

Synthesis of methyl 5-amino-3-arylaminoisoxazole-4-carboxylates

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Abstract

The reaction of arylisothiocyanate derivatives with sodium methyl cyanoacetate in tetrahydrofuran gave the corresponding thioxo-propanoates, the reaction of which with hydroxylamine in ethanol and ammonium acetate under reflux conditions provided a synthetically useful method for the synthesis of methyl 5-amino-3-arylaminoisoxazole-4-carboxylates in good yields.

Keywords: isothiocyanates; isoxazoles; methylcyanoacetate; thioxopropanoates.

Introduction

Synthesis of highly substituted isoxazoles is important due to their biological activity (Giomi et al., 2008; Lee et al., 2009). The chemical properties of isoxazole derivatives have been studied and these compounds have served as a versatile building block in organic synthesis. Thus, synthesis of these molecules with high efficiency is highly desirable (Ghosh and Bandyopadhyay, 2004; Ahmed et al., 2005; Dang et al., 2006; Wang et al., 2008; Gaywood and McNab, 2009; Girardin et al., 2009; Li et al., 2009; Tang et al., 2009). Although a typical strategy for the synthesis of these molecules is the [3+2] cycloaddition reaction between alkynes and nitrile oxides, a cycloaddition reaction with internal alkynes for the direct construction of trisubstituted isoxazole has been less frequently reported (Pevarello et al., 1993; Denmark and Kallemeyn, 2005; Hansen et al., 2005; Moore et al., 2005; Bourbeau and Rider, 2006; Grecian and Fokin, 2008; Willy et al., 2008; Bhosale et al., 2009; Conti et al., 2009; McClendon et al., 2009). These methods require harsh conditions and provide poor chemo- and regioselectivities. As an alternative strategy for efficient construction of isoxazoles, Larock and co-workers recently reported stepwise synthesis of trisubstituted isoxazoles by electrophilic cyclization of *O*-methyl alkynyl oxime ethers and a subsequent palladium-catalyzed coupling reaction of the resulting 4-haloisoxazole (Waldo and Larock, 2005, 2007; Waldo et al., 2008). In this paper, a series of new

methyl 5-amino-3-arylaminoisoxazole-4-carboxylates were synthesized in high yield, which are suitable intermediates for synthesis of a series of new heterocycles.

Results and discussion

The reaction of arylisothiocyanates **1a–g** with sodium methyl cyanoacetate in tetrahydrofuran under reflux gave the corresponding arylaminothioxopropanoates **2a–g** in high yield (Scheme 1).

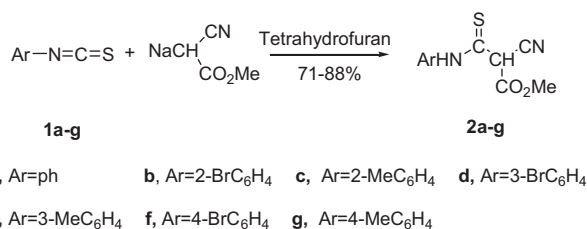
Compounds **2a–g** were allowed to react with hydroxylamine hydrochloride in aqueous ethanol in the presence of ammonium acetate under reflux conditions to afford the corresponding methyl 5-amino-3-arylaminoisoxazole-4-carboxylates **3a–g** in 68–90% yield. The suggested reaction mechanism is shown in Scheme 2 along with the target compounds **3a–g**.

Previously, we have reported (Khalafy et al., 2005, 2006, 2008; Baradarani et al., 2008) that the reaction of arylisothiocyanates with sodium diethyl malonate gave the arylthiocarbamoylmalonates **4**. Subsequent reaction with hydroxylamine under reflux conditions gave 3-arylaminoisoxazol-5(2*H*)-ones **5** as a source of imidazopyrimidine and aminoindole derivatives (Poursattar Marjani and Khalafy, 2010) or ethyl 2,9-dioxo-4,9-dihydro-2*H*-isoxazolo[3,2-*b*]quinazoline-3-carboxylate (**6**) when $X=2\text{-CO}_2\text{Et}$ by intramolecular condensation (Scheme 3). In the case of arylaminothioxopropanoates **2a–g**, formation of isoxazoles instead of isoxazolones in Scheme 2 might be due to the higher electrophilicity of the cyano group over the ester functionality in malonate **4**. Ultimately the reaction of the nucleophilic oximino group with the cyano functionality of **2a–g** produced the corresponding methyl 5-amino-3-arylaminoisoxazole-4-carboxylates **3a–g**.

Experimental

General

Freshly distilled solvents were dried according to Perrin and Armarego (1988). Melting points were determined on an Electrothermal. IA 9000 SERIES digital melting point apparatus (Electrothennal, Essex, UK) and are uncorrected. Elemental microanalyses of the compounds studied were performed using a Carlo-Erba 1104 instrument (Milan, Italy). ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer (Ettlingen, Germany) at 300 MHz and 75.5 MHz, respectively. The spectra were measured in CDCl_3 or $\text{DMSO}-d_6$ using TMS as the internal standard. Infrared spectra were determined on a Thermo-Nicolet 670 Nexus FT-IR spectrometer (Waltham, MA, USA) using KBr disks.



Scheme 1 Synthesis of arylaminothioxopropoates **2a–g**.

Methyl 2-cyano-3-anilino-3-thioxopropoate (**2a**)

Methyl cyanoacetate (0.618 g, 6.24 mmol) in anhydrous tetrahydrofuran (8 ml) was treated with sodium (0.140 g, 6.24 mmol) and the mixture was heated under reflux under an atmosphere of nitrogen for 2 h. The solution was cooled to room temperature, treated dropwise with phenylisothiocyanate (0.977 g, 7.24 mmol), and the resulting yellow solution was stirred at room temperature for 2 h before being quenched with ice cold water. The mixture was extracted with diethylether (4×25 ml) and the aqueous phase was added dropwise to vigorously stirred, ice cold 1 M HCl, yielding a yellow precipitate. The precipitate was washed with water and crystallized from ethanol to give the thioxopropoate **2a** as yellow crystals in 71% yield; mp 115–116°C; ¹H NMR (CDCl₃): δ 3.82 (s, 3H, OCH₃), 4.71 (s, 1H, CH), 7.25–7.28 (m, 2H, ArH), 7.31–7.49 (m, 3H, ArH), 11.68 (s, 1H, exchangeable with D₂O, NH); ¹³C NMR (CDCl₃): δ 51.9, 72.8, 118.9, 126.1, 128.7, 129.8, 137.0, 168.1, 169.2; FT-IR: ν 3134 (NH), 3063, 2959, 2201 (CN), 1680 (C=O), 1544, 1438, 1377, 1263, 1194, 1028, 772/cm. Analysis calculated (calcd) for C₁₁H₁₀N₂O₂S: C, 56.39; H, 4.30; N, 11.96%. Found: C, 56.44; H, 4.39; N, 11.81%.

The following thioxopropoates **2b–g** were made by the same procedure.

Methyl 3-(2-bromoanilino)-2-cyano-3-thioxopropoate (**2b**)

Yellow solid; yield 76%; mp 116–117°C; ¹H NMR (CDCl₃): δ 3.80 (s, 3H, OCH₃), 4.68 (s, 1H, CH), 7.25–7.45 (m, 3H, ArH), 7.70 (d, *J*=7.5 Hz, 1H, ArH), 11.61 (s, 1H, exchangeable with D₂O, NH) ppm;

¹³C NMR (CDCl₃): δ 52.1, 73.4, 118.7, 121.6, 128.4, 128.5, 130.2, 133.8, 135.98, 167.8, 169.3; FT-IR: ν 3150 (NH), 3060, 3020, 2952, 2198 (CN), 1663 (C=O), 1554, 1435, 1273, 1022, 767/cm. Analysis calcd for C₁₁H₉BrN₂O₂S: C, 42.19; H, 2.90; N, 8.95%. Found: C, 42.36; H, 2.78; N, 9.01%.

Methyl 3-(2-methylanilino)-2-cyano-3-thioxopropoate (**2c**)

Pale yellow solid; yield 77%; mp 119–121°C; ¹H NMR (CDCl₃): δ 2.28 (s, 3H, CH₃), 3.80 (s, 3H, OCH₃), 4.58 (s, 1H, CH), 7.20 (d, *J*=7.2 Hz, 1H, ArH), 7.22–7.33 (m, 3H, ArH), 11.45 (s, 1H, exchangeable with D₂O, NH) ppm; ¹³C NMR (CDCl₃): δ 17.7, 51.9, 71.9, 119.0, 127.2, 127.4, 129.4, 131.5, 135.4, 135.8, 168.2, 170.2; FT-IR: ν 3122 (NH), 2955, 2201 (CN), 1666 (C=O), 1541, 1443, 1368, 1270, 1196, 1025, 785/cm. Analysis calcd for C₁₂H₁₂N₂O₂S: C, 58.05; H, 4.87; N, 11.28%. Found: C, 58.21; H, 4.69; N, 11.33%.

Methyl 3-(3-bromoanilino)-2-cyano-3-thioxopropoate (**2d**)

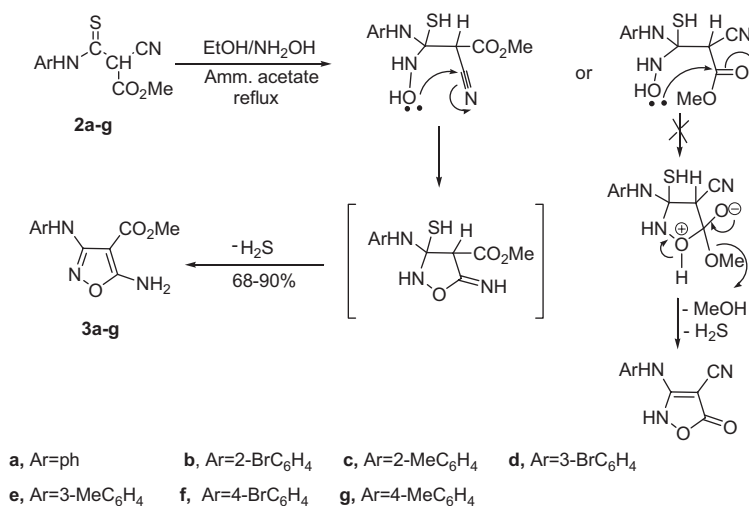
Yellow solid; yield 74%; mp 118–120°C; ¹H NMR (CDCl₃): δ 3.83 (s, 3H, OCH₃), 4.77 (s, 1H, CH), 7.16 (d, *J*=8.1 Hz, 1H, ArH), 7.22–7.46 (m, 2H, ArH), 7.53 (d, *J*=7.5 Hz, 1H, ArH), 11.70 (s, 1H, exchangeable with D₂O, NH); ¹³C NMR (CDCl₃): δ 52.1, 73.4, 118.7, 123.1, 124.7, 129.1, 131.0, 131.7, 138.1, 168.0, 168.9; FT-IR: ν 3147 (NH), 3065, 2951, 2202 (CN), 1660 (C=O), 1547, 1433, 1271, 1021, 774/cm. Analysis calcd for C₁₁H₉BrN₂O₂S: C, 42.19; H, 2.90; N, 8.95%. Found: C, 42.41; H, 2.82; N, 9.14%.

Methyl 3-(3-methylanilino)-2-cyano-3-thioxopropoate (**2e**)

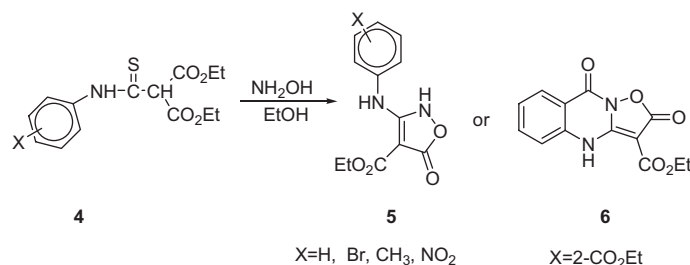
Orange solid; yield 77%; mp 121–123°C; ¹H NMR (CDCl₃): δ 2.36 (s, 3H, CH₃), 3.78 (s, 3H, OCH₃), 4.68 (s, 1H, CH), 7.04 (s, 1H, ArH), 7.18 (d, *J*=7.2 Hz, 1H, ArH), 7.27–7.32 (m, 2H, ArH), 11.62 (s, NH, 1H, exchangeable with D₂O); ¹³C NMR (CDCl₃): δ 21.3, 51.9, 71.8, 119.0, 123.1, 126.6, 127.7, 129.5, 136.8, 140.0, 168.1, 169.3; FT-IR: ν 3158 (NH), 3062, 2953, 2594, 2199 (CN), 1658, 1547, 1435, 1370, 1276, 1193, 1027, 771/cm. Analysis calcd for C₁₂H₁₂N₂O₂S: C, 58.05; H, 4.87; N, 11.28%. Found: C, 58.32; H, 4.79; N, 11.48%.

Methyl 3-(4-bromoanilino)-2-cyano-3-thioxopropoate (**2f**)

Yellow solid; yield 84%; mp 117–119°C; ¹H NMR (CDCl₃): δ 3.79 (s, 3H, OCH₃), 4.74 (s, 1H, CH), 7.14 (d, *J*=7.2 Hz, 2H, ArH), 7.56 (d,



Scheme 2 Synthesis of methyl 5-amino-3-arylaminoisoxazole-4-carboxylates **3a–g**.



Scheme 3 Synthesis of 3-arylaminoisoxazol-5(2H)-ones or ethyl 2,9-dioxo-4,9-dihydro-2H-isoxazolo[3,2-*b*]quinazoline-3-carboxylate.

$J=7.2$ Hz, 2H, ArH), 11.62 (s, 1H, exchangeable with D₂O, NH); ¹³C NMR (CDCl₃): δ 52.1, 73.2, 118.8, 122.4, 127.7, 132.9, 135.9, 168.0, 169.0; FT-IR: ν 3142 (NH), 3062, 3001, 2952, 2197 (CN), 1662 (C=O), 1551, 1440, 1269, 1016, 776/cm. Analysis calcd for C₁₁H₉BrN₂O₂S: C, 42.19; H, 2.90; N, 8.95%. Found: C, 42.01; H, 3.19; N, 8.72%.

Methyl 3-(4-methylanilino)-2-cyano-3-thioxopropanoate (2g)

Brown solid; yield 88%; mp 117–118°C; ¹H NMR (CDCl₃): δ 2.40 (s, 3H, CH₃), 3.84 (s, 3H, OCH₃), 4.68 (s, 1H, CH), 7.15 (d, $J=8.1$ Hz, 2H, ArH), 7.26 (d, $J=8.1$ Hz, 2H, ArH), 11.59 (s, 1H, exchangeable with D₂O, NH); ¹³C NMR (CDCl₃): δ 21.1, 51.9, 72.2, 119.1, 126.1, 130.4, 134.4, 138.9, 168.1, 169.5; FT-IR: ν 3154 (NH), 3069, 3004, 2955, 2197 (CN), 1667 (C=O), 1549, 1439, 1372, 1269, 1192, 1024, 778/cm. Analysis calcd for C₁₂H₁₂N₂O₂S: C, 58.05; H, 4.87; N, 11.28%. Found: C, 58.32; H, 4.65; N, 11.48%.

Methyl 5-amino-3-anilinoisoxazole-4-carboxylate (3a) To a solution of **5a** (0.230 g, 1 mmol), in ethanol (20 ml), were added hydroxylamine hydrochloride (0.070 g, 1 mmol) and ammonium acetate (0.250 g). The mixture was heated under reflux for 12 h, and then poured onto ice cold water. The resulting solid was filtered off, washed with cold water, dried and crystallized from ethanol to give the desired product as white needles in 75% yield; mp 136–137°C; ¹H NMR (DMSO-*d*₆): δ 3.72 (s, 3H, OCH₃), 6.89–7.40 (m, 5H, ArH), 7.80 (s, 2H, exchangeable with D₂O, NH₂), 8.03 (s, 1H, exchangeable with D₂O, NH); ¹³C NMR (DMSO-*d*₆): δ 51.3, 77.0, 118.0, 121.6, 129.4, 140.2, 159.4, 163.9, 169.8 (C=O); FT-IR: ν 3484, 3300 (NH₂), 3273 (NH), 3056, 2948, 1672 (C=O), 1648, 1605, 1587, 1556, 1479, 779/cm. Analysis calcd for C₁₁H₁₁N₃O₃: C, 56.65; H, 4.75; N, 18.02%. Found: C, 56.41; H, 4.89; N, 18.27%.

The methyl 5-amino-3-arylaminoisoxazole-4-carboxylates **3b–g** were made by the same method.

Methyl 5-amino-3-(2-bromoanilino)isoxazole-4-carboxylate (3b)

White needles; yield 90%; mp 155–157°C; ¹H NMR (DMSO-*d*₆): δ 3.78 (s, 3H, OCH₃), 6.88 (t, $J=7.2$ Hz, 1H, ArH), 7.37 (t, $J=7.5$ Hz, 1H, ArH), 7.62 (d, $J=7.5$ Hz, 1H, ArH), 7.97 (s, 2H, exchangeable with D₂O, NH₂), 8.04 (d, $J=8.0$ Hz, 1H, ArH), 8.75 (s, 1H, exchangeable with D₂O, NH); ¹³C NMR (DMSO-*d*₆): δ 51.5, 77.1, 118.9, 122.8, 128.6, 129.3, 132.9, 137.8, 159.2, 163.5, 169.6 (C=O); FT-IR: ν 3446, 3358 (NH₂), 3321 (NH), 2956, 1678 (C=O), 1602, 1550, 1435, 778/cm. Analysis calcd for C₁₁H₁₀BrN₃O₃: C, 42.33; H, 3.23; N, 13.46%. Found: C, 42.41; H, 3.03; N, 13.57%.

Methyl 5-amino-3-(2-methylanilino)isoxazole-4-carboxylate (3c)

White needles; yield 77%; mp 137–138°C; ¹H NMR (DMSO-*d*₆): δ 2.48 (s, 3H, CH₃), 3.78 (s, 3H, OCH₃), 6.85 (t, $J=7.2$ Hz, 1H, ArH), 7.07–7.18 (m, 2H, ArH), 7.82 (d, $J=8.4$ Hz, 1H, ArH), 7.89 (s,

2H, exchangeable with D₂O, NH₂), 8.17 (s, 1H, exchangeable with D₂O, NH); ¹³C NMR (DMSO-*d*₆): δ 17.6, 51.4, 77.1, 117.6, 121.4, 124.3, 127.3, 130.6, 138.6, 159.5, 164.3, 169.5 (C=O); FT-IR: ν 3422 (NH₂), 3322 (NH), 3030, 2950, 1691 (C=O), 1637, 1602, 1562, 1465, 780/cm. Analysis calcd for C₁₂H₁₃N₃O₃: C, 58.29; H, 5.30; N, 16.99%. Found: C, 58.01; H, 5.45; N, 16.88%.

Methyl 5-amino-3-(3-bromoanilino)isoxazole-4-carboxylate (3d)

White needles; yield 68%; mp 141–142°C; ¹H NMR (DMSO-*d*₆): δ 3.80 (s, 3H, OCH₃), 7.07 (d, $J=7.8$ Hz, 1H, ArH), 7.21 (t, $J=7.2$ Hz, 1H, ArH), 7.43 (d, $J=7.5$ Hz, 1H, ArH), 7.80 (s, 1H, ArH), 7.90 (s, 2H, exchangeable with D₂O, NH₂), 8.19 (s, 1H, exchangeable with D₂O, NH); ¹³C NMR (DMSO-*d*₆): δ 51.3, 77.1, 117.1, 120.3, 122.3, 124.0, 131.2, 141.9, 159.1, 163.6, 169.9 (C=O); FT-IR: ν 3448, 3354 (NH₂), 3315 (NH), 2957, 1674 (C=O), 1610, 1562, 1431, 771/cm. Analysis calcd for C₁₁H₁₀BrN₃O₃: C, 42.33; H, 3.23; N, 13.46%. Found: C, 42.21; H, 3.44; N, 13.59%.

Methyl 5-amino-3-(3-methylanilino)isoxazole-4-carboxylate (3e)

Pale brown needles; yield 83%; mp 136–138°C; ¹H NMR (DMSO-*d*₆): δ 2.47 (s, 3H, CH₃), 3.74 (s, 3H, OCH₃), 6.72 (d, $J=7.0$ Hz, 1H, ArH), 7.15 (t, $J=7.2$ Hz, 1H, ArH), 7.17–7.25 (m, 2H, ArH), 7.83 (s, 2H, exchangeable with D₂O, NH₂), 8.02 (s, 1H, exchangeable with D₂O, NH); ¹³C NMR (DMSO-*d*₆): δ 21.6, 51.3, 77.0, 115.1, 118.4, 122.3, 129.2, 138.6, 140.3, 159.4, 163.9, 169.8 (C=O); FT-IR: ν 3484, 3305 (NH₂), 3276 (NH), 2921, 1678 (C=O), 1648, 1601, 1560, 1470, 776/cm. Analysis calcd for C₁₂H₁₃N₃O₃: C, 58.29; H, 5.30; N, 16.99%. Found: C, 58.39; H, 5.22; N, 16.75%.

Methyl 5-amino-3-(4-bromoanilino)isoxazole-4-carboxylate (3f)

White needles; yield 80%; mp 150–151°C; ¹H NMR (DMSO-*d*₆): δ 3.74 (s, 3H, OCH₃), 7.09 (d, $J=7.2$ Hz, 2H, ArH), 7.44 (d, $J=7.2$ Hz, 2H, ArH), 7.89 (s, 2H, exchangeable with D₂O, NH₂), 8.16 (s, 1H, exchangeable with D₂O, NH); ¹³C NMR (DMSO-*d*₆): δ 51.3, 77.0, 112.9, 120.1, 132.0, 139.8, 159.2, 163.7, 169.9 (C=O); FT-IR: ν 3466 (NH₂), 3316 (NH), 2938, 1673 (C=O), 1650, 1598, 1552, 1474, 780/cm. Analysis calcd for C₁₁H₁₀BrN₃O₃: C, 42.33; H, 3.23; N, 13.46%. Found: C, 42.14; H, 3.37; N, 13.69%.

Methyl 5-amino-3-(4-methylanilino)isoxazole-4-carboxylate (3g)

White needles; yield 69%; mp 172°C (dec); ¹H NMR (DMSO-*d*₆): δ 2.48 (s, 3H, CH₃), 3.75 (s, 3H, OCH₃), 7.08 (d, $J=7.8$ Hz, 2H, ArH), 7.34 (d, $J=7.8$ Hz, 2H, ArH), 7.84 (s, 2H, exchangeable with D₂O, NH₂), 7.98 (s, 1H, exchangeable with D₂O, NH); ¹³C NMR (DMSO-*d*₆): δ 20.7, 51.2, 76.9, 117.7, 129.7, 130.2, 137.9, 159.4, 163.9, 169.8 (C=O). FT-IR: ν 3483, 3344 (NH₂), 3224 (NH), 2949, 1672 (C=O), 1649, 1601, 1586, 1555, 1473, 778/cm. Analysis calcd for C₁₂H₁₃N₃O₃: C, 58.29; H, 5.30; N, 16.99%. Found: C, 58.38; H, 5.12; N, 17.08%.

Acknowledgements

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