A Novel and Convenient Synthesis of 'Reversed' Diamidino 2,5-Aryl- and 2,5-Azaheterocycle-Substituted Furans

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Abstract: A novel and convenient two-step synthesis of 'reversed' diamidino 2,5-aryl- and 2,5-azaheterocycle-substituted furans is described. The key step, a Stille cross-coupling reaction between *N*-(bromoaryl)arenecarboxamidines and 2,5-bis(tri-*n*-butylstannyl)furan, is reported for the first time.

Key words: reversed amidines, thioimidates, Stille cross-coupling reaction, furans, N-heterocycles

'Reversed' amidines refer to a series of potentially dicationic compounds that have the imino group attached to an 'anilino' nitrogen in contrast to the original amidines in which the imino group is directly attached to the aryl ring. We first reported a series of 2,5-diarylfuran reversed diamidines that showed strong DNA binding properties and antimicrobial activities against *Candida albicans* and *Mycobacterium tuberculosis*.[1] Recently, 'reversed' amidines have been of much interest, since a series of 2,5-bis(4-{[imino(2-pyridyl)methyl]amino}phenyl)furans **1** (Figure 1) were found to be quite effective against *Trypanosoma cruzi*, *Leishmania donovani*, and *Leishmania infantum*, which infect millions of people in large parts of the world.[2,3]

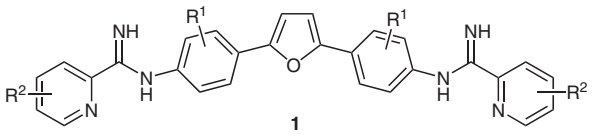
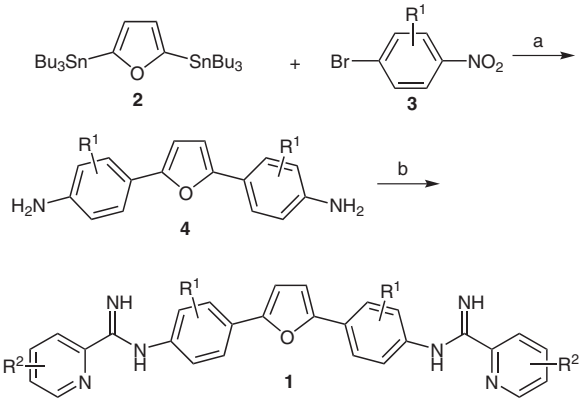


Figure 1 2,5-Diarylfuran reversed diamidines

Our initial preparation of the 'reversed' amidines **1** was achieved in three steps[1,2] beginning with a Stille coupling reaction between 2,5-bis(tri-*n*-butylstannyl)furan (**2**) and 4-bromonitrobenzenes **3** to form 2,5-bis(4-nitrophenyl)furans,[4] which were reduced to form the corresponding 2,5-bis(4-aminophenyl)furans **4** (Scheme 1). The 'reversed' amidines **1** were obtained by reaction of diamines **4** with *S*-(2-naphthylmethyl)thioimidates. It is necessary to prepare the thioimidates in two steps from arylnitriles via the corresponding arylthioamides, which were allowed to react with 2-(bromomethyl)naphthalene.[5,6] The reaction between the thioimidates and the amines gave good yields (60–80%) of the desired reversed amidines **1** as long as the diamines were relatively electron-rich (either phenyls or phenyls substituted with electron donors).[1] However, the thioimidate reactions failed when the phenyl ring was substituted with the electron-withdrawing trifluoromethyl group or replaced with electron-deficient rings including pyridyl, pyrazinyl, or pyrimidinyl systems. Therefore, it is highly desirable to develop a new methodology for the synthesis of diarylfuran reversed amidines that is more direct and accommodates a broad structural range. This report describes the novel and convenient synthesis of reversed diamidino 2,5-aryl- and 2,5-azaheterocycle-substituted furans.



Scheme 1 *Reagents and conditions*: (a) 1. $Pd(PPh_3)_4$, 1,4-dioxane; 2. H_2, Pd/C, EtOAc, EtOH; (b) 1. *S*-(2-naphthylmethyl)-2-pyridylthioimidate hydrobromide, MeCN, EtOH; 2. 1 N aq NaOH; 3. HCl(g), EtOH.

The synthesis of *N*-(substituted phenyl)pyridine-2-carboxamidines by condensation of substituted anilines with 2-cyanopyridine in the presence of aluminum(III) chloride in moderate yields has previously been reported.[7] However, low solubility of some amidine products in organic solvents and the presence of aluminum salts led to emulsion formation during the reaction workup, which resulted in difficulty of isolation of pure amidines.[8,9] The synthesis of arylbenzamidines by reaction of substituted benzonitriles with anilines catalyzed by various bases was reported recently.[9] Best results were obtained when the amidine formation was carried out in tetrahydrofuran with sodium hexamethyldisilazide as a strong non-nucleophilic base.[9] We first attempted to react 2,5-bis(4-aminophenyl)furan directly with 2-cyanopyridine using sodium hexamethyldisilazide in tetrahydrofuran as previously de-

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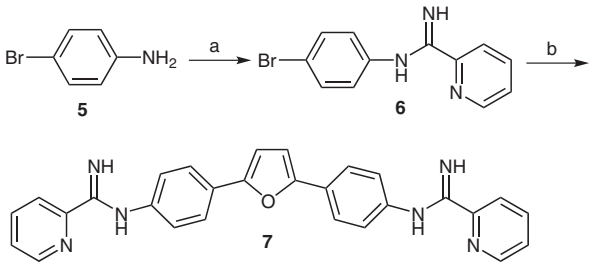
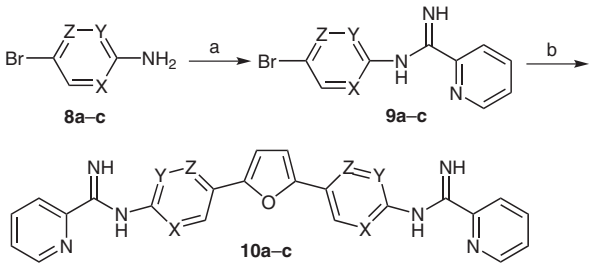
scribed,[9,10] but the 'reversed' amidines could not be isolated from the complex reaction mixture. These unfortunate results may be due, in part, to the low solubility of the putative monoamidine intermediate. We explored an alternative approach (Scheme 2), in which the bromoaryl reversed amidine **6** is first prepared in good yield by reaction of 4-bromoaniline (**5**) with 2-cyanopyridine by the reported Khanna method.[9,10] Direct Stille cross-coupling between 2,5-bis(tri-*n*-butylstannyl)furan and *N*-(bromoaryl)arenecarboxamidine **6** gave the desired bis-'reversed' amidine **7** in reasonable yield. To our knowledge, Stille coupling using unprotected *N*-(bromoaryl)arenecarboxamidines as substrates has not been reported.



Scheme 2 *Reagents and conditions*: (a) 2-cyanopyridine, NaHMDS, THF, 85%; (b) **2**, $Pd(PPh_3)_4$, xylene, 120 °C, 43%.

We explored using this methodology to prepare the reversed diamidino 2,5-azaheterocycle-substituted furans, as shown in Scheme 3. The *N*-(bromoaryl)pyridine-2-carboxamidines **9a** and **9b** were smoothly prepared in good yields (79–83%) from commercially available 5-bromopyridin-2-amine (**8a**) and 5-bromopyrazin-2-amine (**8b**) when sodium hexamethyldisilazide was used (Scheme 3). The reaction of 5-bromopyrimidin-2-amine (**8c**) with 2-cyanopyridine did not furnish product **9c** as easily under the same conditions. The starting material 5-bromopyrimidin-2-amine (**8c**) was less soluble in tetrahydrofuran and thus apparently reacts slowly, yielding a mixture which required recrystallization to provide the product **9c** (65%).

The Stille cross-coupling reaction of *N*-(bromoaryl)pyridine-2-carboxamidines **9a**–**c** with 2,5-bis(tri-*n*-butylstannyl)furan gave the desired reversed amidines **10a**–**c**



a X = N, Y = C, Z = C
b X = N, Y = C, Z = N
c X = N, Y = N, Z = C

Scheme 3 *Reagents and conditions*: (a) 2-cyanopyridine, NaHMDS, THF, 65–83%; (b) 1. **2**, $Pd(PPh_3)_4$, xylene, 120 °C; 2. HCl(g), EtOH, 72–78%.

(Scheme 3). Interestingly, the yields were higher than that for the parent product **7** (Scheme 2). It appears that the electron-deficient azahetaryl bromides are beneficial for this Stille cross-coupling reaction.

In conclusion, we have developed a novel and convenient two-step process for the synthesis of 'reversed' diamidino 2,5-aryl- and 2,5-azaheterocycle-substituted furans, which includes straight-forward product isolation. The Stille cross-coupling reaction of *N*-(bromoaryl)arenecarboxamidines with 2,5-bis(tri-*n*-butylstannyl)furan is reported for the first time.

All commercial reagents were used without purification. Melting points were determined on a Mel-Temp 3.0 melting-point apparatus, and are uncorrected. TLC analysis was carried out on silica gel 60 F254 precoated aluminum sheets, and UV light was used for detection. ^1H and ^{13}C NMR spectra were recorded on a Bruker 400-MHz spectrometer. Mass spectra were obtained from the Georgia State University Mass Spectrometry Laboratory, Atlanta, GA, USA. Elemental analysis were performed by Atlantic Microlab Inc., Norcross, GA, USA.

N-(Bromoaryl)pyridine-2-carboxamidines 6 and 9a–c; General Procedure

A soln of **5** or one of **8a**–**c** (10.0 mmol) in anhyd THF (30 mL) was added dropwise to 1 M NaHMDS in THF (10.5 mL) while the reaction mixture was magnetically stirred under N_2 at ice-bath temperature. After completed addition, the mixture was stirred for 30 min, and 2-cyanopyridine (1.07 g, 10 mmol) was added in one portion. The resulting mixture was stirred overnight at r.t. The precipitate that had formed was collected by filtration, or the reaction mixture was concentrated in vacuo to form a precipitate, which was collected by filtration; washing of the precipitate with H_2O and Et_2O and drying in vacuo gave **6** and **9a**–**c**.

N-(4-Bromophenyl)pyridine-2-carboxamidine (6)

Yield: 85%; mp 85–86 °C (Lit.[7] 85–86 °C).

^1H NMR (400 MHz, DMSO-d_6): δ = 6.68 (s, 2 H), 6.88 (d, *J* = 8.0 Hz, 2 H), 7.46 (d, *J* = 8.0 Hz, 2 H), 7.55 (m, 1 H), 7.94 (m, 1 H), 8.28 (d, *J* = 8.0 Hz, 1 H), 8.62 (d, *J* = 4.4 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 114.1, 121.3, 123.9, 125.5, 131.9, 137.1, 148.0, 149.8, 151.3, 152.0.

N-(5-Bromo-2-pyridyl)pyridine-2-carboxamidine (9a)

Yield: 83%; mp 127–129 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.12 (d, *J* = 8.4 Hz, 1 H), 7.57 (m, 1 H), 7.92 (dd, *J* = 7.2, 2.0 Hz, 1 H), 7.97 (m, 1 H), 8.42 (d, *J* = 8.0 Hz, 1 H), 8.47 (s, 1 H), 8.47 (d, *J* = 1.2 Hz, 1 H), 8.67 (d, *J* = 4.8 Hz, 1 H), 9.65 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 112.4, 121.8, 123.6, 125.8, 137.3, 140.2, 147.0, 148.3, 151.4, 155.2, 161.3.

Anal. Calcd for $C_{11}H_9BrN_4$: C, 47.68; H, 3.27; N, 20.22. Found: C, 47.70; H, 3.25; N, 20.09.

N-(5-Bromopyrazin-2-yl)pyridine-2-carboxamidine (9b)

Yield: 79%; mp 165–167 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.60 (m, 1 H), 8.00 (m, 1 H), 8.28 (d, *J* = 1.2 Hz, 1 H), 8.43 (d, *J* = 8.0 Hz, 1 H), 8.53 (d, *J* = 1.2 Hz, 1 H), 8.69 (d, *J* = 4.4 Hz, 1 H), 9.02 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 122.1, 126.2, 130.4, 137.5, 142.6, 144.2, 148.5, 150.8, 156.9, 157.3.

Anal. Calcd for $C_{10}H_8BrN_5$: C, 43.19; H, 2.90; N, 25.18. Found: C, 42.81; H, 2.86; N, 24.80.

***N*-(5-Bromopyrimidin-2-yl)pyridine-2-carboxamidine (9c)**
Yield: 65%; mp 150–152 °C (THF).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.64 (m, 1 H), 8.04 (m, 1 H), 8.44 (d, *J* = 8.0 Hz, 1 H), 8.72 (d, *J* = 2.0 Hz, 1 H), 8.84 (s, 2 H), 9.08 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 111.3, 122.1, 126.2, 137.5, 148.4, 151.0, 157.5, 158.0, 164.8.

Anal. Calcd for $C_{10}H_8BrN_5$: C, 43.19; H, 2.90; N, 25.18. Found: C, 42.97; H, 2.88; N, 24.99.

2,5-Diarylfurans 7 and 10a–c
2,5-Bis(tri-*n*-butylstannyl)furan (**2**; 0.65 g, 1.0 mmol) was added to a soln of **6** or one of **9a–c** (2.0 mmol) and $Pd(PPh_3)_4$ (0.24 g, 0.2 mmol) in anhyd xylene (20 mL) while the reaction mixture was magnetically stirred under N_2. The mixture was subsequently heated overnight at 120 °C. The resulting mixture was cooled and the precipitate that had formed was collected by filtration, washed with xylene, acetone, and Et_2O, and dried in vacuo; this gave free bases **7** and **10a–c**.

To prepare the hydrochloride salt, the free base (one of **10a–c**) was suspended in EtOH (30 mL) and treated with anhyd HCl gas for 5–10 min at ice-bath temperature, and the mixture was stirred for another 4 h. The resulting soln was concentrated in vacuo and the precipitate that had formed was collected by filtration, washed with Et_2O, and dried in vacuo; this gave hydrochloride salts **10a–c**.

2,5-Bis(4-{[imino(2-pyridyl)methyl]amino}phenyl)furan (7)
Yield: 43%; mp 221–223 °C (Lit.[1] 221–223 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.63 (s, 4 H), 6.94 (s, 2 H), 7.01 (d, *J* = 8.4 Hz, 4 H), 7.57 (m, 2 H), 7.77 (d, *J* = 8.4 Hz, 4 H), 7.95 (m, 2 H), 8.32 (d, *J* = 8.0 Hz, 2 H), 8.64 (d, *J* = 4.4 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 106.5, 121.3, 122.2, 124.4, 124.7, 125.4, 137.1, 148.0, 149.7, 151.4, 151.8, 152.5.

2,5-Bis(6-{[imino(2-pyridyl)methyl]amino}-3-pyridyl)furan Hydrochloride (10a)
Yield: 72%; mp 226–228 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.39 (s, 2 H), 7.87 (m, 2 H), 7.97 (d, *J* = 8.8 Hz, 2 H), 8.25 (m, 2 H), 7.51 (dd, *J* = 8.4, 2.4 Hz, 2 H), 8.59 (d, *J* = 8.0 Hz, 2 H), 8.93 (d, *J* = 4.8 Hz, 2 H), 9.03 (d, *J* = 2.0 Hz, 2 H), 11.28 (s, 2 H), 11.84 (s, 2 H), 12.48 (s, 2 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 111.6, 117.5, 124.9, 126.1, 130.2, 135.8, 139.9, 143.5, 145.3, 151.7, 152.0, 152.2, 160.5.

HRMS: *m*/*z* calcd for $C_{26}H_{21}N_8O$: 461.1838; found: 461.1854.

Anal. Calcd for $C_{26}H_{20}N_8O{\cdot}2HCl{\cdot}2.5H_2O$: C, 53.99; H, 4.70; N, 19.37. Found: C, 54.01; H, 4.35; N, 19.32.

2,5-Bis(5-{[imino(2-pyridyl)methyl]amino}pyrazin-2-yl)furan Hydrochloride (10b)
Yield: 76%; mp 267–269 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.52 (s, 2 H), 7.88 (m, 2 H), 8.25 (m, 2 H), 8.57 (d, *J* = 8.0 Hz, 2 H), 8.93 (d, *J* = 4.4 Hz, 2 H), 9.08 (d, *J* = 0.9 Hz, 2 H), 9.12 (d, *J* = 0.9 Hz, 2 H), 11.28 (s, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 113.2, 124.6, 128.7, 136.1, 138.3, 139.2, 139.8, 144.6, 147.4, 149.7, 151.7, 158.8.

HRMS: *m*/*z* calcd for $C_{24}H_{19}N_{10}O$: 463.1743; found: 463.1735.

Anal. Calcd for $C_{24}H_{18}N_{10}O{\cdot}3HCl{\cdot}1.4H_2O$: C, 48.27; H, 4.02; N, 23.46. Found: C, 48.25; H, 3.87; N, 23.47.

2,5-Bis(2-{[imino(2-pyridyl)methyl]amino}pyrimidin-5-yl)furan Hydrochloride (10c)
Yield: 78%; mp 262–264 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.58 (s, 2 H), 7.87 (m, 2 H), 8.23 (m, 2 H), 8.47 (d, *J* = 8.4 Hz, 2 H), 8.91 (d, *J* = 3.6 Hz, 2 H), 9.47 (s, 4 H), 11.36 (s, 2 H), 11.64 (s, 2 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 112.7, 123.6, 125.3, 130.5, 140.0, 145.2, 150.3, 151.8, 155.0, 157.3, 161.6.

HRMS: *m*/*z* calcd for $C_{24}H_{19}N_{10}O$: 463.1743; found: 463.1738.

Anal. Calcd for $C_{24}H_{18}N_{10}O{\cdot}2HCl{\cdot}H_2O$: C, 52.09; H, 4.01; N, 25.31. Found: C, 52.11; H, 3.75; N, 25.25.

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