CONCISE SYNTHESIS OF 6-CYANOBENZO[b]FURAN, A USEFUL BUILDING BLOCK

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GRAPHICAL ABSTRACT

Abstract A new three-step synthesis of 6-cyanobenzo[b]furan (6) was developed, starting from commercially available 6-hydroxybenzo[b]furan-3-one (18). Key steps in this process were the first step, which was the reductive dehydration of 18 to produce 6-hydroxybenzo[b]furan (19), and the last step, which converted the aryl triflate 20 to the aryl cyanide 6 in a palladium-catalyzed cross-coupling protocol. Overall yield for this new synthesis was 49%.

Keywords Aryl cyanide synthesis; cross-coupling; 6-cyanobenzo[b]furan; reductive dehydration

INTRODUCTION

Benzo[b]furans are important components of drugs and biologically active compounds. Examples of benzo[b]furan-containing drugs include (−)-1-(benzo-furan-2-yl)-2-propylaminopentane ((−)-BPAP),[1] dronedarone,[2] and amiodarone.[3] Consequently, there has been significant effort directed toward the design of new syntheses for benzo[b]furans[4,5]

We have described previously the syntheses of specific benzo[b]furan building blocks. 5-Formylbenzo[b]furan-2-carbonitrile was a previously unknown compound that we required for the preparation of a compound library. We recently reported[6] a seven-step, practical synthesis for this new compound in 17% overall yield. More recently, we developed a new synthesis for 6-cyanobenzo[b]furan (6), which is

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shown in Scheme 1. Starting from 3-hydroxybenzonitrile (1), we prepared triiodo compound 2 in 88% yield by treatment with iodine and then selectively removing two iodo groups from 2 with N-methylmorpholine to give 3-hydroxy-4-iodobenzonitrile (3) in 28% yield. Compound 3 underwent a Sonagashira reaction, using the procedure of Wishka et al. to produce the intermediate phenylacetylene 4 in 79% yield. Subsequent cyclization of 4 with cuprous iodide catalysis gave a 93% yield of 6-cyanobenzofuran (6), after treatment of the initial mixture with sodium hydroxide to convert the 2-trimethylsilylbenzofuran intermediate 5 to the desired product 6.

Although this sequence was relatively short, and four of the five steps proceeded in good yield, the deiodination of compound 2 to produce 3-hydroxy-4-iodobenzonitrile (3) was a poor-yielding reaction that we were unable to improve, and this prompted us to evaluate new methods for the preparation of 6. This report describes an improved, concise synthesis of 6-cyanobenzofuran (6).

RESULTS AND DISCUSSION

In Scheme 2 is shown another known route to 6-cyanobenzofuran (6), starting from 4-nitrosalicylic acid (7). Reduction of 7 with borane-dimethylsulfide complex gave benzyl alcohol 8 in 95% yield. Oxidation of 7 with manganese dioxide furnished 4-nitrosalicylaldehyde (9) in 75% yield. Aldehyde 9 was then used to install the fused furan ring, by treatment with 2-bromomalonic acid diethyl ester under basic conditions. This reaction was reported to produce ester 10 in 59% yield, which actually is a reasonably good yield in view of the complexity of this conversion that involves alkylation, condensation, hydrolysis and decarboxylation processes. Hydrolysis of 10 with potassium hydroxide afforded the corresponding acid 11 in 92% yield and subsequent decarboxylation with copper and quinoline at high temperature gave 6-nitrobenzofuran (12) in 63% yield. Chemical reduction of the nitro group of 12 with ferrie chloride in the presence of N,N-dimethylhydrazine gave 6-aminobenzofuran (13) in 79% yield. Conversion of the amino group in 13 to a cyano group to produce the desired compound 6 was accomplished in a two-step Sandmeyer reaction, in the presence of sodium cyanide. The yield for this reaction was not reported.
The overall process for the preparation of benzofuran 6 shown in Scheme 2 is unattractive because of its length, poor yields with two of the conversions, and an unknown yield for the last two-step Sandmeyer reaction. Also, the Sandmeyer conversion involved the use of sodium cyanide under acidic conditions, which we wished to avoid. Although this chemistry is basically a compilation of known reactions that would undoubtedly work to produce product, it underscored the need for a better synthesis of benzofuran 6.

We looked for cost-effective, commercially available starting materials that potentially could be converted to 6-cyanobenzo\[b\]furan (6). In Fig. 1 are shown four such materials that we identified and attempted to convert to compound 6. All of these potential starting materials had structural elements common to 6, and we made several attempts to use these materials to devise a new route to benzofuran 6.

We first attempted to alkylate 3-hydroxybenzoic acid (14) with a two-carbon synthon, such as bromoacetaldehyde diethyl acetal, reasoning that a subsequent annulation of this unit to the 4-position of the benzene ring could provide a precursor to compound 6. However, the alkylation conditions that we explored all gave mixtures of alkylated products, where alkylation had occurred to produce the desired ether but had also partially produced a dialkylated ether-ester product. Because this complication would lengthen an already long planned sequence, we moved next to 3-bromophenol (15), where only monoalkylation of the phenol could occur.

Figure 1. Potential cost-effective starting materials for the preparation of 6-cyanobenzo\[b\]furan (6).
Alkylation of 15 with bromoacetaldehyde diethyl acetal, using sodium hydride in dimethylformamide, gave us the desired ether in 98% yield. However, when we treated this ether with acidic reagents (e.g., p-toluenesulfonic acid in toluene or xylene; or polyphosphoric acid) in an attempt to produce the desired benzofuran, we observed mixtures of 4-bromobenzofuran and 6-bromobenzofuran. These mixtures were very difficult to separate and yields of either isomer were low (less than 2%).

5-Bromo-2-chlorophenol (16) was a potentially attractive starting material, because problems of regiochemistry would no longer be an issue. We were able to replace the bromo group with cyano in compound 16, using zinc cyanide and Pd(Ph₃P)₄ in dimethylformamide, in 94% yield. We planned to attempt a Sonagashira reaction with this compound (2-chloro-5-cyanophenol), but became discouraged by literature reports that described the lower reactivity of chlorobenzenes.[14] However, it was very useful to develop the cyanation conditions with compound 16, because this replacement reaction was a critical feature of our ultimate, successful route to compound 6.

3-Cyanophenol (17) was also used as a starting point for alkylations that could ultimately produce the desired benzofuran. Treatment of 17 with bromoacetaldehyde diethyl acetal gave a 72% yield of the expected O-alkylated product. Treatment of this ether with polyphosphoric acid, however, gave a mixture from which only 4-cyanobenzofuran could be isolated. We were also able to alkylate 17 with allyl bromide, using potassium carbonate in acetone at 0 °C, to provide a 94% yield of the expected propargyl ether. We had planned to do a Claisen rearrangement with this ether using diethylaluminum chloride,[15] evaluate the regiochemistry of the product or products, and subsequently convert the desired o-allylphenol, if formed, by ozonolysis to 2-hydroxy-4-cyanophenylacetaldehyde, which could then be cyclized to benzofuran 6. However, we did not proceed with this plan because of the result we obtained with the diethyl acetal.

In Scheme 3 is shown the new procedure for the synthesis of 6-cyanobenzofuran (6), starting from commercially available 6-hydroxybenzofuran-3-one (18). We believe that this concise method is now the best procedure that has been reported for the synthesis of 6. The first step in this process involved conversion of 6-hydroxybenzofuran (18) to 6-hydroxybenzofuran (19) using a reductive dehydration protocol. Thus, treatment of 18 (which can be prepared from resorcinol in two steps[16]) with lithium borohydride in tetrahydrofuran, followed by treatment with acid, produced 6-hydroxybenzofuran (19) in 68% yield. Compound 19 has previously been prepared from 18 in a three-step process from 18, by protection of the hydroxyl group using tert-butylsilyl chloride, reduction of the ketone with sodium borohydride, and dehydration of the resulting alcohol by treatment with acid.[17] Conversion of 19 to the triflate 20 proceeded in 88% yield; compound 20 then underwent a cross-coupling
reaction with zinc cyanide, in the presence of palladium-tetrakis(triphenylphosphine) palladium(0), to give 6 in 82% yield. Palladium-catalyzed cyanation of aryl triflates is useful methodology for the preparation of aryl cyanides.[18]

The conditions shown in Scheme 3 for the reductive dehydration of compound 18 are the optimized conditions that were found after several attempts. In Scheme 4 is shown our first attempt, with lithium aluminum hydride in tetrahydrofuran,[19] which made us realize that overreduction to the dihydrobenzofuran 21 was a problematic side reaction that needed to be minimized. To improve the yield of the reductive dehydration process, we screened various other conditions, using different reducing reagents, as shown in Table 1. All reactions in Table 1 were performed at room temperature, which helped to minimize the production of 21. The best conditions found were LiBH₄ in tetrahydrofuran (THF) followed by a HCl/H₂O quench, which provided 19 in 68% yield (first entry). Interestingly, it was observed that if the reaction mixture was quenched with water and kept neutral, we could isolate the intermediate 2,3-dihydrobenzo[b]furan-3,6-diol (22). Thus, addition of HCl was necessary for the elimination of the secondary alcohol to give 19.

**SUMMARY**

In summary, we have developed a concise, three-step synthesis for 6-cyanobenzo[b]furan (6), starting from commercially available 6-hydroxybenzo[b]furan-3-one (18), in 49% overall yield. Key steps that were used in this synthesis were the reductive dehydration of 18 to 6-hydroxybenzo[b]furan (19) and conversion of triflate 20 to 6-cyanobenzo[b]furan (6) with zinc cyanide, using a palladium-catalyzed cyanation protocol.
EXPERIMENTAL

6-Hydroxybenzofuran (19)

LiBH₄ (1.83 mL, 2M in THF) was added to a stirred solution of 6-hydroxybenzo[b]furan-3-one (18) (0.5 g, 3.33 mmol) in THF (10 mL) cooled in an ice bath over 15 min. The ice bath was removed, and after 16 h, ice water (3 mL) was slowly added, followed by HCl (1 mL, concentrated solution). The product was extracted with hexanes (3×10 mL). The combined organic extracts were dried (MgSO₄) and concentrated by rotary evaporation. The residue was purified by silica-gel column chromatography (24 g of SiO₂, hexanes–CH₂Cl₂, 1:0 to 0:1, 20 min) to provide 0.30 g (68% yield) of 19 as a colorless oil. Rᶠ: 0.23 (12% ethyl acetate in hexanes); ¹H NMR (CDCl₃): δ 7.51 (d, J = 2.1 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 1.8 Hz, 1H), 6.78 (dd, J = 8.4, 2.1 Hz, 1H), 6.68 (dd, J = 2.1, 0.6 Hz, 1H), 5.40 (br s, 1H).

6-Cyanobenzo[b]furan (6)

Zn(CN)₂ (0.8 g, 4.5 mmol) and Pd(Ph₃P)₄ (0.26 g, 0.22 mmol) were added to a stirred solution of triflate 20 (prepared as described by Coleman et al.¹⁷) (0.4 g, 1.5 mmol) in DMF (10 mL) under argon. The reaction mixture was placed in an oil bath maintained at 100 °C. After 3 h, the oil bath was removed, and the reaction mixture was allowed to cool to rt. Water (10 mL) was added, and the product was extracted with ether (3×10 mL). The combined organic extracts were dried (MgSO₄) and concentrated by rotary evaporation. The residue was purified by silica-gel column chromatography (24 g of SiO₂, hexanes–CH₂Cl₂, 1:0 to 0:1, 20 min) to provide 0.176 g (82% yield) of 6-cyanobenzo[b]furan (6) as a colorless oil, which solidified on standing. Rᶠ: 0.29 (12% ethyl acetate in hexanes); ¹H NMR (CDCl₃): δ 7.83 (s, 1H), 7.79 (d, J = 6.9 Hz, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.51 (dd, J = 8.1, 1.2 Hz, 1H), 6.86 (dd, J = 2.4, 0.9 Hz, 1H).

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher’s website.

REFERENCES

1. Shimazu, S.; Takahata, K.; Katsuki, H.; Tanigawa, A.; Tsunekawa, H.; Yoneda, F.; Knoll, J.; Akaike, A. Eur. J. Pharmacol. 2001, 421, 181–189.
2. Singh, B. N.; Connolly, S. J.; Crijns, H. J. G. M.; Roy, D.; Kowey, P. R.; Capucci, A.; Radzik, D.; Aliot, E. M.; Hohnloser, S. H. New Engl. J. Med. 2007, 357, 987–999.
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3. Rosenbaum, M. B.; Chiale, P. A.; Haedo, A.; Lazzari, J. O.; Elizari, M. V. *Am. Heart J.* 1983, *106*, 957–964.

4. For reviews of benzo[b]furan syntheses, see (a) Hou, X.-L.; Yang, Z.; Wong, H. N. C. In *Progress in Heterocyclic Chemistry*, Vol. 15; G. W. Gribble and J. A. Jouly (Eds.); Pergamon: Amsterdam, 2003; pp.167–205; (b) McCallion, G. D. *Curr. Org. Chem.* 1999, 3, 67–76; (c) Zeni, G.; Larock, R. C. *Chem. Rev.* 2004, *104*, 2285–2310.

5. For selected recent syntheses, see (a) Kumar, M. P.; Liu, R. S. *J. Org. Chem.* 2006, *71*, 4951–4955; (b) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* 2005, *70*, 10292–10296; (c) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* 2005, *127*, 15022–15023; (d) Chen, C.; Dormer, P. G. *J. Org. Chem.* 2005, *70*, 6964–6967; (e) del Carmen Cruz, M.; Tamariz, J. *Tetrahedron Lett.* 2004, *45*, 2377–2380; (f) Thielges, S.; Meddah, E.; Bisseret, P.; Eustache, J. *Tetrahedron Lett.* 2004, *45*, 907–910.

6. Lee, J.; Khanapure, S. P.; Kim, H. O.; Rajur, R. S. B.; Li, B.; Williams, J. D.; Pai, R.; Peet, N. P. *Synth. Commun.* 2010, *40*, 3390–3396.

7. Williams, J. D.; Ding, X.; Nguyen, S.; Vines, K. K.; Peet, N. P. *Synth. Commun.* 2013, *43*, 1974–1979.

8. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* 1975, *4467–4470*.

9. Wishka, D. G.; Walker, D. P.; Yates, K. M.; Reitz, S. C.; Jia, S.; Myers, J. K.; Olson, K. L.; Jacobsen, E. J.; Wolfe, M. L.; Groppi, V. E.; Hanchar, A. J.; Thornburgh, B. A.; Cortes-Burgos, L. A.; Wong, E. H. F.; Staton, B. A.; Raub, T. J.; Higdon, N. R.; Wall, T. M.; Hurst, R. S.; Walters, R. R.; Hoffman, W. E.; Hajos, M.; Franklin, S.; Carey, G.; Gold, L. H.; Cook, K. K.; Sands, S. B.; Zhao, S. X.; Soglia, J. R.; Kalgutkar, A. S.; Arneric, S. P.; Rogers, B. N. *J. Med. Chem.* 2006, *49*, 4425–4436.

10. MacMillan, K. S.; Nguyen, T.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* 2009, *131*, 1187–1194.

11. Perreaut, P.; Jegham, S.; Bourrie, B.; Casellas, P.; Labrosse, J.; Durand, F. US patent 2009/48277 A1, 2009.

12. Brown, A. D.; Calabrese, A. A.; Ellis, D.; Smith, C. R. WO patent 2005/82866 A2, 2005.

13. Sandoz, A. G. NL patent 6613360, 1965.

14. Chinchilla, R.; Najera, C. *Chem. Rev. 2007, 107*, 874–922.

15. Sonnenberg, F. M. *J. Org. Chem.* 1970, *35*, 3166–3167.

16. (a) Haudecoeur, R.; Ahmed-Belkacem, A.; Yi, W.; Fortune, A.; Brillet, R.; Belle, C.; Nicolle, E.; Pallier, C.; Pawlowski, J.-M.; Boumendjel, A. *J. Med. Chem.* 2011, *54*, 5395–5402; (b) Ge, M.; He, J.; Lau, F. W. Y.; Liang, G.B.; Lin, S.; Liu, W.; Walsh, S. P.; Yang, L. US patent 2007/0265332 A1, 2007.

17. Coleman, P. J.; Brasher, K. M.; Askew, B. C.; Hutchinson, J. H.; McVean, C. A.; Duong, L. T.; Feuston, B. P.; Fernandez-Metzler, C.; Gentile, M. E.; Hartman, G. D.; Kimmel, D. B.; Leu, C.-T.; Lipfert, L.; Merkle, K.; Pennypacker, B.; Preuksaritanont, T.; Rodan, G. A.; Wesolowski, G. A.; Rodan, S. B.; Duggan, M. E. *J. Med. Chem.* 2004, *47*, 4829–4837.

18. Zhu, Y.-Z.; Cai, C. *Synth. Commun.* 2008, *38*, 2753–2760.

19. Junino, A.; N’Guyen, Q. L.; Tuloup, R.; Blaise, C. US patent 5730962 A1, 1998.