SYNTHESIS OF 2,5-Bis-(4-CYANOPHENYL)-FURAN

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Abstract: The synthesis of 2,5-bis-(4-cyanophenyl)-furan by three different approaches is reported.

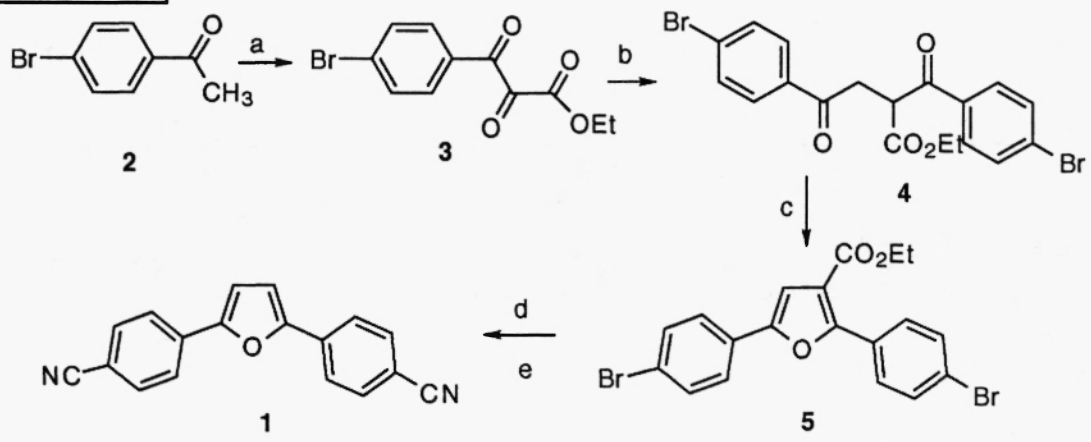
Introduction

2,5-Bis-(4-cyanophenyl)-furan (**1**) is the key intermediate in the synthesis of 2,5-bis-amidinoarylfurans (1,2). The furan bis-amidines are valuable probes of the minor groove of DNA (3-5) and have been shown to hold promise as therapeutic agents (2). Previously, we reported the synthesis of **1** in four step process which began with the preparation of 1,2-di-(4-brombenzoyl)ethene by the Friedel-Crafts reaction between bromobenzene and fumaryl chloride (1). During a program of study of 2,5-bis-amidinoarylfurans it became apparent that a more efficient method of synthesis of **1** was needed. This report describes our approaches to this problem.

Results and Discussion

Earlier a Claisen condensation approach to make the 1,4-diketone needed for the preparation of 2,5-bis-(4-bromophenyl)-3-methylfuran was used(1). The reaction sequence outline in Scheme 1 was explored based upon the earlier approach. Reaction of 4-bromoacetophenone (**2**) with diethyl carbonate in the presence of sodium hydride gave the ester **3** in good yield. Reaction of the ester **3** with 4-bromophenacyl bromide gave the 1,4-diketone **4.** Acid catalyzed cyclodehydration of the 1,4-diketone **4** was achieved to give the furan ester **5** in good yield. Saponification of **5** gave the corresponding furan-3- carboxylic acid. The carboxylic acid derivative was concurrently decarboxylated and converted into **1** by the action of CuCN in refluxing quinoline. The overall yield obtained from this four step approach was 26%.

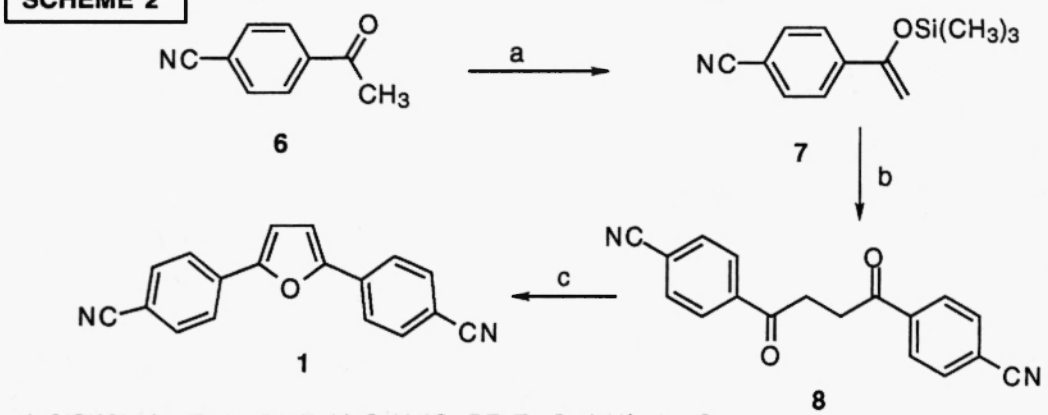
SCHEME 1



a) NaH, diethyl carbonate b) NaOEt, 4-bromophenacylbromide c) HCl, ethanol d) KOH, H_2O
e) quinoline, CuCN, reflux.

Numerous methods for oxidative coupling of acetophenone enols or their derivatives have been reported (6,7), however, the coupling yields for acetophenones bearing electron attracting substituents is often low. The method reported by Moriarty, et al using hypervalent iodine as the oxidant was explored (8). The silylated enol of 4-cyanoacetophenone (**6**) was prepared as outlined in Scheme 2. Oxidation of the enol derivative **7** gave the 1,4-diketone **8** in modest yields. The 1,4-diketone **8** was subjected to acid catalyzed cyclodehydration in acetic anhydride (1,9). The overall yield of this process was 16%.

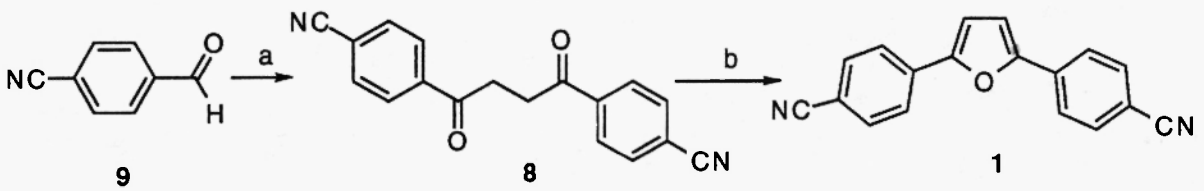
SCHEME 2



a) $ClSi(CH_3)_3$, Et_3N, DMF b) C_6H_5IO, BF_3Et_2O c) H^+, Ac_2O

The method of Stetter (10) for preparation of 1,4-diketones which employs thiazolium catalyzed nucleophlic addition of aldehydes to divinylsulfone was explored using 4-cyanobenzaldhyde (**9**) as outlined in Scheme 3. Stetter's comprehensive paper reported that the yields of 1,4-diketone were reduced when electron withdrawing groups were present in aromatic aldehydes (11). Furthermore, it was observed that the reaction fails for nitro-substituted aromatic aldehydes (12). Despite the similarity in electron withdrawing ability of cyano and nitro groups, the over all simplicity of the Stetter approach led us to attempt the reaction involving 4-cyanobenzaldehyde (**9**) as shown in Scheme 3. Employing this approach, we found that the 1,4-diketone **8** was obtained in moderate yields. The review by Stetter recommends that 3,4-dimethyl-5-(2-hydroxyethyl)thiazolium iodide be used as the catalyst for reactions involving aromatic aldehydes and that 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride be used for reactions involving aliphatic aldehydes (12). However, in this particular case we observe that use of 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride leads to yields (40%) of the 1,4-diketone **8** almost twice that obtained with 3,4-dimethyl-5-(2-hydroxyethyl)thiazolium iodide (25%). The 1,4-diketone **8** was converted into the furan **1** by cyclodehydration using acid catalysis in acetic anhydride as previously described in Scheme 2. The overall yield for the method outlined in Scheme 3 was 30%.

SCHEME 3



9 8 1

a) divinylsulfone, NaOAc, thiazolium salt b) H^+, Ac_2O

The reaction sequence employing Stetter chemistry gives better yields of 2,5-bis-(4-cyanophenyl)-furan (**1**) than the two other approaches described here, as well as the one previously published (1). The simple manipulations required for the steps outlined in Scheme 3 make it a particularly attractive process (13).

Experimental

Melting points were recorded using a Thomas Hoover(Uni-Melt) capillary melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Varian GX400 spectrometer and chemical shifts(δ) are in ppm relative to TMS and coupling constants are in Hertz. Mass spectra were recorded with a Shimadzu GC-MS 5000 instrument at 70ev chamber voltage (direct inlet system). Elemental analysis were by Atlantic Microlab Inc. (Norcross, GA).

2,5-Bis(4-cyanophenyl)-furan Method 1

Diethyl carbonate (11.8 g, 0.1 mole) in 20 ml THF was added to a suspension of NaH (2.5 g, 0.11 mole) in 50 ml THF (under N_2). After stirring for 5 m. 4'-bromoacetophenone (19.9 g, 0.1 mole) in 60 ml THF was added dropwise and the mixture was stirred overnight, the solvent was removed under vacuum, the remaining oil was treated with water, and the mixture was extracted with ether (2x100 ml). The solution was dried (Na_2SO_4) and the ether was removed to yield an oil. The oil was purified by chromatography over silica gel (elution: hexane-5:1 hexane:ether) or distillation (0.01 mm) to yield an oil 18.8 g (70%) and used as soon as possible directly in the next step. Ethyl 3-[4-bromophenyl]-3-oxopropionate (13.5 g, 0.05 mole), used as obtained above, in 20 ml dry ethanol was added to a solution of sodium ethoxide (1.15 g Na, 0.05 g-atm in 30 ml ethanol) under N_2. The solution was stirred for 30 m, cooled and 4-bromophenacyl bromide (13.85 g, 0.05 mole) in 75 ml ethanol was added slowly over a period of 40 m. The mixture was allowed to stir at room temperature for 3 days. The solvent was removed under vacuum, the oil was treated with water, extracted with ether, washed with water and dried ($MgSO_4$). The solution was filtered, the solvent removed to give a crude oil to yield 16.0 g (68%). The crude oil (0.034mole), ethyl 2,3-bis[4-bromobenzoyl]propionate, was used directly by dissolving in 75-80 ml ethanol which had been saturated with HCl at 0°C. The mixture was allowed to stir at room temperature for 24 h. The solid which formed was filtered, washed with cold ethanol and suspended in water and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and the solvent removed to yield the furan

ester **5** as a white crystalline solid 7.4 g (48%) mp 125-127°C. ^{1}H NMR ($CDCl_3$) 7.97(d, 2H, J=8.8), 7.58(d, 2H, J=8.8), 7.56 - 7.52(m, 4H), 7.07(s, 1H), 4.34(q, 2H, J=8.8), 1.38(t, 3H, J=8.8). ^{13}C NMR ($CDCl_3$) 163.2, 155.5, 151.5, 132.1, 131.5, 129.8, 128.5, 128.4, 125.5, 123.9, 122.2, 116.4, 108.7, 60.9, 14.3. MS: m/e 450 (M^+ for $C_{19}H_{14}Br_2O_3$). The ester (7.0 g, 0.015 mole) suspended into 75 ml 20% KOH and 10 ml ethanol and was heated at reflux for 4-5 h . After cooling and acidification with concentrated HCl the precipitate was filtered, washed with water, dried under vacuum to yield 5.4 g (82%) of the acid; mp 252-254°C. ^{1}H NMR ($CDCl_3$) 8.03(d, 2H, J=8.8), 7.77(d, 2H, J=8.4), 7.67(d, 2H, J=8.8), 7.62(d, 2H, J=8.4), 7.37(s, 1H), 3.4(br, 1H). ^{13}C NMR ($CDCl_3$) 163.8, 153.9, 150.8, 131.7, 131.1, 129.6, 128.2, 128.1, 125.7, 122.7, 121.2, 117.2, 109.6. MS: m/e 422 (M^+ for $C_{17}H_{10}Br_2O_3$). A mixture of 2,5-bis(4-bromophenyl)-3-furan carboxylic acid (0.85 g, 0.002 mole), CuCN (0.45 g, 0.005 mole) in 10 ml quinoline was heated at reflux for 3h. The mixture was cooled, 100 ml dilute HCl was added and the mixture was stirred for 30 m. The solid was filtered, washed with water and hexane. The solid was dissolved in acetone and passed through an alumina (neutral) column to yield a yellow crystalline solid 0.37 g (68%), mp 293 - 5°C. The product gave physical properties which were identical with 2,5-bis(4-cyanophenyl)-furan synthesized as previously described (1).

2,5-Bis(4-cyanophenyl)-furan Method 2

4-Acetylbenzonitrile (3.63 g, 0.025 mol) was added to a solution of chlorotrimethylsilane (7.0 g,0.0 64 mol) and triethylamine (12.6 g, 0.125 mol) in dimethylformamide (25 ml) under N_2 . The resulting mixture was stirred at reflux for 46 h and cooled, diluted with pentane (80 ml) and washed with three 40 ml portions of cold aqueous $NaHCO_3$. The aqueous layer was extracted with two 20 ml portions of pentane and the combined organic extracts were washed with 40 ml of cold brine. The resulting pentane solution was dried ($MgSO_4$) and concentrated under reduced pressure to yield crude silyl enol ether (5.5 g); distillation gave 3.7 g, (68%), bp 76-78°C(0.11 mm Hg), ^{1}H NMR ($CDCl_3$) 7.68 (d, 2H, J=8.8), 7.61(d, 2H, J=8.8), 5.03(d, 1H, J=2.2), 4.58(d, 1H, J=2.), 0.29(s, 12H). ^{13}C NMR ($CDCl_3$) 153.9, 141.8, 131.9, 125.6, 118.8, 111.5, 93.7, -0.06. Boron trifluoride etherate (1.5 g, 10 mmol) was added to a suspension of iodosobenzene (0.85 g, 4 mmol) in dichloromethane (35 ml) under N_2 was added with stirring, cooled to -40°C and the silyl enol ether (1.5 g, 7 mmol) was added. The mixture was stirred for 1 hr at -40°C and for an additional 1 hr at room temperature. The solution was made basic with a saturated solution of $NaHCO_3$ and the aqueous layer was extracted with three 10 ml portions of CH_2Cl_2. The organic extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to yield crude product; which on addition of ethanol (2 ml) gave crystalline 1,4-bis(4-cyanophenyl)-1,4-butadione (0.3 g, 30%), mp 265-7°C, ^{1}H NMR ($CDCl_3$) 8.13 (d, 4H, J=8.7), 7.98 (d, 4H, J=8.7), 3.46 (s, 4H). ^{13}C NMR ($CDCl_3$) 197.0, 139.7, 132.6, 128.5, 117.8, 116.8, 32.3. Anal. Calcd. for $C_{18}H_{12}N_2O_2$: C, 74.98; H, 4.19; N, 9.72. Found: C, 74.90; H, 4.25; N, 9.67. The 1,4-diketone **8** (0.5 g, 0.0017 mol) was suspended in 8 ml of acetic anhydride and the mixture was heated to reflux. One drop of concentrated sulfuric acid was added to the boiling mixture and reflux was continued for 5 m. The solution was poured

into a water-ice mixture (10 ml), stirred and filtered to yield 0.38 g (76%) of 2,5-bis(4-cyanophenyl)furan which gave physical properties in accord with those previously reported.

2,5-Bis(4-cyanophenyl)-furan Method 3

A mixture of 4-cyanobenzaldehyde (13.1 g, 0.1 mol) , 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (1.35 g, 0.005 mol) and anhydrous sodium acetate (2.46 g, 0.03 mol) in absolute ethanol (100 ml) was heated to a gentle reflux (under the nitrogen). Divinyl sulfone (5.9 g, 0.05 mol) in absolute ethanol (20 ml) was added dropwise to the hot mixture and the solution was heated at reflux for additional 16 h. On cooling a precipitate formed, which was filtered and washed first with cold water and then ethanol. The solid was extracted several times with hot chloroform. The chloroform solution was washed with aqueous $NaHCO_3$ and the aqueous phase was reextracted with chloroform. The combined organic phases were dried (Na_2SO_4) and passed through a short alumina (neutral) column and the eluent was concentrated to yield 1,4-bis(4-cyanophenyl)-1,4-butadione (5.8 g , 40 %) which gave physical properties in accord with the sample prepared by Method 2.

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