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

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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 (N_2), (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.[1] In addition, isoxazol-5(2H)-ones exhibit herbicidal,[2] bacterical[3] and anticholestermic and hypolipemic properties.[4]

Khalafy and co-workers have reported[5,6] 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[7–10] the reaction of 2-chloro-5-nitropyridine and 2,3-dichloroquinoxaline with isoxazolone[11] **1** 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.

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2. Results and Discussion

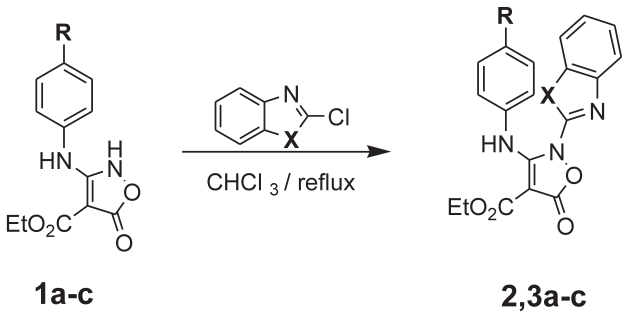
The isoxazolones **1a–c** were prepared from the reaction of the corresponding thiocarbamates **6a–c** with hydroxylamine by the general method of Worrall[11] (Scheme 3).

The synthesis of the starting material generally involves the displacement of an activated halide in a heterocyclic system by a suitable 2*H*-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(2*H*)-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.[12] Melting points were determined on a Philip Harris C4954718 apparatus and are uncorrected. Infrared spectra were recorded on a Thermonicolet

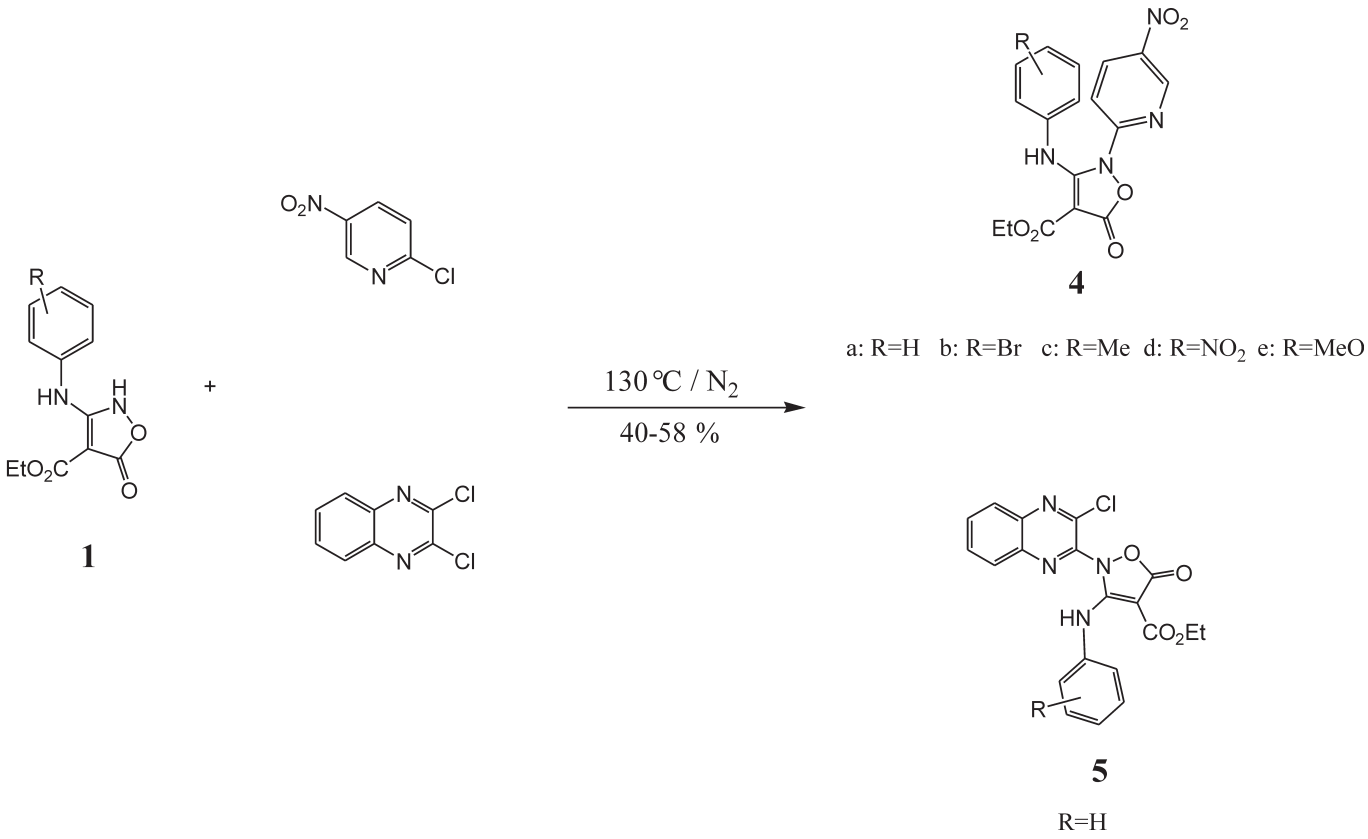


1a-c **2,3a-c**

a: **R**=H **b**: R=Br c: **R**=Me

2 X=0 3 X=S

Scheme 1.



Scheme 2.

(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

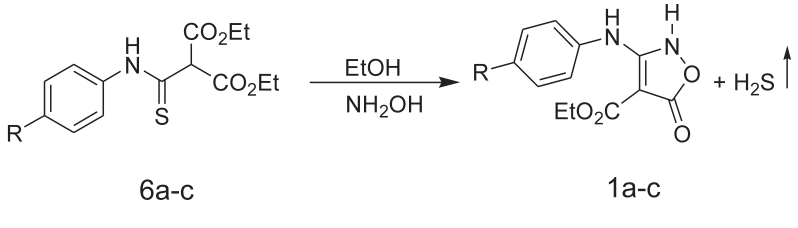
A mixture of isoxazolone **1** (2 mmol) and chloroheterocycle (2 mmol) was mixed and ground in a mortar and pestle until a fine homogeneous powder was obtained (5 min). The mixture was then irradiated under microwave irradiation for 5 min at 130 °C. The resulting product was recrystalized from ethanol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

Ethyl 2-(benzoxazol-2-yl)-3-phenylamino-5-oxo-2, 5-dihydro-isoxazole-4-carboxylate (2a)

As white needles (66 mg, 90 %), mp 113–114 °C (lit.[6] 114–116 °C) ^{1}H NMR ($CDCl_3$) δ 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_2O addition, 1H, NH). ^{13}CNMR ($CDCl_3$) δ 14.78, 61.54, 79.11, 111.26, 120.98, 122.85, 125.83, 127.26, 129.76, 135.63, 139.71, 150.04, 151.58, 164.55, 165.21. FT-IR (KBr) ν_{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)

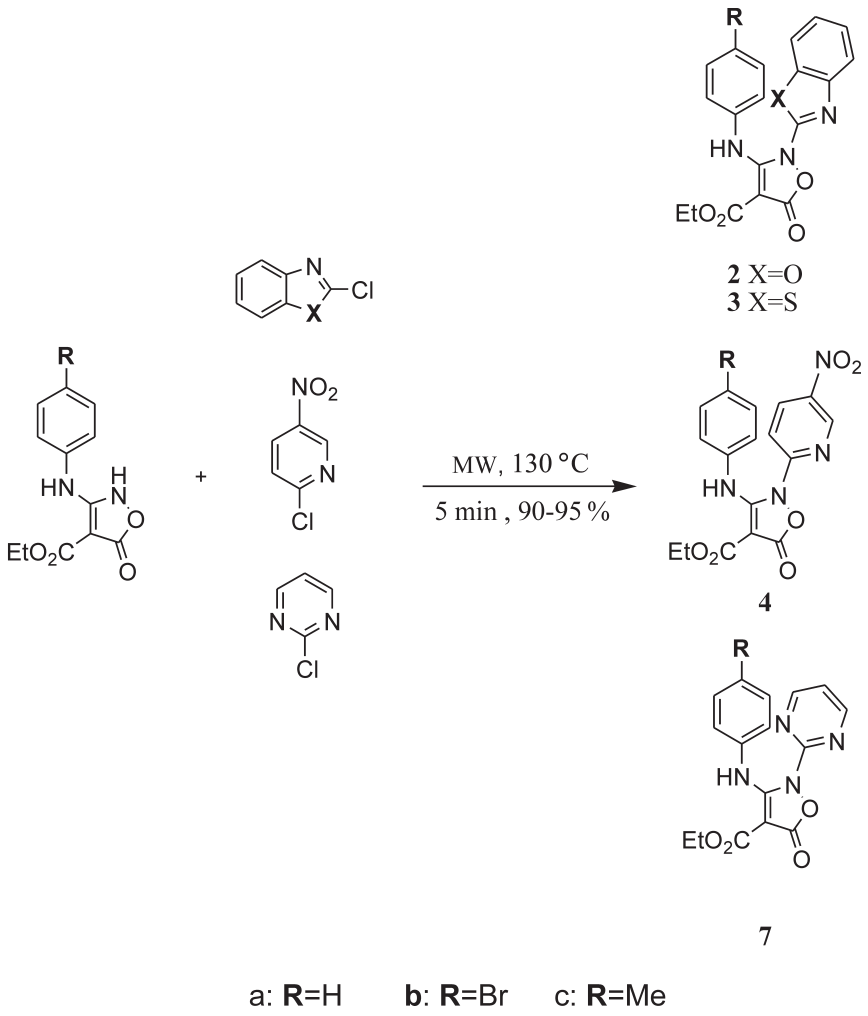
As white needles (0.82g, 92 %), mp 151–152 °C (lit.[6] 151–153 °C). ^{1}H NMR($CDCl_3$) δ 1.45 (t, J = 7.1 Hz, 3H), 4.44 (q, J = 7.1 Hz, 2H), 7.11 (d, J = 8.7 Hz, 2H, Ar), 7.30 (d, J = 8.7 Hz, 2H, Ar), 7.36 (t, J = 7.7 Hz, 1H, Ar), 7.42 (t, J = 7.4 Hz, 1H, Ar), 7.51 (d, J = 8.2 Hz, 1H, Ar), 7.54 (d, J = 8.0 Hz, 1H, Ar), 9.99 (s, exchanged by D_2O addition, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 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, 163.61, 164.38, 165.24. FT-IR (KBr) ν_{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],



6a-c 1a-c

a: **R**=H b: **R**=Br c: **R**=Me:

Scheme 3.



Scheme 4.

355 (21), 353 (21), 275 (28), 274 (95), 246 (21), 216 (36), 173 (24), 145 (33), 117(40), 102 (30), 90 (41), 77 (37), 44 (30), 43 (68), 29 (100).

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 ($CDCl_3$) δ 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), 7.53 (d, J = 7.9 Hz, 1H, Ar), 9.90 (s, exchanged by D_2O addition, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 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) ν_{max} cm^{-1}: 3267, 1790, 1683, 1667, 1632, 1561, 1514, 1356, 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 ($CDCl_3$) δ 1.29 (t, J = 7.1Hz, 3H), 4.27 (q, J = 7.1Hz, 2H), 7.04–7.08 (m, 1H), 7.18–7.23 (m, 4H), 7.35 (td, J_1 = 7.6 Hz, J_2= 1.3 Hz, 1H), 7.40 (td, J_1 = 7.6 Hz, J_2 = 1.3 Hz, 1H), 7.65 (dd, J_1 = 7.9 Hz, J_2 = 0.88 Hz, 1H), 7.76 (dd, J_1 = 7.75 Hz, J_2 = 1 Hz, 1H), 10.15 (s, 1H, exchanged by D_2O addition, NH). ^{13}C NMR ($CDCl_3$) δ 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, 157.23, 161.68, 163.35, 163.99. FT-IR (KBr) ν_{max}/cm^{-1}: 3190, 1782, 1686, 1569, 1497, 1456, 1442, 1378, 1282, 1224, 1177, 950, 765.

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 ($CDCl_3$) δ 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_2O addition, 1H, NH). ^{13}C NMR($CDCl_3$) δ 14.31, 61.14, 79.10, 119.70, 121.62, 122.98, 123.93, 126.03, 127.10, 132.27, 136.00, 149.08, 157.19, 161.43, 163.02, 163.94. FT-IR (KBr) ν_{max} cm^{-1}: 3188, 2971, 1783, 1696, 1602, 1556, 1515, 1371, 1204, 764. GC-MS (EI, 70ev):*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.[6] 138–140 °C). ^{1}H NMR ($CDCl_3$) δ 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 = 7.2Hz, 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),7.93 (d, J = 8.1 Hz, 1H, Ar), 9.21 (s, exchanged by D_2O addition, 1H, NH). ^{13}C NMR

($CDCl_3$) δ 14.46, 20.88, 60.47, 75.55, 121.12, 121.76, 122.53, 122.85, 125.81, 126.74, 126.93, 129.74, 130.43, 132.68, 136.45, 164.51, 165.41, 167.25. FT-IR (KBr) ν_{max} cm^{-1}: 3218, 3075, 1979, 1778, 1708, 1573, 1448, 1390, 1201, 726.

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.[7] 218 °C). ^{1}HNMR (d_6-DMSO+$CDCl_3$): δ 0.99 (t, J = 7 Hz, 3H), 3.94 (q, J = 7 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 9.1 Hz, 1H), 8.40 (dd, J_1 = 9.1 Hz, J_2 = 2.3 Hz, 1H), 8.75 (d, J = 2.3 Hz, 1H), 10.29 (br s, 1H, NH); ^{13}C NMR (d_6-DMSO+$CDCl_3$): δ 14.41, 60.99, 79.05, 114.63, 119.46, 124.11, 132.46, 135.08, 137.21, 141.66, 143.79, 153.92, 158.31, 161.38, 165.88; FT-IR (KBr) ν_{max} cm^{-1}: 3140, 2965, 1773, 1683, 1591, 1531, 1324, 1188, 1114, 1010, 961, 832; MS m/z: 450 (M^++2, 27 %), 448(M^+, 30 %), 406(74), 404(77), 279(100), 251(20), 184(35), 182(36), 157(29), 155(29), 102(22), 72(23), 44(59).

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

As orange needles (0.7 g, 92 %) mp 62–64 °C (lit.[9] 59–61 °C). ^{1}H NMR ($CDCl_3$): δ 10.31 (br s, 1H), 8.89 (d, 1H, J = 2.7 Hz), 8.53 (dd, 1H, J_1 = 9.1, J_2 = 2.7 Hz), 7.52 (d, 1H, J = 9.1 Hz), 7.03 (br s, 4H), 4.23 (q, 2H, J = 7.1 Hz), 2.27 (s, 3H), 1.26 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 163.8, 163.1, 160.6, 153.9, 143.5, 141.5, 136.4, 135.0, 134.2, 129.9, 122.0, 115.0, 78.7, 60.9, 20.9, 14.2. FT-IR (KBr) ν_{max} cm^{-1}: 3389, 1780, 1669, 1602, 1525, 1456, 1419, 1337.

Ethyl 5-oxo-3-(4-bromophenylamino)-2-(pyrimidin-2-yl)-2, 5-dihydroisoxazole-4-carboxylate (7b)

As white prisms (0.64 g, 95 %), mp 202–204 °C (lit.[13] 202–204 °C). ^{1}H NMR ($CDCl_3$): δ 1.36 (t, J = 7.2 Hz, 3H), 4.33(q, J = 7.2 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H, Ar), 7.14 (t, J = 4.8 Hz, 1H, Ar), 7.32 (d, J = 8.7 Hz, 2H, Ar), 8.57 (d, J = 4.8 Hz, 2H, Ar), 10.19 (s, 1H, NH, removed by D_2O addition); ^{13}C NMR ($CDCl_3$): δ 14.33, 60.96, 79.27, 118.96, 119.37, 123.24, 132.29, 136.56, 156.16, 158.59, 161.13, 163.44, 164.58 ppm; FT-IR (KBr) ν_{max} cm^{-1}: 3310, 3208, 3083, 1759, 1698, 1601, 1578, 1556, 1392, 1069, 835, 781.

Ethyl 5-oxo-2-(pyrimidin-2-yl)-3-(p-tolylamino)-2, 5-dihydro-isoxazole-4-carboxylate (7c)

As pale yellow prisms (0.77 g, 95 %), mp 187–189 °C (lit.[13] 187–189 °C). ^{1}H NMR ($CDCl_3$): δ 1.35 (t, J = 7.2 Hz, 3H), 2.23 (s, 3H), 4.32 (q, J = 7.1 Hz, 2H), 6.98 (d, J = 8.7 Hz, 2H, Ar), 7.03 (d, J = 8.7 Hz, 2H, Ar), 7.09 (t, J = 4.8 Hz, 1H, Ar), 8.53 (d, J = 4.8 Hz, 2H, Ar), 10.10 (s, 1H, NH, removed by D_2O addition); ^{13}C NMR ($CDCl_3$): δ 14.36, 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}: 3207, 3083, 2985, 1761, 1699, 1579, 1558, 1393, 1371, 1069, 781.

4. Conclusion

In conclusion, we have developed a rapid, convenient and efficient method for synthesis of *N*-aryl isoxazolones under solvent-free conditions. The main advantages of this method are: (i) elimination of the nitrogen gas (N_2), (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. The synthesis of *N*-aryl isoxazolones appear to be generally applicable to the synthesis of heterocycles, which are suitable synthetic intermediates for a series of new polycyclic heterocycles with possible pharmaceutical applications and they are expected to intercalate with DNA.[14–16]

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