A new synthesis of 2,5-bis(4-cyanophenyl)furan

Nisaraporn Suthiwangcharoen and Chad E. Stephens*

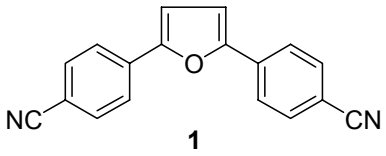
Department of Chemistry and Physics, Augusta State University, Augusta, Georgia 30904
E-mail: cstephe7@aug.edu

Abstract
A new 3-step synthesis of 2,5-bis(4-cyanophenyl)furan, a key intermediate in the preparation of the antimicrobial agents Furamidine and Pafuramidine, is presented. The key step of the synthesis is the preparation of a 1,4-diketone via the modified Stetter reaction of a 4-cyanophenyl Mannich base as a vinyl ketone precursor with 4-cyanobenzaldehyde. The synthesis has potential for use in the large scale preparation of the two antimicrobial agents.

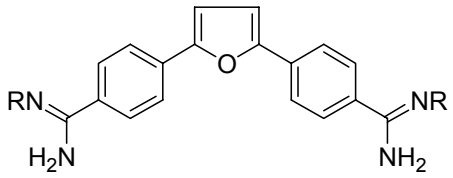
Keywords: 2,5-Diarylfuran, 1,4-diketone synthesis, Stetter reaction, furamidine, pafuramidine

Introduction

2,5-Bis(4-cyanophenyl)furan (**1**) is a key intermediate in the synthesis of 2,5-bis-amidinoarylfurans, a well studied class of DNA minor groove binders.[1-4] Furamidine (**2**) is the parent compound of this class, and it's methoxime prodrug (**3**) (Pafuramidine) is currently in clinical trials for treatment of African Sleeping sickness, malaria, and pneumocystis carinii pneumonia.[4-5] Satisfactory methods for conversion of the intermediate bis-nitrile **1** to **2** and **3** are available.[1,6] Several methods for the synthesis of bis-nitrile **1** are also available;[6-8] however many of these methods require multiple steps and/or are not high yielding. In some cases, there have been problems in scaling the synthesis of intermediate **1** to kilogram scale. The use of toxic organotin reagents[8] in one approach also remains a concern. Herein, we wish to report a new synthesis of bis-nitrile **1** that is based on the initial preparation of a 1,4-diketone by a modified Stetter reaction.[9] Starting with commercial reagents, this synthesis of **1** involves just 3 steps, and can be accomplished in 20% overall yield without the use of extraction or chromatography.



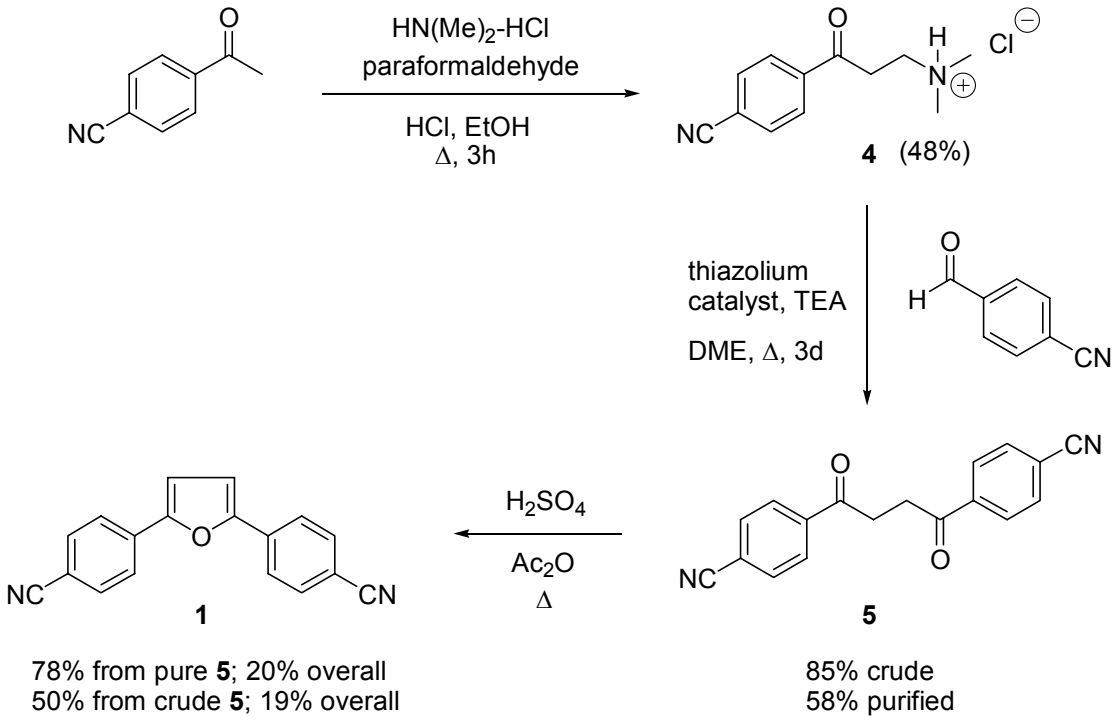
1



2 R = H (Furamidine)
3 R = OCH_3 (Pafuramidine)

Plan of research

Several of the previously published routes to bis-nitrile **1** involve synthesis of 1,4-diketone **5** as an intermediate.[7] Of the various routes to diketone **5**, the most direct is the Stetter reaction of 2 equivalents of 4-cyanobenzaldehyde with divinyl sulfone. This reaction, however, is complicated by formation and removal of the divinyl sulfone polymer, which is likely formed in large amounts due to the slow reactivity of 4-cyanobenzaldehyde.[10] As a result, the yield for this single step is about 40% at best,[7] and in our hands, is often lower (20% usually obtained). This approach to diketone **5** has been examined on large scale, and has been abandoned as a candidate for scale-up due to the need to remove the polymer by liquid/solid extraction or chromatography. An alternative to the Stetter reaction with divinyl sulfone is the so-called modified Stetter reaction. Instead of using divinyl sulfone as a vinyl donor, the modified reaction involves the use of a Mannich base, which is decomposed to the vinyl ketone and reacted with a separate aldehyde to give the 1,4-diketone all in one step.[9] The usefulness of this two-step approach has been that it allows for the synthesis of "mixed" or disymmetric 1,4-diketones[2,11] that can not be prepared using divinyl sulfone, although, in theory, it can also be used to prepare symmetrical diketones such as **5** if so desired. To our knowledge, however, the use of 4-cyanobenzaldehyde in such a modified Stetter reaction has not been explored thus far. We were thus interested to know if this benzaldehyde could be used in the modified approach to prepare diketone **5** in good yield, and without the need for removal of any polymeric byproduct. If so, cyclodehydration of 1,4-diketone **5** would then give furan **1** in a fairly direct approach.



Scheme 1. Synthetic approach to 2,5-bis(4-cyanophenyl)furan **1**.

Results and Discussion

As shown in Scheme 1, the synthesis of the Mannich base of 4-cyanoacetophenone was accomplished in 48% yield as previously reported.[12] Pale yellow to colorless crystals of **4** were typically obtained when absolute EtOH was used as solvent, while a lower melting powdery solid was obtained when 95% EtOH was used. Interestingly, very little product was obtained when the reaction was allowed to go much longer than 2-3 hours (i.e., overnight, as done when using 4-bromoacetophenone[11]), possibly due to this Mannich base being more readily decomposed to the vinyl ketone upon heating. Efforts to optimize the yield of this step, such as the use of amines other than dimethylamine, have not been pursued thus far.

Next, Mannich base **4** was reacted with 4-cyanobenzaldehyde under standard Stetter conditions[9] using a thiazolium salt as catalyst and triethylamine as base. Dimethoxyethane (DME) has been previously found by us to be a good solvent for Stetter reactions (unpublished work), and thus it was used as solvent here.[12] Previous unpublished work has also shown that an extended reaction time of several days gives optimal yield with such reactions, perhaps due to their heterogeneous nature. To our delight, 1,4-diketone **5** was obtained in 85% crude yield, and 58% purified yield following recrystallization from DMF/MeOH. Comparable yields were obtained for this reaction when repeated several times. Thus, 4-cyanobenzaldehyde appears to react better in this modified Stetter reaction than in the original reaction with divinylsulfone.

With 1,4-diketone **5** in hand, furan bis-nitrile **1** was readily prepared by acid-catalyzed cyclodehydration in acetic anhydride.[7] Instead of decomposing the acetic anhydride by addition

of water, as usually done, we allowed the product to crystallize directly from the reaction mixture upon cooling. This eliminated the large exotherm that occurs when decomposing the anhydride. Recrystallization of the filtered product from n-BuOH gave **1** in 78% purified yield (20% overall from 4-cyanoacetophenone), with the ^{1}H-NMR, IR and mp being in good agreement with previously reported data.[7] Importantly, no extraction or chromatography was needed at any point in the 3-step synthesis.

In order to improve upon our overall yield of **1**, we were interested to know if the use of crude 1,4-diketone **5**, instead of the pure, would lead to better results. To this end, the use of crude **5** gave a 50% purified yield of furan **1**, which was a lower yield for the one step than when using purified **5**. However, the overall yield for the 3-step synthesis was ultimately about the same (19%, compared to 20%). Thus, although the overall yield of **1** was not actually improved, we did learn that the purification of the 1,4-diketone is not necessary, a finding that is applicable to larger scale production.

Finally, we were also interested to know if the less expensive thiamine hydrochloride could serve as the Stetter catalyst for the synthesis of the 1,4-diketone in place of the thiazolium salt. Unfortunately, an experiment in which the thiazolium was replaced with a molar equivalent of thiamine hydrochloride was unsuccessful in giving **5**, with only an oily residue being obtained from which no 1,4-diketone could be isolated.

Conclusions

In conclusion, a new synthetic approach to 2,5-bis(4-cyanophenyl)furan **1**, a key intermediate in the synthesis of Furamidine and Pafuramidine, has been described. The 3-step synthesis, which is based on the preparation of 1,4-diketone **5** via a modified Stetter reaction employing 4-cyanobenzaldehyde, gave **1** in 20% overall yield from commercially available 4-cyanoacetophenone. A comparable overall yield of furan **1** was obtained when crude 1,4-diketone was used instead of pure, thus eliminating the need for a purification step. As the intermediates are readily isolated by simple filtration and the final product is purified by standard recrystallization (no extraction or chromatography required at any step), the synthesis is operationally simple compared to the original Stetter approach using divinylsulfone and is thus attractive for further optimization and larger scale preparation.

Experimental Section

General Procedures. Melting points were recorded using a Mel-Temp capillary melting point apparatus. A MAGNA-IR® 560 Spectrometer was used for IR spectroscopy. TLC was performed on silica gel plates with 1:1 hexane:ethyl acetate as eluent. ^{1}H-NMR spectra were recorded on a Varian Unity+300 instrument at Georgia State University, Atlanta, GA.

Mannich base 4. To a mixture of 4-acetylbenzonitrile (i.e., 4-cyanoacetophenone) (Aldrich, white solid, 1.14 g, 7.85 mmol), paraformaldehyde (0.236 g, 7.85 mmol), and dimethylamine hydrochloride (0.640 g, 7.85 mmol) in absolute EtOH (1.6 ml) was added one drop of a 10% (v/v) solution of concentrated aqueous HCl in EtOH. The mixture was refluxed for 3 hours and the resulting light yellow solution was then diluted with 3 mL of acetone. After standing in the freezer overnight, pale yellow fine crystals were filtered off and rinsed with acetone to yield 0.892 g (48% yield); mp 168-170 °C; Lit mp 159-160 °C.[13] Note: When 95% EtOH was used, a less crystalline, powdery solid was consistently obtained with mp 156-158 ^{o}C. A reaction time of 2 hrs gave similar yield.

1,4-Bis(4-cyanophenyl)-1,4-butadione (5). A mixture of 4-cyanobenzaldehyde (1.31 g, 10 mmol), Mannich base **4** (2.39 g, 10 mmol), 5-(2-hydroxyethyl)-3,4-dimethyl-1,3-thiazolium iodide (0.57 g, 2 mmol) and triethylamine (2.02 g, 20 mmol) was refluxed in 35 mL of 1,2-dimethoxyethane (DME) at 100 ˚C (oil bath temp) under N_2 for 72 hours. Water (10 ml) was then added and the yellow-orange solid was filtered off and rinsed with water. The product (2.44 g, 85%) (mp 243-246 ^{o}C) was dissolved in ~100 mL of DMF, and after hot filtration, was diluted with 10 mL of methanol. After standing overnight, the product was filtered off and rinsed with cold methanol to yield 1.52 g (53% yield) of light yellow fluffy solid; mp 260-265 ^{o}C; Lit mp[7] 265-267 ^{o}C; TLC homogeneous; IR (cm^{-1}): 3091, 3080, 2970, 2917, 2228, 1683, 1323, 1197, 1013, 861, 786. ^{1}H-NMR (DMSO-d_6): 3.47 (s, 4H), 8.03 (d, J = 8.4Hz, 4H), 8.16 (d, J = 8.7Hz, 4H).

2,5-Bis(4-cyanophenyl)furan (1). To a gently refluxing solution of **purified** 1,4-diketone **5** (1.56 g, 8.32 mmol) in acetic anhydride (~33 ml) was added a mixture of 4 drops of H_2SO_4 in acetic anhydride (1 ml). The solution turned darker and was immediately removed from the heat. The solution was allowed to cool on its own to room temperature over about 1hr to give a crystalline solid, which was filtered off and rinsed with hexanes. The crude product (1.23 g) (mp 288-290 ^{o}C) was recrystallized from 400 mL n-butanol with hot filtration to give, after filtering and rinsing with MeOH, the pure furan as yellow crystals (1.15 g, 78%) (20% overall yield from 4-cyanoacetophenone), mp 294-297˚C; lit mp[7] 293-295 ^{o}C; TLC homogeneous; IR (cm^{-1}): 2224, 1608, 1496, 1294, 1178, 1036, 929, 843, 796, 666, 547 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 7.43 (s, 2H), 7.91 (d, J = 8.4Hz, 4H), 8.04 (d, J = 8.7Hz, 4H). ^{13}C-NMR (DMSO-d_6): 109.9, 112.1, 118.9, 124.4, 133.1, 133.6, 152.4. When **crude** 1,4-diketone was used, a 70% crude yield of **1** was obtained, which upon recrystallization from n-butanol gave a 50% purified yield (19% overall yield) of pure **1**.

Acknowledgements

We thank our Department for partial support of this research. We also thank the Department of Chemistry at Georgia State University for use of their NMR facility.

References

1. Boykin, D. W. *J. Braz. Chem. Soc.* **2002,** *13*, 763.
2. Chaires, J. B.; Ren, J.; Hamelberg, D.; Kumar, A.; Pandya, V.; Boykin, D. W.; Wilson, W. D. *J. Med. Chem.* **2004**, *47*, 5729.
3. Ismail, M. A.; Brun, R.; Easterbrook, J. D.; Tanious, F. A.; Wilson, W. D.; Boykin, D. W. *J. Med. Chem.* **2003**, *46*, 4761.
4. Tidwell, R. R.; Boykin, D. W. Dicationic DNA Minor Groove Binders as Anti-microbial Agents. In Demeunynck, M.; Bailly, M. C.; Wilson, D. C. Eds.; *DNA and RNA Binders: From Small Molecules to Drugs*; Wiley-VCH: Weinheim, 2003; pp 414-460.
5. See: http://www.immtechpharma.com/documents/news_031306.pdf (accessed 1/16/07)
6. Das, B. P.; Boykin, D. W. *J. Med. Chem.* **1977**, *20*, 531. More current methods for conversion of bis-nitriles to amidines can be found in ref. 3.
7. Bajic, M.; Kumar, A.; Boykin, D. W.; Bajic, M. *Heterocyclic Comm.* **1996***, 2*, 135.
8. Kumar, A.; Stephens, C. E.; Boykin, D. W. *Heterocyclic Comm.* **1999***, 5*, 301.
9. Stetter, H.; Kuhlmann, H. "The Catalyzed Nucleophilic Addition of Aldehydes to Electrophilic Double Bonds" In *Organic Reactions*, Vol. 40, John Wiley & Sons: New York, 1991.
10. Benzaldehydes with electron withdrawing substituents are known to give low yields in this reaction (see ref. 9).
11. Pandya, V. *Synthesis of 2-[4-(N-alkylamidino)phenyl]-5-[3-(N-alkylamidino)phenyl]furans as Anti-Opportunistic Infections Agents.* Master's Thesis. Georgia State University, Atlanta, Ga., 1998.
12. In the analogous Stetter synthesis of 1,4-bis(4-bromophenyl)-1,4-butadione, DME proved to be a better solvent than DMF, DMSO, MeCN, EtOH, and 1,4-dioxane (unpublished work). Results with these other solvents ranged from lower yields (1,4-dioxane>MeCN>DMSO), to increased byproduct formation (EtOH), to formation of intractable oils (DMF). These other solvents were not examined in this work.
13. Mehta, L. K.; Parrick, J.; Sadiq, S. *J. Chem. Research (M).* **2000**, 1211.