Accepted Manuscript

A novel efficient protocol for preparation of 3-formyl-2-arylbenzo[*b*]furan derivatives

Benren Liao, Libo Ruan, Min Shi, Nian Li, Liang Chang, Leping Liu, Fan Yang, Jie Tang

PII: S0040-4039(14)00662-5
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.04.050
Reference: TETL 44512

To appear in: *Tetrahedron Letters*

Received Date: 17 February 2014
Revised Date: 8 April 2014
Accepted Date: 15 April 2014

Please cite this article as: Liao, B., Ruan, L., Shi, M., Li, N., Chang, L., Liu, L., Yang, F., Tang, J., A novel efficient protocol for preparation of 3-formyl-2-arylbenzo[*b*]furan derivatives, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.04.050

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

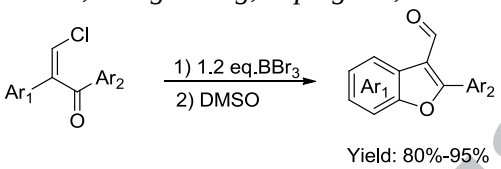
ACCEPTED MANUSCRIPT

Graphical Abstract

A novel efficient protocol for preparation of 3-formyl-2-arylbenzo[*b*]furan derivatives

Leave this area blank for abstract info.

Benren Liao, Libo Ruan, Min Shi, Nian Li, Liang Chang, Leping Liu, Fan Yang, Jie Tang



Yield: 80%-95%

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

A novel efficient protocol for preparation of 3-formyl-2-arylbenzo[*b*]furan derivatives

Benren Liao[¶], Libo Ruan[¶], Min Shi, Nian Li, Liang Chang, Leping Liu, Fan Yang*, Jie Tang*

Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, East China Normal University, Shanghai 200062, China

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
3-formyl-2-arylbenzo[*b*]furan
vinyl chloride
demethylation reaction
cyclization reaction

ABSTRACT

An efficient method for preparation of 3-formyl-2-arylbenzo[*b*]furan derivatives **4** from 3-chloro-2-(2-methoxyaryl)-1-arylprop-2-en-1-one **2** was developed, and the desired product were obtained in good to excellent yields. By converting 2-(2-methoxyphenyl)-3-oxo-3-phenylpropanal **1** to **2**, the regioselectivity problem occurred in the reaction when using **1** as the starting material was successfully avoided. Furthermore, a one-pot procedure for the successively demethylation, cyclization and hydrolysis was evolved, although the intermediate 3-(dibromomethyl)-2-phenylbenzo[*b*]furan **3a** could be isolated. A plausible mechanism was proposed based on some *in situ* investigations.

2014 Elsevier Ltd. All rights reserved.

The 3-formyl-2-arylbenzo[*b*]furan scaffold widely presented in unnatural products, such as XH-14,[1] Puerariafuran,[2] Ebenfurans[3] which showed interesting biological activities.[4] In addition, 3-formyl-2-arylbenzo[*b*]furan derivatives are key precursors in preparation of natural products, such as vibsanol,[5] (±)-Rocaglamide,[6] and many pharmacologically active compounds.[7] Therefore, 3-formyl-2-arylbenzo[*b*]furan scaffold has been served as a versatile building block via a variety of chemical transformations.[8,7b,9]

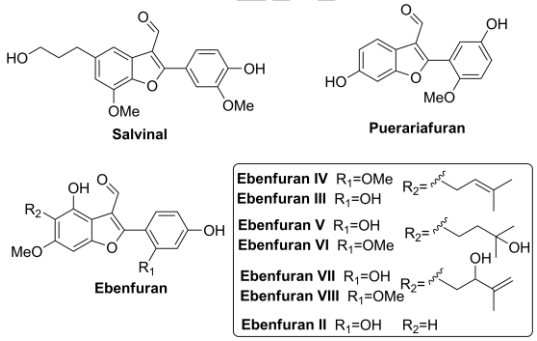


Figure 1. 3-Formyl-2-arylbenzo[*b*]furan scaffold presented in natural products.

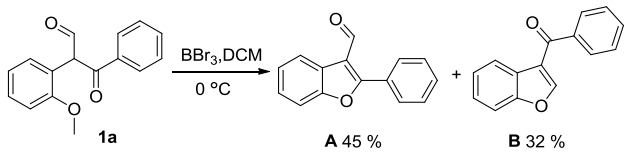
Due to the importance of this class of molecules, synthetic access to 3-formyl-2-arylbenzofuran attracts considerable interests. Over the past decade, several routes for constructing 3-formyl-2-arylbenzofuran cores have been exhibited in literature, and the direct formylation of 2-phenylbenzofuran into 3-formyl-2-arylbenzofuran derivatives appears to be the most popular method.[7] Other methods include Pd(0)-catalyzed cross-coupling of 1-benzofuran-3-carbaldehyde with aryl iodide,[10] oxidation of 3-(α-alkoxyalkyl)benzofurans with DDQ,[5,11] selective oxidation of the hydroxy group at the 3-position with manganese oxide,[12] oxidative cleavage of 3-vinyl benzofuran,[6] and oxidation of the trimethylsilylethyl ether at 3-position, constructed from a $PtCl_2$-catalyzed cycloisomerization reaction, with $(NH_4)_2Ce(NO_3)_6$/CH_3CN.[8] However, most of them suffered from drawbacks such as expensive metal catalysts, toxic reagents, analogues synthesis difficulties and low yields as well, significantly limiting their applications as practical protocols. Therefore, the development of practical synthetic diversity-oriented methods for 3-formyl-2-arylbenzofurans are still of great necessary. Based on the previous work in our group,[13] we attempted to conduct demethylation of 2-(2-methoxyphenyl)-3-oxo-3-phenylpropanal (**1a**), readily prepared from the rearrangement of the corresponding chalcone epoxide by standard literature procedures,[14,15] and then carry out cyclization of the generated intermediate in the presence of BBr_3 to afford 3-formyl-2-arylbenzo[*b*]furan. To our satisfaction, the results showed that the desired cycloisomerization products, 2-phenylbenzo[*b*]furan-3-carboxaldehyde (**A**, 45% yield determined by ^{1}H NMR analysis) along with its regioisomer 3-benzofuranphenylmethanone (**B**, 32% yield determined by ^{1}H NMR analysis), were obtained under the mild conditions (Scheme 1). However, they were very difficult to separate by silica gel chromatography due to their similar polarities. Nevertheless, we envisioned that the regioselectivity problem could be avoided if the starting material **1a** was previously transformed to an aldehyde precursor. Therefore, we prepared 3-chloro-2-(2-methoxyphenyl)-1-

* Corresponding author. Tel.: +86-21-62232764; E-mail: fyang@chem.ecnu.edu.cn; jtang@chem.ecnu.edu.cn

[¶]These authors contributed equally to this work.

ACCEPTED MANUSCRIPT

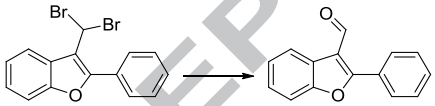
phenylprop-2-en-1-one (**2a**) from **1a** according to the synthetic method in literature.[16] When **2a** was treated with 2 equivalents of BBr_3 in DCM, product **3a** was obtained in 96% yield. It is well known that gem-dihalo compounds are widely used as starting material for preparation of aldehydes.[17,18] Actually, treatment of **3a** under certain reaction conditions afforded the desired product **4a** in excellent yield and the regioselectivity problem was completely prevented. Herein, we reported this efficient method for preparation of 3-formyl-2-arylbenzo[*b*]furans starting from 3-chloro-2-(2-methoxyaryl)-1-arylprop-2-en-1-one.



Scheme 1. Direct demethylation and cyclization of **1a**.

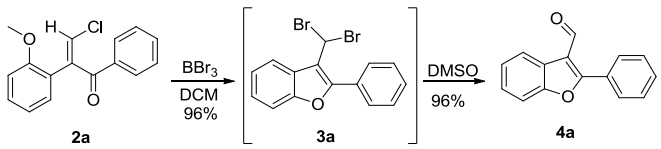
The reaction conditions for converting the *gem*-dibromide **3a** into the corresponding aldehyde were firstly screened (Table 1). It was sluggish and the product was obtained in low yields while the reaction was carried out with 20% acetic acid (Table 1, entry 1), 20% sulfuric acid (Table 1, entry 2) or saturated sodium carbonate solution (Table 1, entry 3) in THF, and the conversion was incomplete during the giving reaction time. While treatment of **3a** with DMSO[18] at 60 °C for 0.5 h, **4a** was afforded in 100% conversion and 96% isolated yield (Table 1, entry 5). Although $AgNO_3$[19] was a competent reagent for this reaction (Table 1, entry 4), from the standpoint of overall cost and workup difficulty, DMSO was chosen as the reagent and solvent as well in this reaction. By further simplifying the procedure, we tried to perform the demethylation, cyclization and hydrolysis successively in one pot without isolating the intermediate 3-(dibromomethyl)-2-phenylbenzo[*b*]furan **3a**, and the result was satisfactory, affording the desired product **4a** in 92% yield (Scheme 2). To the best of our knowledge, it should be a new practical protocol for synthesis of this scaffold.

Table 1
Optimization of reaction conditions for converting **3a** to **4a**[a]



Entry	Conditions	Time (h)	Temperature (°C)	Yield (%)[b]
1	5 mL 2N AcOH/ 5 mLTHF	4	66	44
2	5 mL20 % H_2SO_4/ 5 mLTHF	4	66	60
3	5 mL Na_2CO_3/ 5mLTHF	4	66	32
4	2 eq. $AgNO_3$/ 5mL EtOH	1	66	90
5	2 mL DMSO	0.5	60	96

[a] All reactions were carried out at 1 mmol scale.
[b] Isolated yield.

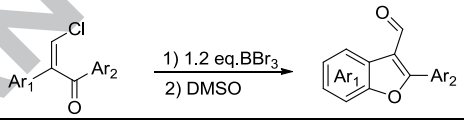


Scheme 2. Synthesis of 3-formyl-2-phenylbenzo[*b*]furan from **2a** in one pot.

To optimize the demethylation and cyclization reaction conditions, the amount of BBr_3 was investigated. Reducing the usage of BBr_3 from 2 to 1.5 equivalents and further to 1.2 equivalents didn't affect the yield of the product (**3a**) which was still isolated in as high as 96%. However, partial of the starting material (**2a**) remained unchange when 1.0 equivalent of BBr_3 was employed in the reaction. Hence, 1.2 equivalents of BBr_3 were chosen as the optimal amount for the demethylation reaction.

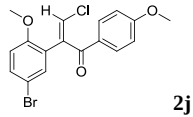
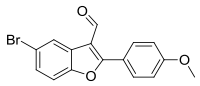
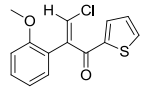
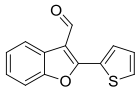
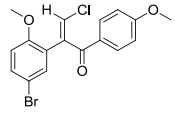
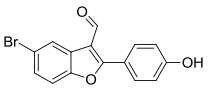
With the optimal conditions in hand, the substrate scope was then examined. As shown in Table 2, 3-formyl-2-arylbenzofuran derivatives were obtained in good yields for most cases. There was no significant difference in reactivity between 2-(2-methoxyphenyl)-3-oxo-3-phenylpropanal (Table 2, entry 1) and its derivatives containing electron-donating groups (Table 2, entries 2 and 10) or electron-withdrawing groups (Table 2, entries 3-9). It was noteworthy that when Ar_2 was altered with heterocyclic groups (Table 2, entry 11), the corresponding heteroaromatic products **4k** was also obtained in excellent yield (92%). For substrate **2j**, a methoxy group substituted at the para position, product **4j** with the *p*-methoxy group was given when 1.2 equivalents of BBr_3 was presented, whereas the demethylated product **4l** was observed in 80% yield when 3 equivalents of BBr_3 was used(Table 2, entry 11).

Table 2
Conversion of 3-chloro-2-(2-methoxyaryl)-1-arylprop-2-en-1-one to 3-formyl-2-arylbenzo[*b*]furans[a]



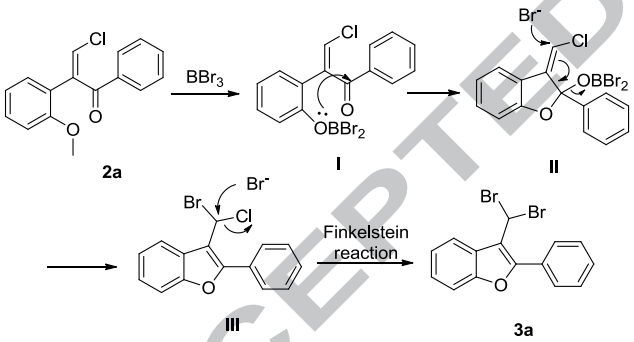
Entry	Substrate	Product	Yield (%)[b]
1	**2a**	**4a**	92
2	**2b**	**4b**	90
3	**2c**	**4c**	93
4	**2d**	**4d**	93
5	**2e**	**4e**	95
6	**2f**	**4f**	89
7	**2g**	**4g**	88
8	**2h**	**4h**	91
9	**2i**	**4i**	94

ACCEPTED MANUSCRIPT

10		**2j**		**4j**	86
11		**2k**		**4k**	92
12[c]		**2l**		**4l**	80

[a] All reactions were run under the same conditions: 1 mmol of start material was dissolved in 10 mL of CH_2Cl_2, BBr_3 (1 M in CH_2Cl_2, 1.2 mL, 1.2 mmol) was added dropwise, the mixture was stirred at 0 °C. After the reaction was complete, the crude intermediate was obtained by extraction and concentration. Then it was dissolved in 2 mL of DMSO and the reaction mixture was stirred at 60 °C, monitored by TLC.
[b] Isolated yield.
[c] 3 equivalents of BBr_3 was used, reaction time 5 h.

To clarify the reaction mechanism, the demethylation reaction was investigated carefully, and the results showed that the product **3a** was formed before the reaction was quenched with water (detected by NMR analysis, however, no any other intermediates were detected). Based on the experimental results, a plausible mechanism for the formation of **3a** is illustrated in Scheme 3. Initially, reaction of vinyl chloride **2a** with BBr_3 generates intermediate **I** which converts to intermediate **II** by intramolecular condensation. Next, addition of Br^- to intermediate **II** to form intermediate **III** and the 2-arylbenzo[*b*]furan ring is formed via this addition/elimination sequence. At last, intermediate **III** transformed to **3a** by Finkelstein reaction.[20]



Scheme 3. Proposed mechanism for the formation of the key intermediate **3a.**

In conclusion, we have developed an efficient and practical method for synthesis of 3-formyl-2-arylbenzofurans via a two-step one-pot protocol. Various derivatives bearing functional groups can be obtained in good to excellent yields. Notably, the products that have halogen substituents on aromatic ring allow further functionalization to give more sophisticated 3-formyl-2-arylbenzofuran derivatives. This synthetic method shows a number of attracting advantages, including high function group compatibility, low cost, relatively short reaction time, easy workup and high overall yield. Furthermore, due to the easy access of a variety of β-ketoaldehyde substrates by Meinwald rearrangement of chalcone epoxides, this work provides a convenient method to construct 3-formyl-2-arylbenzofuran derivatives from easy obtainable starting materials. Further studies of other related applications of this protocol are currently ongoing in our laboratory.

Acknowledgments

This research was supported by Shanghai Science and Technology Council (No. 12142200800 and 13142200900). We also thank "Laboratory of Organic Functional Molecules and The SINO-FRENCH INSTITUTE OF ECNU" for support.

References and notes

1. (a) Chang, H. M.; Cheng, K. P.; Choang, T. F.; Chow, H. F.; Chui, K. Y.; Hon, P. M.; Tan, F. W. L.; Yang, Y.; Zhong, Z. P.; Lee, C. M.; Sham, H. L.; Chan, C. F.; Cui, Y. X.; Wong, H. N. C. *J. Org. Chem.* **1990**, *55*, 3537-3543. (b) Yang, Z.; Hon, P.M.; Chui, K.Y.; Xu, Z. L.; Chang, H. M.; Lee, C. M.; Cui, Y. X.; Wong, H. N. C.; Poon, C. D.; Fung, B. M. *Tetrahedron Lett.* **1991**, *32*, 2061-2064. (c) Chang, J. Y.; Chang, C. Y.; Kuo, C. C.; Chen L. T.; Wein, Y. S.; Kuo, Y. H. *Mol Pharmacol.* **2004**, *65*, 77-84. (d) Wang, E. C.; Wein, Y. S.; Kuo, Y. H. *Tetrahedron Lett*. **2006**, *47*, 9195-9197.
2. (a) Zhang, D. W.; Yang, Y.; Yao, F.; Yu, Q. Y.; Dai, S. *J. J. Nat. Med*. **2012**, *66*, 362-366. (b) Kim, N. H.;, Kim, Y. S.; Lee, Y. M.; Jang, D. S.; Kim, J. S. *Biol. Pharm. Bull*. **2010**, *33*, 1605-1609. (c) Jang, D. S.; Kim, J, M.; Lee, Y. M.; Kim, Y, S.; Kim, J. H.; Kim, J. S. *Chem. Pharm. Bull*. **2006**, *54*, 1315-1317.
3. (a) Halabalaki, M.; Aligiannis, N.; Papoutsi, Z.; Mitakou, S.; Moutsatsou, P.; Sekeris, C.; Skaltsounis, A. L. *J. Nat. Prod.* **2000**, *63*, 1672-1674. (b) Halabalaki, M.; Alexi, X.; Aligiannis, N.; Alexis, M. N.; Skaltsounis, A. L. *J. Nat. Prod*. **2008**, *71*, 1934–1937.
4. (a) Cheung, W. T.; Shi, M. -M.; Young, J. D.; Lee, C. M. *Biochem. Pharmacol*. **1987**, *36*, 2183-2186. (b) Tsai, L. -L.; Hsieh, C. -F,; Duh, C. Y. *Phytochemistry* **1998**, *48*, 1371-1375.
5. Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022-15023.
6. (a) Malona, J. A.; Cariou, K.; Spencer, W. T. III, Frontier, A. J. *J. Org. Chem.* **2012**, *77*, 1891-1908. (b) Malona, J. A.; Cariou, K.; Frontier, A. J. *J. Am. Chem. Soc*. **2009**, 7560-7561.
7. (a) Chen, W.; Deng, X. Y.; Li, Y.; Yang, L. J.; Wan, W. C.; Wang, X. Q.; Zhang, H. B.; Yang, X. D. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4297-4302. (b) Fournier Dit Chabert, J.; Marquez, B.; Neville, L.; Joucla, L.; Broussous, S.; Bouhours, P. ; David, E.; Pellet-Rostaing, S.; Marquet, B.; Moreau, N.; Lemaire, M. *Bioorg. Med. Chem.* **2007**, *15*, 4482-4497.
8. Fürstner, A.; Heilmann, E. K.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 4760-4763.
9. Fischer, J.; Savage, G. P.; Coster, M. J. *Org. Lett.* **2011**, *13*, 3376-3379.
10. Bresser, T.; Mosrin, M.; Monzon, G.; Knochel, P. *J. Org. Chem.* **2010**, *75*, 4686-4695.
11. Nakamura, I.; Mizushima, Y.; Yamagishi, U.; Yamamoto, Y.; *Tetrahedron* **2007**, *63*, 8670–8676.
12. Kao, C.-L.; Chern, J.-W. *J. Org. Chem*. **2002**, *67*, 6772-6787.
13. (a) Ruan, L.-B.; Shi, M.; Li, N.; Ding, X.; Yang, F.; Tang, J. *Org. Lett.* **2014**, *16*, 733-735. (b) Ruan, L.-B.; Shi, M.; Mao, S.-W.; Yu, L.-F.; Yang, F.; Tang, J. *Tetrahedron* **2014**, *70*, 1065-1070. (c) Luo, W.-R.; Mu, Q.-C.; Qiu, W.-W.; Liu, T.; Yang, F.; Liu, X.-F.; Tang, J. *Tetrahedron* **2011**, *67*, 7090-7095.
14. Mathew, P.; Mathew, D; Asokan, C. V. *Synth. Commun*. **2007**, *37*, 661-665.
15. House, H. O. *J. Am. Chem. Soc.***1956**, *78*, 2298-2302.
16. (a) D'Alo, F.; Masserini, A. *Boll. Chim. Farm.* **1965**, *104*, 241-247. (b) Echigo, Y.; Mukaiyama, T. *Chem. Lett.* **1978**, *7*, 465-466.
17. Segesser, J. R.; Calvin, M. *J. Am. Chem. Soc.* **1942**, *64*, 825-826.
18. Li, W.; Li, J. ; DeVincentis, D.; Mansour, T. S. *Tetrahedron Lett.* **2004**, *45*, 1071-1074.
19. Gilman, H.; Brannen, C. G.; Ingham, R. K. *J. Am. Chem. Soc.* **1956**, *78*, 1689-1690.
20. (a) Darwish, T. A.; James, M.; Triani, G.; Hanley, T. L.; Evans, R. A.; Malic, N. *J. Am. Chem. Soc.* **2010**, *132*, 10748-10755. (b) Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14844-14845. (c) Baughman, T. W.; Sworen, J. C.; Wagener, K. B. *Tetrahedron* **2004**, *60*, 10943-10948.