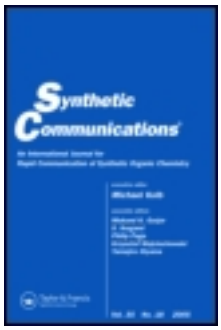

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Accepted author version posted online: 11 Jan 2013.

To cite this article: John D. Williams , Xiaoyuan Ding , Son Nguyen , Kimberly K. Vines & Norton P. Peet (2013): Syntheses of Benzo[b]furan-6-carbonitrile and 6-Cyanobenzo[b]furan-2-boronic Acid Pinacol Ester, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, DOI:10.1080/00397911.2012.684086

To link to this article: http://dx.doi.org/10.1080/00397911.2012.684086

Syntheses of Benzo[*b*]furan-6-carbonitrile and 6-Cyanobenzo[*b*]furan-2-boronic Acid Pinacol Ester

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Abstract

6-Cyanobenzo[*b*]furan-2-boronic acid pinacol ester (**10**) is a potentially useful 2-point scaffold for the construction of specific compounds or compound libraries with benzofuran cores. Using a per-iodination/de-iodination strategy coupled with a Sonogashira alkynylation and Cu-catalyzed heteroannulation, we have developed a procedure that allows the preparation of benzo[*b*]furan-6-carbonitrile (**9**) and 6-cyanobenzo[*b*]furan-2-boronic acid pinacol ester (**10**) in gram quantities.

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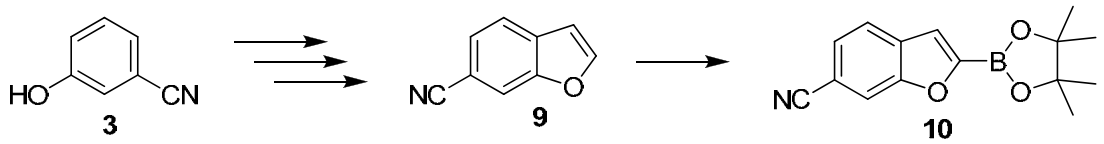

KEYWORDS: Benzo[*b*]furan, Sonogashira alkynylation, heteroannulation, heterocycle synthesis

INTRODUCTION

Benzo[*b*]furans are commonly found substructures in both natural products and medicinal compounds, and have been the frequent target of synthetic efforts by numerous groups (see references 1–4 for reviews). The approved drugs methoxsalen, amiodarone, saprisartan, trioxsalen, and numerous investigational drugs all contain benzo[*b*]furan cores, as do the natural products machicendiol, khellin, egenol, ailanthoidol, and others. The wide-ranging biological activity of benzo[*b*]furan-containing compounds has thus spawned considerable interest from a medicinal chemistry perspective.

RESULTS AND DISCUSSION

In conjunction with our program investigating broad-spectrum antibacterial compounds, we required the synthesis of substantial amounts of 6-cyanobenzo[*b*]furan-2-boronic acid pinacol ester (**10**), which is conveniently obtained from benzo[*b*]furan-6-carbonitrile (**9**). Although it is commercially available, benzo[*b*]furan-6-carbonitrile (**9**) is quite expensive and the supply is limited. This prompted us to investigate a synthetic procedure that would be capable of producing the desired compound efficiently, inexpensively, and in quantities suitable for our research purposes.

There is one reported synthesis for benzo[*b*]furan-6-carbonitrile (**9**),[5] but this process relies upon a late-stage Sandmeyer-type conversion of 6-aminobenzo[*b*]furan into the corresponding nitrile. We viewed this process as impractical because of the inherently low yields often associated with Sandmeyer-type reactions, the hazardous nature of the intermediate diazonium species, and the lengthy synthesis that would be necessary to synthesize the amine substrate.

Converting other 6-subsituted benzo[*b*]furans, such as the 6-carboxy-, 6-formyl-, or 6-bromo-analogs into the corresponding 6-carbonitrile (*via* dehydration of the corresponding amide, dehydration of the corresponding oxime, or the Rosenmund-von Braun reaction, respectively) can all be achieved. However, these compounds all require lengthy syntheses to produce the necessary substrate for conversion. Availability of 6-substituted benzo[*b*]furans is hindered largely by synthetic considerations. Many common strategies involve annulations of corresponding phenol derivatives; the 5-substituted benzo[*b*]furans thus do not require a directional ring closure, but the corresponding 6-substituted benzo[*b*]furans are always produced in tandem with the 4-substituted congeners using this methodology.[6,7] Alternatively, the 2-carboxy analogs of 6-substituted benzo[*b*]furans can be readily synthesized from the corresponding 4-substituted salicylaldehydes, but these must be decarboxylated to provide the desired 2-unsubstituted analogs,[8] and only limited examples of the requisite salicylaldehydes are commercially available.

One useful entry into the benzofuran series would be the metal-catalyzed cyclization of a 2-ethynyl-5-cyanophenol,[9] which could be made from the corresponding 2-bromo- or 2-iodo-5-cyanophenol. Our initial efforts at producing 2-iodo-5-cyanophenol (**5**) using traditional methodologies (direct mono-iodination with ICl in acetic acid,[10] or with iodine in either aqueous sodium acetate[11] or aqueous ammonia[12]) were hampered by low yields and/or mixtures of isomers; we did not attempt analogous reactions using

common thallium salt procedures[13] because of the inherent toxicity concerns about working with this heavy metal.

While searching for an alternative approach to compound **5**, we were intrigued by a report from the Chern group at the National Taiwan University who reported that heating iodinated phenols in the presence of organic bases (especially pyridine, TEA, or *N*-methylmorpholine) resulted in selective de-iodination of the investigated iodophenols, leaving the iodo substituent *para* to the hydroxy group intact.[14] One notable exception was 2,4,6-triiodo-3-hydroxybenzaldehyde, in which the iodo group *para* to the aldehyde was maintained (Scheme 1).

We surmised that the corresponding reaction, applied to 3-hydroxy-2,4,6-triiodobenzonitrile (**4**), would provide compound **5**. Indeed, after refluxing the per-iodinated phenol in *N*-methylmorpholine, we isolated 3-hydroxy-4-iodobenzonitrile (**5**) in modest yield. Encouraged by these results, we sought to optimize the synthesis such that this sequence could be carried out in high yield on a multi-gram scale.

3-Hydroxy-2,4,6-triiodobenzonitrile (**4**) is known,[15] but no analytical data was provided for the compound, and the reagent used (IPy_2BF_4) for the preparation of this material from 3-hydroxybenzonitrile (**3**) was viewed as uneconomical. Fortunately, we were able to use an alternative procedure, which has previously been used to prepare 2,4,6-triiodo-3-hydroxybenzaldehyde,[11] to per-iodinate 3-hydroxybenzonitrile. Optimization

provided a procedure capable of producing 3-hydroxy-2,4,6-triiodobenzonitrile (**4**) in 88% on a multi-gram scale.

We next used the Chern procedure to produce the desired 3-hydroxy-4-iodobenzonitrile (**4**) in moderate-to-low yield (Scheme 2). Before optimizing this reaction, we wanted to unambiguously assign the regiochemistry of the product. The NMR spectrum of 3-hydroxy-4-iodobenzonitrile (**5**) matched literature precedent;[10] however, that synthesis also relied upon an iodination reaction that could have provided multiple products. We were, unfortunately, unable to validate the structure using HMBC/HSQC because of overlapping resonances in the ^{13}C spectrum. Upon synthesis of the corresponding mesylate ester (**6**, Scheme 2), however, a highly crystalline product was obtained. Determination of the X-ray crystal structure of mesylate **6** proved that the desired material was, in fact, obtained from the de-iodination reaction (see Supplementary Material, Figure S1, available online).

Optimization of the de-iodination procedure was hampered initially by the production of very dark, viscous, insoluble materials using the Chern protocol. We believe that this insoluble material contributed in part to lower yields, as unreacted or partially reacted starting material was sequestered into the insoluble mass. Upon further exploration, we discovered that we could eliminate the insoluble material by increasing the amount of water in the reaction. Although the modified reaction is significantly slower, the result is a cleaner and higher-yielding process.

With suitable quantities of 3-hydroxy-4-iodobenzonitrile (**5**) in hand, we turned our attention to the synthesis of benzo[*b*]furan-6-carbonitrile (**9**; Scheme 3). Using the procedure of Wishka, et al.,[16] we synthesized the intermediate phenylacetylene **7**, which was subsequently cyclized to a mixture of the desired benzo[*b*]furan **9** and its silylated congener (**8**) in a 1:1 mixture (Table 1). By lowering the reaction temperature to 50 °C, we were able to increase the ratio of silylated material to 2:1, but further decreasing the temperature did not further alter the product ratio, and did lower the overall yield. The silylated material **8** was easily desilylated using aqueous base to produce the desired benzo[*b*]furan-6-carbonitrile (**9**) in good yield.

To synthesize the requisite boronic acid ester **10** from the 2-unsubstituted benzo[*b*]furan **9**, we used a modification of Hartwig's boronylation procedure[17] to provide the target compound in good yield (Scheme 3). Boronic acid ester **10** is a useful two-point scaffold for the preparation of compounds with a benzofuran core that exhibit biological activity

CONCLUSION

By utilizing a unique sequence of per-iodination and de-iodination of 3-hydroxybenzonitrile (**3**), we were able to produce 3-hydroxy-4-iodobenzonitrile (**5**) in useful quantities. This useful intermediate was then further converted to benzo[*b*]furan-6-carbonitrile (**9**) and 6-cyanobenzo[*b*]furan-2-boronic acid pinacol ester (**10**), both of which are useful intermediates for medicinal chemistry. Additional benzo[*b*]furan-6-carbonitriles, such as the corresponding 2-aryl, 2-alkyl, or 2-carboxy congeners should also be accessible using this methodology.

EXPERIMENTAL

3-Hydroxy-4-Iodobenzonitrile (5)

3-Cyano-2,4,6-triiodophenol (**4**, 21.97 g, 44.2 mmol) was dissolved in *N*-methylmorpholine (160 mL) and H_2O (40 mL). The resulting solution was heated to gentle reflux (160 °C oil bath) for 24 h, then cooled to room temperature. The excess solvent was removed by evaporation at reduced pressure, and the residual oil was partitioned between EtOAc (300 mL) and 0.5 M aq. HCl (200 mL). The organic extract was then washed with brine (200 mL), dried over $MgSO_4$, filtered, and evaporated to yield an orange oil. The oil was subjected to flash chromatography (50 × 450 mm) on silica gel with 5:1 hex:EtOAc. Product-containing fractions were pooled and evaporated to yield 3.38 g (28%) of **5** as a white powder: mp 121-124 °C; R_f 0.35 (3:1 hex:EtOAc); ^{1}H-NMR ($CDCl_3$) δ 7.79 (d, 1H), 7.23 (d, 1H), 6.95 (dd, 1H), 5.63 (s, 1H); HRMS calculated for C_7H_5INO, $[M+H]^+$, 245.9410 found 245.9411.

Benzo[*b*]furan-6-carbonitrile (9)

To a solution of 3-Hydroxy-4-[(trimethylsilyl)ethynyl]benzonitrile (**7**, 1.14 g, 5.3 mmol) in 1:1 EtOH:triethylamine (20 mL) was added cuprous iodide (51 mg, 0.26 mmol). The resulting solution was heated to 75 °C (oil bath) for 6.5 h, then cooled to room temperature and evaporated to yield a brown syrup that contained a ~1:1 mixture of silylated:desilylated material (by NMR). The crude material was dissolved in $CHCl_3$ (70 mL), and 1.0 M aq. NaOH (50 mL) was added. The biphasic mixture was stirred

vigorously for 18 h. The pH of the aqueous phase was adjusted by dropwise addition of conc. aq. HCl. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were then dried over Na_2SO_4, filtered, and evaporated to yield a brown oil. The oil was subjected to flash chromatography (80 g) on silica gel with 0-25% EtOAc/hex. Product-containing fractions were pooled and evaporated to yield 700 mg (93%) of **9** as a clear, colorless oil: R_f 0.50 (6:1 hex:EtOAc); ^{1}H-NMR ($CDCl_3$) δ 7.83-7.81 (m, 2H), 7.69 (d, 1H), 7.50 (dd, 1H), 6.87-6.86 (m, 1H); HRMS calculated for C_9H_6NO, $[M+H]^+$, 144.0444 found 144.0443.

ACKNOWLEDGEMENT

We wish to thank Dr. Peter Mueller of the MIT crystallography facility for expert analysis of X-ray crystal structure data.

This publication was made possible in part by grants R43 AI082799 and U01 AI082052 from the National Institute of Allergy and Infectious Disease (NIAID) at the National Institutes of Health NIH).

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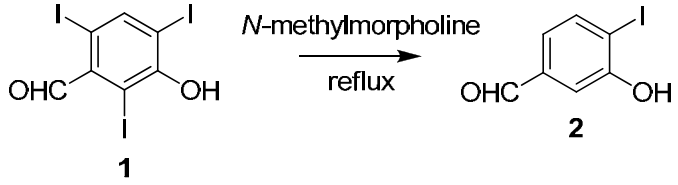
Table 1. Effect of temperature on benzofuran annulation.

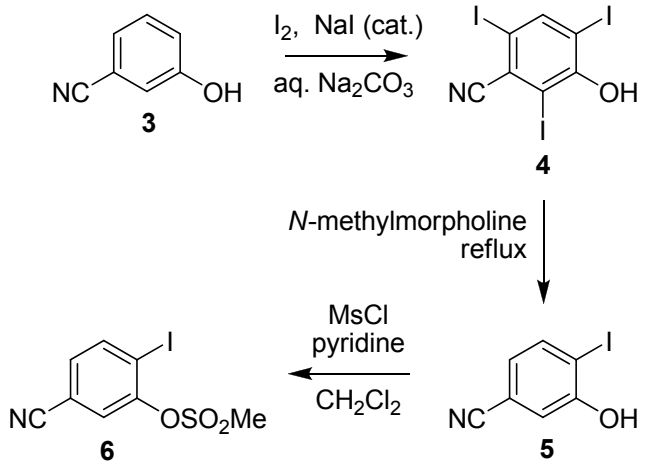
Entry	T (°C)	t (h)	% yield	7:8
a	75	2	97	1:1
b	50	5	94	1:2
c	25	5	72	1:2

[a]The yield was determined from the weight of the crude product mixture which contained only products **3** and **4**. [b]The ratio of **3** and **4** was calculated from the integrations of the 3- and 3'- protons of the crude NMR.

Scheme 1. Reported de-iodination of 2,4,6-triiodo-3-hydroxybenzaldehyde.



Scheme 2. Per-iodination and de-iodination of 3-hydroxybenzonitrile.



Scheme 3. Syntheses of benzo[*b*]furan-6-carbonitrile and 6-cyanobenzo[*b*]furan-2-boronic acid pinacol ester.