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AN EFFICIENT SYNTHETIC METHOD FOR 3-BROMOFURAN DERIVATIVES *VIA* STEREOSELECTIVE CYCLIZATION OF γ,δ-EPOXY-(*E*)-α-BROMOACRYLATES†

Fumihiko Yoshimura, Masaki Takahashi, Keiji Tanino, and Masaaki Miyashita*,‡

Division of Chemistry, Graduate School of Science, Hokkaido University, Sapporo 060-0810, Japan; E-mail: bt13149@ns.kogakuin.ac.jp

† Dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

‡ Current address: Department of Applied Chemistry, Kogakuin University, Tokyo 192-0015, Japan

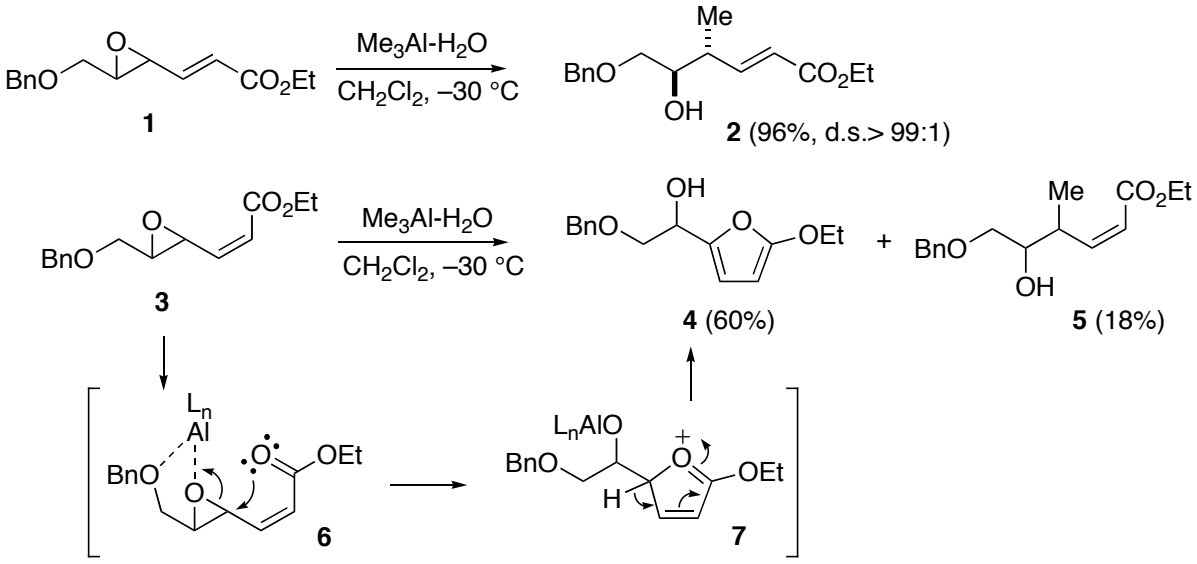
Abstract – A novel and efficient synthetic method for 3-bromofuran derivatives *via* stereoselective cyclization of γ,δ-epoxy-(*E*)-α-bromoacrylates is described. The reaction of a γ,δ-epoxy-(*E*)-α-bromoacrylate with $MeAl_3$-H_2O gave rise to a 3-bromo-2-methylfuran derivative, i.e., methylated bromofuran at the 2-position, while the reaction with Me_3Al-$(CF_3)_2CHOH$ reagent produced a 2-alkoxy-3-bromofuran derivative in high yield. The 3-bromofuran obtained was transformed into various functionalized furan derivatives.

Substituted furans not only constitute an important class of five-membered heterocycles which have been found in many natural products and important pharmaceuticals,[1] but also they have been used as useful building blocks in organic synthesis.[2] Therefore, a large number of synthetic methods for substituted furans have been reported so far,[3] among which representatives include cyclocondensation of 1,4-dicarbonyl compounds (Paal-Knorr synthesis), the base-promoted condensation of 1,3-dicarbonyl compounds with α-haloketones (Feist-Bénary synthesis), and various substitution reactions on a furan ring. Recently, alternative synthetic strategies *via* cycloisomerization of alkynes and allenyl compounds have been explored.[4]

Amongst furans, bromo-substituted ones have played particularly important roles as useful counterparts for coupling reactions as well as versatile synthetic intermediates for functionalized furans.

Bromo-substituted furans are generally prepared by an electrophilic substitution reaction of furan derivatives with bromine atom(s), halogen-induced cyclization, and cyclocondensation or cycloisomerization of halogenated precursors.[5] However, these methods often suffer from the following synthetic limitations: (1) inaccessibility to cyclization precursors having halogen-sensitive functional groups; (2) a furan ring essentially undergoes an electrophilic substitution reaction mainly at the 2- or 5-position rather than at the 3- or 4-position.[6] Thus, development of an alternative synthetic method that allows the regioselective synthesis of bromofurans including 3- and 4-bromo derivatives has remained as an important subject. We report herein an efficient synthetic method for 3-bromofuran derivatives via the Me_3Al-mediated stereoselective 5-*exo* cyclization of γ,δ-epoxy-(*E*)-α-bromoacrylates.

As a program of new acyclic stereocontrol based on the stereospecific methylation reaction of epoxides, we previously reported that the reaction of *trans*-γ,δ-epoxy-(*E*)-acrylate **1** with Me_3Al-H_2O produced *anti*-δ-hydroxy-γ-methyl-(*E*)-acrylate **2** stereospecifically in high yield (Scheme 1).[7] Similarly, the reaction of various γ,δ-epoxy-(*E*)-acrylates with the Me_3Al-H_2O system occurred highly stereoselectively giving rise to γ-methylated compounds with inversion of configuration. On the contrary, the reaction of γ,δ-epoxy-(*Z*)-acrylate **3** with Me_3Al-H_2O produced 2-ethoxyfuran **4** as the major product along with a small amount of γ-methylated compound **5**.[8] We assumed that **4** was probably formed via the reaction mechanism shown in Scheme 1. Namely, the reaction would be initiated by activation of the oxygen atom of the epoxide by an aluminum reagent as shown in **6** and subsequent attack of the carbonyl oxygen would lead to oxonium ion **7**, which was then aromatized by elimination of a proton to afford the furan **4**.

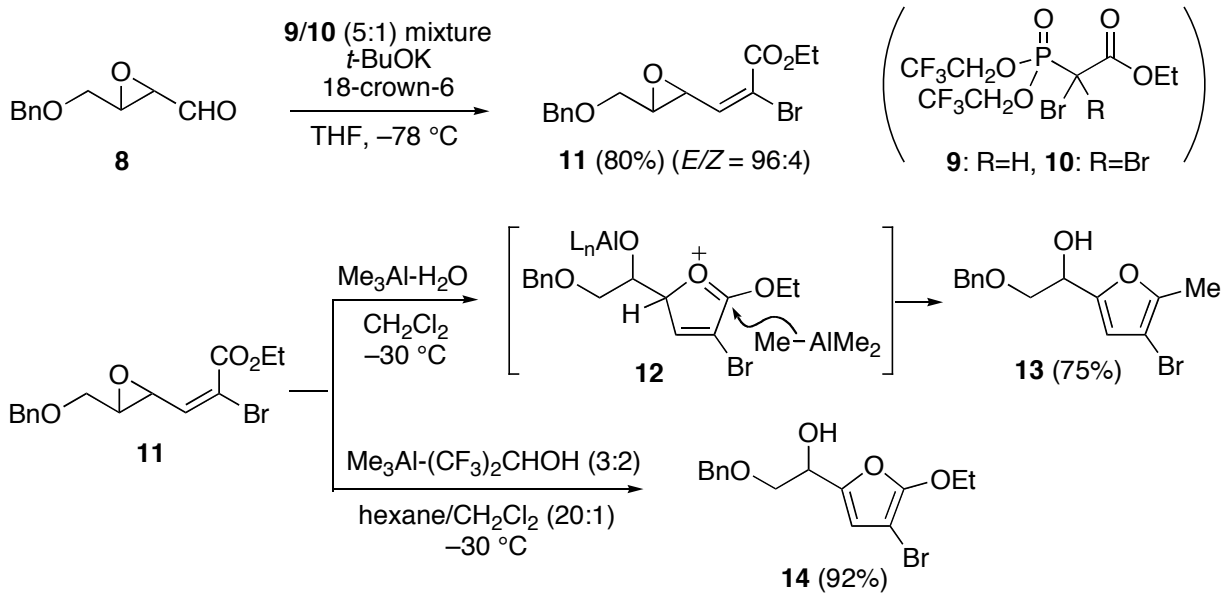


Scheme 1. The reactions of γ,δ-epoxy-(*E*)-acrylate **1** and (*Z*)-acrylate **3** with Me_3Al-H_2O.

Although formation of **4** was unexpected, this particular furan-forming reaction prompted us to investigate synthetic potential of the Lewis acid-mediated cyclization of γ,δ-epoxy-(*Z*)-acrylates, since

various γ,δ-epoxy-(*Z*)-acrylates including the optically active ones are easily obtainable by the *Z*-selective Honer-Emmons reaction using the Ando reagent.[9]

Initially, a number of Lewis acids were surveyed to optimize conversion from **3** to **4**. Lewis acids such as Me_3Al,[10] Me_2AlCl, *i*-Pr_3Al, $ZnCl_2$, $Ti(Oi\text{-}Pr)_4$, $TiCl(Oi\text{-}Pr)_3$, $Ti(OEt)_4$, and $BF_3{\cdot}OEt_2$ were found, however, to be totally fruitless, probably due to instability of both **3** and **4** under the reaction conditions. Then, we hypothesized that replacement of a hydrogen atom at the α-position of the acrylate moiety with a bromine atom might enhance the reactivity of the cyclization reaction which would culminate in the synthesis of 3-bromofurans. In expectation for this idea, we prepared *trans*-γ,δ–epoxy-(*E*)-α-bromo-acrylate **11** as a model substrate. The α-bromoacrylate **11** was readily prepared from aldehyde **8** according to the procedure of Tago and Kogen[11] in high yield (Scheme 2).[12,13] With the model substrate **11** in hand, the key cyclization reaction was examined. Thus, upon treatment of **11** with Me_3Al-H_2O at –30 °C, not the expected 3-bromo-2-ethoxyfuran **14**, but 3-bromo-2-methylfuran **13** was obtained as a single product in 75% isolated yield.[14] Apparently, **13** was produced by way of an oxonium ion **12** with a methyl group transfer from Me_3Al as shown in Scheme 2. In order to synthesize 3-bromo-2-ethoxy furan **14**, we assumed that addition of an appropriate alcohol bearing electron-withdrawing substituent(s) might prevent transfer of a methyl group from Me_3Al, so **14** might be obtainable.

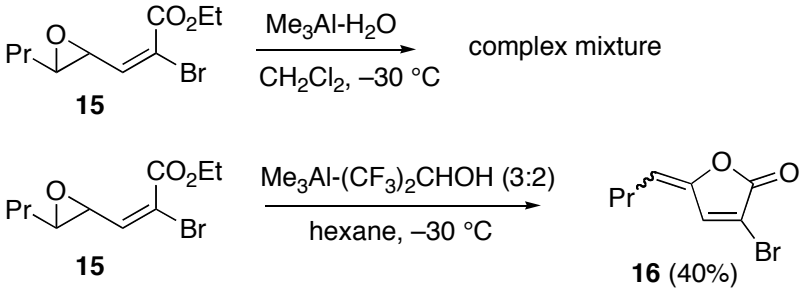


Scheme 2. Synthesis of two types of 3-bromofuran derivatives from (*E*)-α-bromoacrylate **11**.

To this end, several alcohol additives were examined and finally we found that addition of 1,1,1,3,3,3-hexafluoro-2-propanol [$(CF_3)_2CHOH$] gave the satisfactory results. Namely, treatment of **11** with Me_3Al-$(CF_3)_2CHOH$ reagent[15] in a mixed solvent of hexane and CH_2Cl_2 at –30 °C produced the desired 3-bromo-2-ethoxyfuran **14** as a single product in high yield (Scheme 2). It should be noted that

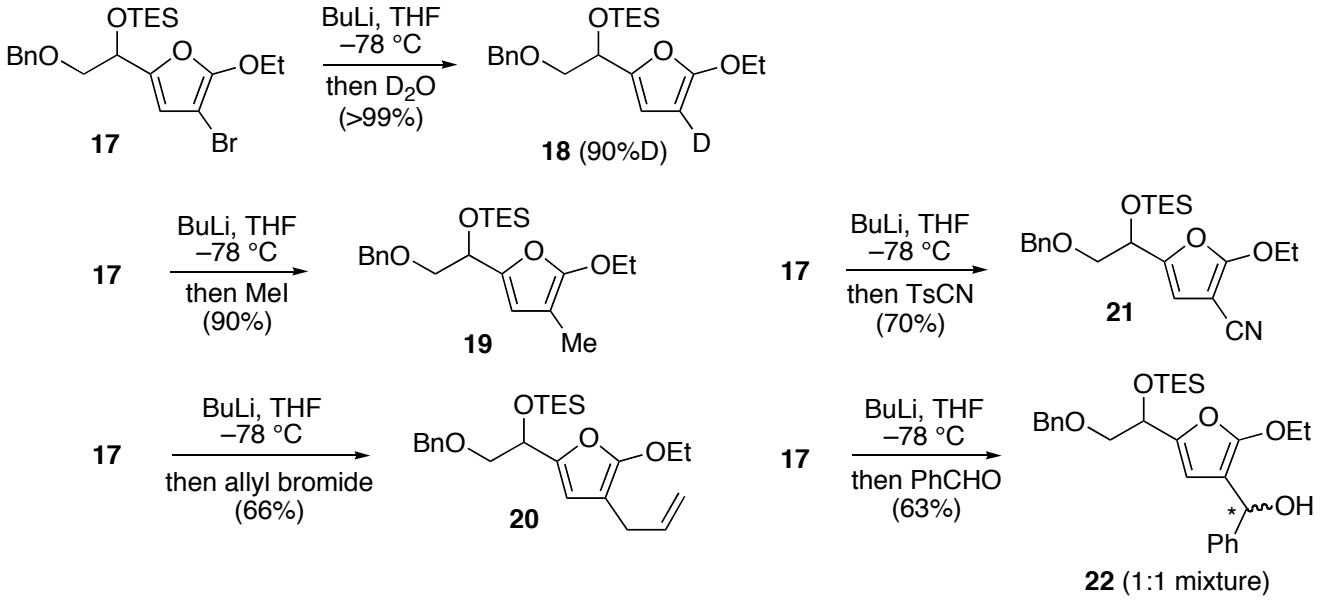
the yield of **14** varied depending on a ratio of Me_3Al and $(CF_3)_2CHOH$[16] and the best result was obtained when the reaction was carried out at –30 °C using a 3:2 molar ratio of Me_3Al and $(CF_3)_2CHOH$ in a 20:1 mixed solvent of hexane and CH_2Cl_2.[17]

On the other hand, the Lewis acid-mediated reaction of (*E*)-α-bromoacrylate **15** bearing no alkoxy group on the side chain did not afford any bromofurans and, instead, bromo-substituted butenolide **16** was obtained in 40% yield. These results clearly suggest that chelation of the aluminum reagent by the oxygen atoms of the epoxide and the ether moiety plays critical roles for the formation of bromofurans.



Scheme 3. The reaction of (*E*)-α-bromoacrylate **15** bearing no alkoxy group on the side chain.

In order to demonstrate the synthetic potential of the new method, a number of 3-substituted furans (**18**–**22**) were synthesized using the silylated 3-bromofuran **17**[18] as shown in Scheme 4. Thus, the reaction of **17** with butyllithium in THF at –78 °C generated the corresponding 3-lithiofuran quantitatively,[19] which smoothly reacted with a variety of electrophiles in a one-pot operation to afford various functionalized 3-substituted furans in 63-90% isolated yield. These reactions demonstrate a promising entry to a variety of 3-substituted furans which are inaccessible by known methods.



Scheme 4. Conversion of 3-bromofuran **17** to various 3-substituted furans (**18**–**22**).

In conclusion, we developed a new synthetic method for 3-bromofurans, which involves a novel Me_3Al-mediated 5-*exo* cyclization of γ,δ-epoxy-(*E*)-α-bromoacrylates. Two types of 3-bromofuran derivatives were obtainable from the same starting material by the use of Me_3Al-H_2O and Me_3Al-$(CF_3)_2CHOH$ reagents. The 3-bromofuran **17** was efficiently transformed into various 3-substituted furans by the substitution reactions with a variety of nucleophiles. Since it is well known that the substitution reaction of a furan ring at the 3- or 4-position is difficult, the present method provides useful tools in organic synthesis including natural product synthesis and pharmaceutical synthesis.

ACKNOWLEDGEMENTS

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8. Recently, we found that the correct structure of the product formed by the reaction of **3** with Me_3Al-H_2O is not originally assigned 5-hydroxy allenic ester,[7] but the furan **4**.
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10. The reaction without addition of water resulted in lower yield (<51%).

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12. Bromophosphonates **9**/**10** (5:1 mixture) were prepared by treatment of ethyl bis(2,2,2-trifluoroethoxy)phosphonoacetate with NaH and $Br(CH_2)_2Br$ in THF.
13. Preparation of **11** from **8** by the Olpp and Brückner method with diphenoxybromophosphonoacetate resulted in lower *E*-selectivity of **11** (*E*/*Z* = 77:23); T. Olpp and R. Brückner, *Synthesis*, 2004, 2135.
14. To a solution of **11** (36.4 mg, 0.11 mmol) in CH_2Cl_2 (1.1 mL) were added H_2O (1.2 μL, 0.66 mmol) and then Me_3Al (2.0 M solution in hexane, 0.55 mL, 1.1 mmol) at –30 °C, and the mixture was vigorously stirred at the same temperature for 30 min. The reaction was quenched with aqueous HCl (0.05 M) and the mixture was thoroughly extracted with Et_2O. The combined organic layers were washed with water, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc = 85:15) to give **13** (25.0 mg, 75%) as a pale yellow oil.
15. The reactive species generated from Me_3Al and $(CF_3)_2CHOH$ is probably $Me_2AlOCH(CF_3)_2$ (dimethyl(1,1,1,3,3,3-hexafluoro-2-propanolato)aluminum.
16. When the ratio of Me_3Al and $(CF_3)_2CHOH$ was changed in 3:1, 3:2, 1:1, and 1:2, **14** was obtained in 76%, 92%, 77%, and <20% yield, respectively.
17. $(CF_3)_2CHOH$ (21 μL, 0.20 mmol) was added dropwise to a solution of Me_3Al (a 2.0 M solution in hexane, 0.15 mL, 0.30 mmol) in hexane (0.3 mL) at 0 °C. After being stirred at the same temperature for 10 min, a solution of **11** (35.5 mg, 0.10 mmol) in hexane-CH_2Cl_2 (14:1, 0.75 mL) was added. After stirring was continued at 0 °C for 15 min, the reaction mixture was treated with saturated Rochelle's salt (aq.) and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc = 8:2) to give **14** (32.7 mg, 92%) as a pale yellow oil.
18. **17** was prepared in 92% yield from **14** (TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C).
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