.9 Hz, J = 1.3 Hz, 1H), 7.40 (td, J = 7.6 Hz, J = 1.3 Hz, 1H), 7.65 (dd, J = 7.9 Hz, J = 0.88 Hz, 1H), 7.76 (dd, J = 7.75 Hz, J = 1.1 Hz, 1H), 10.15 (s, 1H, exchanged by D$_2$O addition, NH).

$^{13}$C NMR (CDCl$_3$) $\delta$ 14.30, 60.97, 78.72, 121.56, 122.48, 123.01, 125.92, 126.54, 126.93, 129.20, 133.47, 136.72, 149.12, 157.44, 161.43, 163.02, 163.94.

FT-IR (KBr) $\nu$ max cm$^{-1}$: 3190, 2971, 1783, 1696, 1602, 1556, 1515, 1497, 1371, 1204, 764.

Ethyl 2-(benzothiazol-2-yl)-3-(4-bromophenyl)amino-5-oxo-2,5-dihydro-4-carboxylate (3b)

As white needles (0.85 g, 92 %), mp 172–173 °C (lit. 6 172–174 °C).

$^1$H NMR (CDCl$_3$) $\delta$ 1.34 (t, J = 6.9 Hz, 3H), 4.33 (q, J = 6.9 Hz, 2H), 7.1 (d, J = 8.7 Hz, 2H, Ar), 7.36 (d, J = 8.7 Hz, 2H, Ar), 7.40 (td, J = 7.5 Hz, J = 1.5 Hz, 1H, Ar), 7.46 (td, J = 7.2 Hz, J = 1.5 Hz, 1H, Ar), 7.67 (d, J = 7.5 Hz, 1H, Ar), 7.81 (d, J = 7.5 Hz, 1H, Ar), 10.16 (s, exchanged by D$_2$O addition, NH).

$^{13}$C NMR (CDCl$_3$) $\delta$ 14.31, 61.14, 79.10, 119.70, 121.62, 122.98, 123.93, 126.03, 127.10, 132.27, 136.60, 149.08, 157.19, 161.43, 163.02, 163.94. FT-IR (KBr) $\nu$ max cm$^{-1}$: 3188, 2971, 1783, 1660, 1556, 1515, 1371, 1204, 764.

GC-MS (EI, 70 ev): m/z (%) 461 [(M+ + 2), 4], 459 (M+, 4), 417 [(M-CO$_2$), 31], 415 [(M-CO$_2$), 30], 371 (25), 369 (23), 291 (23), 290 (100), 263 (12), 262 (26), 224 (11), 177 (14), 161 (16), 135 (11), 134 (15), 108 (10), 29 (13).

Ethyl 2-(benzothiazol-2-yl)-3-(4-methylphenyl)amino-5-oxo-2,5-dihydro-4-carboxylate (3c)

As white needles (0.75 g, 95 %), mp 139–141 °C (lit. 7 138–140 °C).

$^1$H NMR (CDCl$_3$) $\delta$ 1.35 (t, J = 7.2 Hz, 3H), 2.31 (s, 3H), 4.27 (q, J = 7.2 Hz, 2H), 7.00 (d, J = 8.1 Hz, 1H, Ar), 7.07 (d, J = 7.2 Hz, 1H, Ar), 7.27 (d, J = 6.9 Hz, 1H, Ar), 7.30–7.52 (m, 2H, Ar), 7.69 (d, J = 8.1 Hz, 1H, Ar), 7.87 (d, J = 7.8 Hz, 1H, Ar), 9.93 (d, J = 8.1 Hz, 1H, Ar), 9.21 (s, exchanged by D$_2$O addition, NH).

$^{13}$C NMR
Ethyl 3-(4-bromophenyl) amino-2-(5-nitropyrid-2-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (4b)

As yellow crystals (0.85 g, 95 %), mp 216–218 °C (lit.21 218–220 °C).

1H NMR (d6-CDCl3): δ 9.99 (t, J = 7 Hz, 3H), 3.94 (q, J = 7 Hz, 2H) 7.69 (d, J = 9 Hz, 2H), 7.52 (d, J = 9 Hz, 2H), 7.01 (d, J = 9 Hz, 2H), 6.96 (d, J = 9 Hz, 2H), 3.87 (d, J = 9 Hz, 2H), 3.77 (d, J = 9 Hz, 2H), 3.44 (q, J = 7 Hz, 2H), 2.56 (s, 3H), 1.26 (t, 3H, J = 7 Hz); 13C NMR: δ 163.44, 164.58 ppm; FT-IR (KBr) max cm–1: 3207, 3083, 2985, 1761, 1699, 1579, 1558, 1393, 1371, 1069, 781.

Ethyl 3-(4-methylphenyl) amino-2-(5-nitropyrid-2-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (4c)

As orange needles (0.77 g, 95 %), mp 187–189 °C (lit.13 187–189 °C). 1H NMR (CDCl3): δ 1.36 (t, J = 7 Hz, 3H), 2.23 (s, 3H), 4.32 (q, J = 7 Hz, 2H), 6.98 (d, J = 8.5 Hz, 2H), 7.03 (d, J = 8.7 Hz, 2H), 7.09 (t, J = 4.8 Hz, 2H), 6.97 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 9 Hz, 2H), 7.52 (d, J = 9 Hz, 2H), 7.01 (d, J = 9 Hz, 2H), 6.95 (d, J = 9 Hz, 2H), 3.87 (d, J = 9 Hz, 2H), 3.77 (d, J = 9 Hz, 2H), 3.44 (q, J = 7 Hz, 2H), 2.56 (s, 3H), 1.26 (t, 3H, J = 7 Hz); 13C NMR (CDCl3): δ 14.46, 20.85, 60.78, 78.62, 119.24, 121.71, 129.73, 134.64, 135.83, 156.35, 158.48, 161.61, 163.87, 164.74; FT-IR (KBr) ν max/cm–1: 3027, 3083, 2985, 1761, 1699, 1579, 1558, 1393, 1371, 1069, 781.