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BF₃·OEt₂-Promoted Concise Synthesis of Difluoroboron-Derivatized Curcumins from Aldehydes and 2,4-Pentanedione

Kai Liu, Jiangmin Chen, Jeremy Chojnacki, and Shijun Zhang*

Department of Medicinal Chemistry, Virginia Commonwealth University, Richmond, Virginia 23298

Abstract

A concise and one-pot cascade method has been developed to achieve the synthesis of difluoroboron-derivatized curcumins (BF₂C). Treatment of 2,4-pentanedione with BF₃·OEt₂, followed by condensation with aldehydes in the presence of tributyl borate and butylamine at 65 °C in toluene furnished the corresponding symmetric (s-BF₂C) and unsymmetric difluoroboron-derivatized curcumins (us-BF₂C) in good (60 - 99%) and moderate yields (23 - 42%) within 6 - 12 h, respectively.

Keywords

BF₃·Et₂O promoted reaction; concise synthesis; difluoroboron complex; Curcumin analog

Curcumin, a yellow spice and pigment isolated from the rhizome of *Curcuma longa*, has been traditionally and widely used as a food coloring additive.¹ Recently, curcumin has attracted extensive attention in biomedical research as multiple biological activities of curcumin have been revealed including antioxidant, anti-inflammatory, biometal chelating, anti-proliferative, and anti-Aβ activities, among others.²⁻⁵ Consequently, curcumin has been tested in various disease models, such as arthritis, cancer, and Alzheimer's disease (AD) as both a preventive and treatment agent.⁶⁻¹⁰ Since curcumin itself possesses a number of properties that limit its potential as an effective medicinal agent, e.g., poor solubility and bioavailability, extensive efforts have been made to develop more effective analogues with improved pharmacokinetic and pharmacological properties. Among the analogues developed, a difluoroboron complex of curcumin was initially developed with increased

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*Correspondence Address: Department of Medicinal Chemistry School of Pharmacy Virginia Commonwealth University Richmond, Virginia 23298-0540 Tel: 804-6288266, Fax: 804-8287625 szhang2@vcu.edu.

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stability and inhibitory potency against HIV protease.¹¹ Furthermore, the difluoroboron-derivatized curcumin analogues such as **CRANAD-2** and **BF₂C** have been demonstrated as novel near-infrared imaging (NIR) probes to detect A β plaques in AD and as chemical sensors for cyanide detection. In addition, detailed photophysical and photochemical research disclosed that the optical properties can be optimized for different purposes by phenyl ring modifications, thus indicating both therapeutic and diagnostic applications of such difluoroboron-derivatized curcumin analogues.^{12,13}

Despite the broad spectrum of biological activities and potential applications for boron complexes of curcumin analogues, the synthetic methodology to produce such analogues has remained quite limited. The **BF₂C** analogues are typically prepared by a two-step process employing A) 2,4-pentanedione and aldehydes or B) curcumin in the presence of BF₃·OEt₂ and Et₃N (Scheme 1). But these methods generally require long reaction times and give typical low yields over the two steps. In addition, curcumin analogues with substituents on phenolic oxygens are typically synthesized by employing the Pabon reaction in another two-step process with low yields.¹⁴ Therefore, a more concise and more efficient method is needed to prepare such analogues. As part of our ongoing studies developing novel curcumin analogues as multifunctional ligands for AD treatment,^{15,16,17} we herein report a new and concise method that allows one-pot selective synthesis of symmetrical (**s-BF₂C**) or unsymmetrical difluoroboron-curcumin analogues (**us-BF₂C**) *via* a BF₃·OEt₂ promoted system. Furthermore, these **BF₂C** analogues can be used as intermediates to deliver a wide range of symmetric and unsymmetric substituted curcumin analogues for biological screening.

First, we selected 2,4-pentanedione and vanillin as the model system to optimize the reaction conditions. Preliminary studies revealed that reaction of vanillin with 2,4-pentanedione in DMF in the presence of excess of BF₃·OEt₂ (1.5 equiv) and catalytic amount of *n*-BuNH₂ afforded only a trace amount of **2a** (Table 1, entry 1). Efforts were then made to optimize the reaction conditions. As shown in Table 1, the addition of tributyl borate as dehydrating agent greatly improves the yield in this type of reaction. Of the solvents screened, toluene afforded **2a** in 94% yield at 65 °C (entry 8). No significant improvement in reaction yield was observed when the reaction was carried out at 100 °C (entry 9). Notably, the difluoroboron-curcumin analogue **2a** was precipitated from toluene, and the purity was determined to be > 92% by HPLC, thus making the isolation and purification process in this method quite practical and accessible.

With the optimized reaction conditions established (Table 1, entry 8), the scope of the BF₃·OEt₂-mediated reaction of 2,4-pentanedione and aldehydes was then studied. As shown in Table 2, all the aldehydes tested yielded **s-BF₂C** in good to excellent yields. In general, substitutions on the phenyl ring of aryl aldehydes are well tolerated under the experimental conditions, and both electron-donating and electron-withdrawing substituents improved the yield slightly compared to unsubstituted compound (entry 2) while with electron-donating substituents being better than electron-withdrawing substituents. Notably, the current method provided significantly improved reaction yield when compared to the reported procedure as demonstrated by the synthesis of compound **2f** (Table 2, entry 6).¹² Furthermore, when benzaldehyde (entry 2) was replaced with a naphthalene-2-carbaldehyde (entry 11) or pyridine-3-carbaldehyde (entry 12), the yield was significantly improved, while replacement with cinnamaldehyde (entry 13) afforded a significantly reduced reaction yield. These observations may indicate that the benzylidene moiety is essential for the complex formation. This notion is further supported by the reduced yield of cyclopropanecarboxaldehyde (entry 14, 60% yield). Since cyclopropanecarboxaldehyde also gave a reasonable yield of 60%, this may suggest that non-aromatic aldehydes could be good substrates for this reaction system. To further confirm this, we tested propionaldehyde and

3-phenyl-propionaldehyde in this reaction system. Surprisingly, no reaction was observed for both non-aromatic aldehyde substrates. The reaction of cyclopropanecarboxaldehyde may be due to the increased sp^2 nature of the cyclopropane in this specific aldehyde, thus indicating that aromatic aldehyde is best suited to this reaction system.

The transformation of aldehyde and 2,4-pentanedione to **BF₂C** under the **BF₃·OEt₂**-promoted reaction likely proceeds via a similar mechanism to that of reported procedure¹² as is outlined in Scheme 2. The significant improvement of reaction yield in our method may be due to the fact that the product can be precipitated from the reaction mixture, thus driving the continuing consumption of the starting aldehyde and the difluoroboron-2,4-pentanedione intermediate. Further studies are needed to understand the mechanism of this method better. Multicomponent reactions are becoming increasingly important because they deliver complex and diverse chemical entities from relatively simple starting materials in a one-pot reaction.¹⁸ With the optimal reaction conditions established for the synthesis of **s-BF₂C**, we investigated the feasibility of developing a multicomponent version of this method to achieve synthesis of **us-BF₂C**. If successful, such a methodology will provide an efficient way to deliver unsymmetric curcumin analogues and this will consequently facilitate the drug development process of such compounds. We initially employed four aldehydes to react with vanillin to test the feasibility and the results are summarized in Table 3. Under the same conditions employed in Table 2, one pot reaction with two different aldehydes afforded **us-BF₂C** (Table 3) in acceptable yields, albeit significantly lower than the mono-aldehyde versions. The reactions afforded the **us-BF₂C** either as a major product (entry 1, Table 3) or with comparable yield to the **s-BF₂C** (entries 2, 3, and 4 of Table 3, two **s-BF₂C** products), thus suggesting that further optimization is necessary to improve the yield of **us-BF₂C**. Notably, the 4-HO-benzaldehyde provided the best yield among the aldehydes tested, consistent with results from Table 2. However, the yield from pyridine-3-carbaldehyde was lower when compared to the results from Table 2.

Finally, we employed **2a** as a model compound to investigate whether the difluoroboron-complex can be deprotected to deliver curcumin efficiently. As shown in Scheme 3, the boron-complex can be deprotected in DMSO-MeOH at 100 °C to afford curcumin in 90% yield, thus confirming that this method can be employed to produce curcumin analogues with substituents on the phenolic oxygens in both symmetric and unsymmetric formats efficiently.

In summary, we have developed a concise and efficient method to allow the one-pot synthesis of difluoroboron-derivatized curcumins (**BF₂C**) employing a **BF₃·OEt₂**-promoted system. When mono aldehyde is employed in the reaction, the **s-BF₂C** can be obtained in good to excellent yields. The improved yield could be due to the precipitation of the product from the solvent of toluene, thus driving the reaction to completion. When two different aldehydes were introduced into this one-pot reaction system, the reaction afforded the **us-BF₂C** in moderate yield. Lastly, this method could also be an efficient choice for preparation of curcumin analogues. Based on the scope of this method and the commercial availability of starting materials, this method should be of high interests for both organic and pharmaceutical chemistry research.

Supplementary Material

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Scheme 1.
Traditional Methods for preparation of BF_2C .

Scheme 2.
Possible pathways towards symmetric s-BF₂C.

Scheme 3. Deprotection of BF₂ group from Difluoroboron-derivatized Curcumin

Table 1Optimization of the $\text{BF}_3 \cdot \text{OEt}_2$ -Promoted One-Pot Synthesis of Difluoroboron-Derivatized Curcumin (BF_2C)^a

entry	solvent	additive	temp	time (h) ^b	yield of 2a (%) ^c
1	DMF	none	65	12	<5 ^d
2	DMF	(<i>n</i> -BuO) ₃ B	65	12	30 ^d
3	DMF	(<i>n</i> -BuO) ₃ B	100	24	32 ^d
4	EtOAc	none	65	12	15 ^d
5	EtOAc	(<i>n</i> -BuO) ₃ B	65	12	80
6	Hexane	(<i>n</i> -BuO) ₃ B	65	12	74
7	CHCl ₃	(<i>n</i> -BuO) ₃ B	65	12	81
8	Toluene	(<i>n</i>-BuO)₃B	65	12	94
9	Toluene	(<i>n</i> -BuO) ₃ B	100	12	95
10	MeCN	(<i>n</i> -BuO) ₃ B	65	12	70
11	cyclohexane	(<i>n</i> -BuO) ₃ B	65	12	68
12	THF	(<i>n</i> -BuO) ₃ B	65	12	54
13	DMAC	(<i>n</i> -BuO) ₃ B	65	24	35 ^d
14	1,4-dioxane	(<i>n</i> -BuO) ₃ B	65	12	70
15	DMSO	(<i>n</i> -BuO) ₃ B	65	24	40 ^d

^aReaction conditions: 2,4-pentanedione (0.2 mmol) and $\text{BF}_3 \cdot \text{OEt}_2$ (0.3 mmol) were reacted in 2 mL of solvent under a nitrogen atmosphere in a Schlenk tube for 2 h. Then vanillin (**1a**, 0.4 mmol), tributyl borate (0.4 mmol except entries 1 and 4) and butylamine (0.04 mmol) were added subsequently, and the reaction was continued for indicated intervals.

^bThe reaction was monitored by TLC.

^cYield of precipitated product.

^dIsolated yields from flash chromatography.

Table 2

Reaction of Aldehydes **1** and 2,4-Pentanedione for the Synthesis of Symmetric Difluoroboron-derivatized Curcumins **2** (s-BF₂C) ^a

entry	Ar ₁	time (h) ^b	purity (%) ^c	yield of 2 (%) ^d
1	3-MeO-4-OH-C ₆ H ₃ -	12	96	94(2a)
2	C ₆ H ₅ -	12	94	80(2b)
3	4-HO-C ₆ H ₄ -	6	95	99(2c)
4	4-MeO-C ₆ H ₄ -	8	93	95(2d)
5	4-Me-C ₆ H ₃ -	12	97	87(2e)
6	4-Me ₂ N-C ₆ H ₄ -	8	96	85(2f)
7	4-F-C ₆ H ₄ -	12	97	79(2g)
8	4-Cl-C ₆ H ₄ -	12	97	75(2h)
9	4-Br-C ₆ H ₄ -	12	95	84(2i)
10	3-NO ₂ -C ₆ H ₄ -	12	99	81(2j)
11		12	98	94(2k)
12		12	99	96(2l)
13		12	99	60(2m)
14		24	97 ^e	60(2n)
15	3,4,5-(MeO) ₃ C ₆ H ₂ -	12	96	92(2o)

^aReaction conditions: 2,4-pentanedione (0.2 mmol) and BF₃·OEt₂ (0.3 mmol) were reacted in 2 mL of solvent under a nitrogen atmosphere in a Schlenk tube for 2 h. Then aldehyde (**1**, 0.4 mmol), tributyl borate (0.4 mmol) and butylamine (0.04 mmol) were added subsequently, and the reaction was continued for several hours.

^bThe reaction was monitored by TLC.

^cDetermined by HPLC.

^dIsolated yields.

^ePurified by silica gel column chromatography.

Table 3

Reaction of Vanillin (**1a**), Aldehydes **3** and 2,4-Pentanedione for the Synthesis of Asymmetric Difluoroboron-Derivatized Curcumins **4**^a

entry	Ar ₂	time (h) ^c	yield of 4 (%) ^c
1	4-HO-C ₆ H ₄ -	6	42(4a)
2	4-Br-C ₆ H ₄ -	12	23(4b)
3	4-NO ₂ -C ₆ H ₄ -	24	25(4c)
4		12	28(4d)

^aReaction conditions: 2,4-pentanedione (0.2 mmol) and BF₃·OEt₂ (0.3 mmol) were reacted in 2 mL of solvent under a nitrogen atmosphere in a Schlenk tube for 2 h. Then vanillin (0.2 mmol), aldehyde (**3**, 0.2 mmol), tributyl borate (0.4 mmol) and butylamine (0.04 mmol) were added subsequently, and the reaction was continued for several hours.

^bThe reaction was monitored by TLC.

^cIsolated yields.