Synthesis of New Ethyl 3-Amino-4-arylfuran-2-carboxylates

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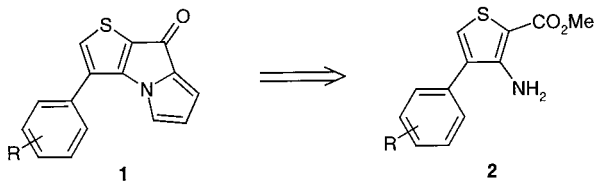
Abstract: An efficient method for the preparation of new ethyl 3-amino-4-arylfuran-2-carboxylates is described. The synthesis proceeds via the corresponding hydroxyacrylonitrile sodium salt and an intermediate malonate vinyl ether. The last step of ring closure afforded the ethyl 3-amino-4-arylfuran-2-carboxylates in 15% to 40% yields.

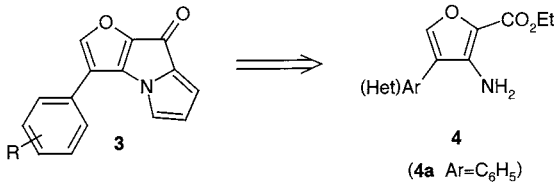
Key words: furans, amino esters, ring closure

We recently reported that a series 3-aryl-8*H*-thieno[2,3-*b*]pyrrolizin-8-ones **1** possess a very important antimitotic activity in the nanomolar range towards various cell lines. These compounds were prepared in several steps starting from 3-amino-4-arylthiophen-2-carboxylates **2**[1] (Scheme 1).



Scheme 1

During the course of a project aimed at preparing bioisosters of compounds **1** and particularly furan analogues **3**, we needed a general route for the preparation of 3-amino-4-arylfuran-2-carboxylates **4**. At the beginning of this study, an in depth survey of the literature showed only one description of one of this type of compound: the ethyl 3-amino-4-phenylfuran-2-carboxylate (**4a**), which was obtained by Gewald in very poor yield[2] (Scheme 2).



Scheme 2

Although, several groups have published recent work on substituted 3-aminofuran-2-carboxylates, none of these papers were concerned with the title compounds **4**. Redman[3] has described an efficient method limited to the preparation of 5-substituted 3-aminofuran-2-carboxylate esters **5** based on the reaction of an α-cyanoketone with ethyl glycolate under Mitsunobu conditions followed by an intramolecular ring closure with an appropriate base (Figure). A second recent publication[4] describes the synthesis of 3-amino-4-(arylmethyl)furan-2-carboxylate esters **6** by reaction of 2-arylmethyl-3-hydroxyacrylonitrile with diethyl chloromalonate followed by ring closure in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN). We therefore decided to investigate the synthesis of the new compounds **4**.

At the initiation of this project, three routes A, B, C were envisaged starting from 2-aryl-3-hydroxyacrylonitriles sodium salts **7a**–**j** as depicted in Scheme 3. The first common step of these three routes was the formylation[5] of the corresponding arylacetonitriles **8a**–**j** with sodium methoxide and ethyl formate which gave **7a**–**j** with good yields. These sodium salts **7a**–**j** were easily purified with diethyl ether and appeared very stable over several months as underlined by Morris[4] for compounds **6**.

Figure

The first route A we tested to prepare the ethyl 3-amino-4-arylfuran-2-carboxylates **4a**–**j** used a method for which we have acquired good experience during the preparation of thiophenes.[6] Thus, in the second step the sodium salt **7b** gave the 2-aryl-2-cyanovinyltosylate **9b** by reaction with tosyl chloride in DMF, but unfortunately, **9b** in the presence of ethyl glycolate and NaOEt or other bases such as *t*-BuOK, never furnished the furan **4b** but in all cases led to an unworkable mixture.

The second route B used the cyanovinyl ether **10b** prepared by reaction of **7b** with ethyl bromoacetate in DMF. However, and as opposed to what Gewald[2] had described concerning the ring closure of this type of compounds, all our attemps to perform a ring closure using different bases including Et_3N, NaOEt, *t*-BuOK, DBN always failed. Only the cyanovinyl ether **11b** was isolated when NaOEt or DBN were used in ethanol. Facing these difficulties and in the light of the recent works of Elliot[7] and Morris,[4] we

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investigated route C, using a diethyl chloromalonate derivative in place of ethyl bromoacetate. The reaction of **7b** with diethyl chloromalonate in DMF gave the crude malonic ester intermediate **12b** as an orange syrup. This product was found to be unstable and its purification through silica gel gave unsatisfactory results. This observation was the reason why we decided to use **12b** without any purification directly in ethanol to which DBN was added and the mixture was stirred overnight at room temperature. Finally in a rather unexpected way, the ethyl 4-(3,4-dimethoxyphenyl)-3-aminofuran-2-carboxylates **4b** was isolated in 37% yield. In order to study and to extend this methodology, we then synthesized a series of amino esters with various aryl substituents **4a**–**g** and heteroaryl substituents **4h**–**j** in satisfactory yields (Scheme 3).

In summary, contrary to what had been described in the past, we have developed an efficient methodology for the preparation of 3-amino-4-arylfuran-2-carboxylate esters in three steps from economical and commercially available starting materials. These new compounds could be very interesting building blocks for the development of furan chemistry.

Commercial reagents were used as received without additional purification. Melting points were determined on a Kofler melting point apparatus and are uncorrected. IR spectra were taken with a Genesis Series FTIR spectrometer. ^{1}H NMR (400 MHz) were recorded on a JEOL Lambda 400 Spectrometer. Chemical shifts are expressed in parts per million downfield from TMS as an internal standard. Elemental analyses for new compounds were performed at the 'Institut de Recherche en Chimie Organique Fine' (Rouen).

2-Aryl-3-hydroxyacrylonitrile Sodium Salts 7a–j; General Procedure

Arylacetonitrile **8a**–**j** (100 mmol) was added dropwise to a solution of ethyl formate (8.9 mL, 110 mmol) and NaOMe (5.9 g, 110 mmol) in MeOH (150 mL). The mixture was stirred for 2 h at reflux. The resulting precipitate was collected and washed with Et_2O (100 mL).

3-Hydroxy-2-phenylacrylonitrile Sodium Salt (7a)[6]

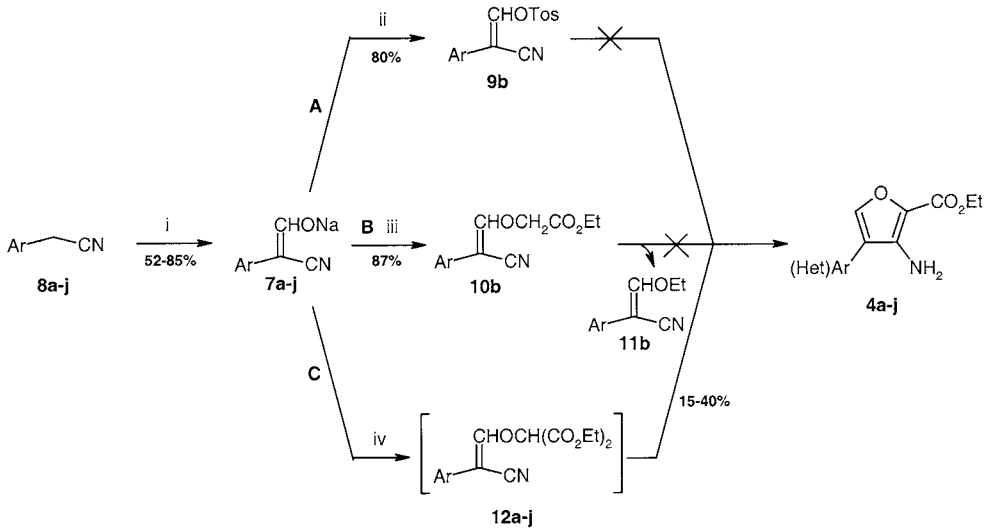
From phenylacetonitrile (**8a**; 11.7 g); white powder (13.54 g, 81%); mp >260 °C.

IR (KBr): 2170 cm^{-1} (CN).

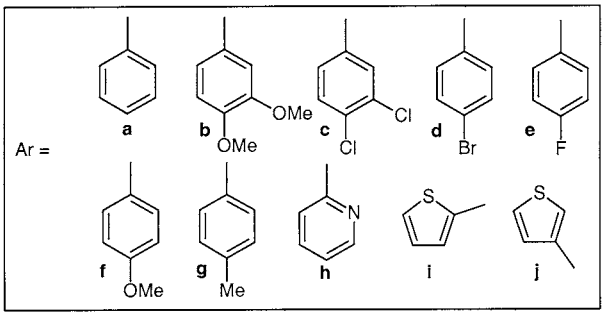
2-(3,4-Dimethoxyphenyl)-3-hydroxyacrylonitrile Sodium Salt (7b)

From (3,4-dimethoxyphenyl)acetonitrile (**8b**; 17.7 g); white powder (14.08 g, 62%); mp >260 °C.

IR (KBr): 2166 cm^{-1} (CN).



i) ethylformate, sodium methoxide, 60 °C, 2 h, MeOH ; ii) tosyl chloride, rt, 3 h, DMF ; iii) ethylbromoacetate, 5 h, rt, DMF ; iv) diethylchloromalonate, rt, 5 h, DMF ; v) 1,5-diazabicyclo[4.3.0]non-5-ene, rt, 10 h, EtOH.



Scheme 3

2-(3,4-Dichlorophenyl)-3-hydroxyacrylonitrile Sodium Salt (7c)
From (3,4-dichlorophenyl)acetonitrile (**8c**;1 8.6 g); white powder (18.41 g, 78%); mp >260 °C.

IR (KBr): 2172 cm^{-1} (CN).

2-(4-Bromophenyl)-3-hydroxyacrylonitrile Sodium Salt (7d)
From (4-bromophenyl)acetonitrile (**8d**; 19.6 g); beige powder (17.71 g, 72%); mp >260 °C.

IR (KBr): 2170 cm^{-1} (CN).

2-(4-Fluorophenyl)-3-hydroxyacrylonitrile Sodium Salt (7e)
From (4-fluorophenyl)acetonitrile (**8e**; 13.5 g); beige powder (15.55 g, 84%); mp >260 °C.

IR (KBr): 2175 cm^{-1} (CN).

3-Hydroxy-2-(4-methoxyphenyl)acrylonitrile Sodium Salt (7f)[6]
From (4-methoxyphenyl)acetonitrile (**8f**; 14.7 g); white powder (10.25 g, 52%); mp >260 °C.

IR (KBr): 2170 cm^{-1} (CN).

3-Hydroxy-2-(4-methylphenyl)acrylonitrile Sodium Salt (7g)[6]
From (4-methylphenyl)acetonitrile (**8g**;13.1 g); white powder (11.77 g, 65%); mp >260 °C.

IR (KBr): 2180 cm^{-1} (CN).

3-Hydroxy-2-(pyridin-2-yl)acrylonitrile Sodium Salt (7h)
From (2-pyridinyl)acetonitrile (**8h**; 11.8 g); beige powder (10.26 g, 61%); mp >260 °C.

IR (KBr): 2171 cm^{-1} (CN).

3-Hydroxy-2-(thien-2-yl)acrylonitrile Sodium Salt (7i)
From (2-thienyl)acetonitrile (**8i**; 12.3 g); white powder (14.20 g, 82%); mp >260 °C.

IR (KBr): 2168 cm^{-1} (CN).

3-Hydroxy-2-(thien-3-yl)acrylonitrile Sodium Salt (7j)
From (3-thienyl)acetonitrile (**8j**; 12.3 g); white powder (14.72 g, 85%); mp >260 °C.

IR (KBr): 2170 cm^{-1} (CN).

Ethyl 3-Amino-4-arylfuran-2-carboxylates 4a–j; General Procedure
To 2-aryl-3-hydroxyacrylonitrile sodium salt **7a–j** (50 mmol) in DMF (80 mL) was added diethyl chloromalonate (8.9 mL, 55 mmol). The reaction mixture was allowed to stir for 5 h at r.t. and then the solvent was removed under reduced pressure. The dark oil was extracted with CH_2Cl_2 (100 mL), the organic layer was washed with H_2O (2 × 100 mL), dried ($CaCl_2$) and evaporated to give an orange syrup. The syrup was dissolved in EtOH (50 mL) to which 1.5-diazabicyclo[4.3.0]non-5-ene (6.8 mL, 55 mmol) was added and the mixture was allowed to stir overnight. The solution was concentrated and an analytical sample was prepared by silica gel chromatography (EtOAc–cyclohexane, 1:2).

Ethyl 3-Amino-4-phenylfuran-2-carboxylate (4a)[2]
From **7a** (8.4 g); yellow powder (1.7 g, 15%); mp 67–68 °C.

IR (KBr): 3472 (NH), 3369 (NH), 2961 (CH), 1671 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 1.28 (t, 3 H, *J* = 7.1 Hz, CH_3), 4.27 (q, 2 H, *J* = 7.1 Hz, CH_2), 4.51 (br s, 2 H, NH_2), 7.37 (m, 6 H, H_{phenyl} and H_{furan}).

Ethyl 3-Amino-4-(3,4-dimethoxyphenyl)furan-2-carboxylate (4b)
From **7b** (11.4 g); yellow powder (5.4 g, 37%); mp 117 °C.

IR (KBr): 3467 (NH), 3370 (NH), 2962 (CH), 1670 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 1.41 (t, 3 H, *J* = 7.1 Hz, CH_3), 3.88 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 4.39 (q, 2 H, *J* = 7.1 Hz, CH_2), 4.69 (br s, 2 H, NH_2), 6.82 (s, 1 H, H-2_{phenyl}), 6.95 (m, 2 H, H-5 and H-6_{phenyl}), 7.36 (s, 1 H, H_{furan}).

Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found : C, 61.87; H, 5.92; N, 4.96.

Ethyl 3-Amino-4-(3,4-dichlorophenyl)furan-2-carboxylate (4c)
From **7c** (11.8 g); yellow powder (4.6 g, 31%); mp 81 °C.

IR (KBr): 3450 (NH), 3339 (NH), 2989 (CH), 1674 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 1.39 (t, 3 H, *J* = 7.1 Hz, CH_3), 4.38 (q, 2 H, *J* = 7.1 Hz, CH_2), 4.69 (br s, 2 H, NH_2), 7.27 (d, 1 H, *J* = 8.4 Hz, H-5_{phenyl}), 7.40 (s, 1 H, H_{furan}), 7.51 (s, 1 H, H-2_{phenyl}), 7.53 (d, 1 H, *J* = 8.4 Hz, H-6_{phenyl}).

Anal. Calcd for $C_{13}H_{11}Cl_2NO_3$: C, 52.02; H, 3.69; N, 4.67. Found : C, 52.07; H, 3.97; N, 5.05.

Ethyl 3-Amino-4-(4-bromophenyl)furan-2-carboxylate (4d)
From **7d** (12.3 g); beige powder (4.3 g, 28%); mp 65 °C.

IR (KBr): 3453 (NH), 3356 (NH), 2978 (CH), 1675 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 1.41 (t, 3 H, *J* = 7.2 Hz, CH_3), 4.39 (q, 2 H, *J* = 7.2 Hz, CH_2), 4.67 (br s, 2 H, NH_2), 7.30 (d, 2 H_{phenyl}, *J* = 8.4 Hz), 7.39 (s, 1 H_{furan}), 7.57 (d, 2 H_{phenyl}, *J* = 8.4 Hz).

Anal. Calcd for $C_{13}H_{12}BrNO_3$: C, 50.34; H, 3.90; N, 4.52. Found: C, 50.35; H, 4.12; N, 4.69.

Ethyl 3-Amino-4-(4-fluorophenyl)furan-2-carboxylate (4e)
From **7e** (9.3 g); yellow powder (4.7 g, 38%); mp 98 °C.

IR (KBr): 3440 (NH), 3339 (NH), 2984 (CH), 1673 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 1.41 (t, 3 H, *J* = 7.2 Hz, CH_3), 4.39 (q, 2 H, *J* = 7.2 Hz, CH_2), 4.64 (br s, 2 H, NH_2), 7.14 (m, 2 H_{phenyl}), 7.35 (s, 1 H_{furan}), 7.39 (m, 2 H_{phenyl}).

Anal. Calcd for $C_{13}H_{12}FNO_3$: C, 62.65; H, 4.85; N, 5.62. Found: C, 62.73; H, 4.98; N, 5.74.

Ethyl 3-Amino-4-(4-methoxyphenyl)furan-2-carboxylate (4f)
From **7f** (9.9 g); yellow powder (4.4 g, 34%), mp 87 °C.

IR (KBr): 3465 (NH), 3368 (NH), 2954 (CH), 1667 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 1.33 (t, 3 H, *J* = 7.1 Hz, CH_3), 4.32 (q, 2 H, *J* = 7.1 Hz, CH_2), 4.58 (br s, 2 H, NH_2), 6.90 (d, 2 H_{phenyl}, *J* = 8.8 Hz,), 7.24 (s, 1 H_{furan}), 7.26 (d, 2 H_{phenyl}, *J* = 8.8 Hz).

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.48; H, 5.82; N, 5.55.

Ethyl 3-Amino-4-(4-methylphenyl)furan-2-carboxylate (4g)
From **7g** (9.1 g); yellow powder (3.8 g, 31%); mp 68 °C.

IR (KBr): 3478 (NH), 3380 (NH), 2963 (CH), 1672 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 1.41 (t, 3 H, *J* = 7.2 Hz, CH_3), 2.39 (s, 3 H, CH_3), 4.38 (q, 2 H, *J* = 7.2 Hz, CH_2), 4.69 (br s, 2 H, NH_2), 7,25 (d, 2 H_{phenyl}, *J* = 8.1 Hz), 7.31 (d, 2 H_{phenyl}, *J* = 8.1 Hz), 7.36 (s, 1 H_{furan}).

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.59; H, 6.41; N, 5.89.

Ethyl 3-Amino-4-(pyridin-2-yl)furan-2-carboxylate (4h)
From **7h** (8.4 g); yellow powder (3.7 g, 32%); mp 154 °C.

IR (KBr): 3392 (NH), 3284 (NH), 2969 (CH), 1678 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 1.35 (t, 3 H, *J* = 7.1 Hz, CH_3), 4.33 (q, 2 H, *J* = 7.1 Hz, CH_2), 6.45 (br s, 2 H, NH_2), 6.99 (m, 1 H, H-5), 7.33 (d, 1 H, *J* = 8.1 Hz, H-6), 7.49 (s, 1 H_{furan}), 7,63 (m, 1 H, H-4); 8.46 (d, 1 H, *J* = 4.5 Hz, H-3).

Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.05. Found: C, 62.32; H, 5.28; N, 11.79.

Ethyl 3-Amino-4-(thien-2-yl)furan-2-carboxylate (4i)
From **7i** (8.7 g); yellow powder (3.6 g, 30%); mp 60–61 °C.

IR (KBr): 3456 (NH), 3364 (NH), 2984 (CH), 1673 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 1.32 (t, 3 H, *J* = 7.1 Hz, CH_3), 4.30 (q, 2 H, *J* = 7.1 Hz, CH_2), 4.71 (br s, 2 H, NH_2), 7.05 (m, 2 H, H-3 and H-$5_{thiophene}$), 7.26 (dd, 1 H, *J* = 1.7, 1.8 Hz, H-$4_{thiophene}$), 7.36 (s, 1 H_{furan}).

Anal. Calcd for $C_{11}H_{11}NO_3S$: C, 55.68; H, 4.67; N, 5.90. Found: C, 55.97; H, 5.01; N, 6.02.

Ethyl 3-Amino-4-(thien-3-yl)furan-2-carboxylate (4j)
From **7j** (8.7 g); yellow powder (3.9 g, 33%); mp 87 °C.

IR (KBr): 3470 (NH), 3376 (NH), 2984 (CH), 1668 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 1.41 (t, 3 H, *J* = 7.2 Hz, CH_3), 4.38 (q, 2 H, *J* = 7.2 Hz, CH_2), 4.69 (br s, 2 H, NH_2), 7.18 (d, 1 H, *J* = 4.2 Hz, H-$4_{thiophene}$), 7.35 (d, 1 H, *J* = 3.0 Hz, H-$2_{thiophene}$), 7.41 (s, 1 H_{furan}), 7.44 (dd, 1 H, *J* = 4.2, 3.0 Hz, H-$5_{thiophene}$).

Anal. Calcd for $C_{11}H_{11}NO_3S$: C, 55.68; H, 4.67; N, 5.90. Found: C, 55.68; H, 4.81; N, 5.95.

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