Atom-Economical and Metal-Free Synthesis of Multisubstituted Furans from Intramolecular Aziridine Ring Opening

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Supporting Information

ABSTRACT: Multisubstituted furans were prepared from dialkyl 2-(aziridin-2-ylmethylene)malonate and/or 1,3-dione through aziridine ring opening by the internal carbonyl oxygen with the assistance of BF3·OEt₂, followed by aromatization. This synthetic method is free from any metal and is atom-economical with all of the atoms in the starting material retained in the final product.

INTRODUCTION

Furans as oxygen-containing five-membered heterocycles are an important class of biologically active compounds. They are found in nature and in various pharmaceuticals as well as in flavor and fragrance. Synthesis of multisubstituted furans is important not only because of their presence in various biologically active compounds but also because they may serve as key synthetic precursors. Especially, 2-aminomethylfurans are found in many important drugs and natural products (Figure 1). 2-Amino-methylated furans are well accessible from readily available furan building blocks such as furfural via reductive amination reaction, but the synthesis of substituted 2-aminomethylfurans requires multiple steps. However, a metal-free method is highly desired to avoid metal impurities in the synthetic products, especially in biologically relevant compounds. A few methods other than the Paal–Knorr furan synthesis were developed for the synthesis of substituted furans without metal catalysts. Most of them proceeded in an intramolecular fashion with strong acid or iodine as reagents. Some of the reactions required a prerequisite of highly reactive intermediates including silyl enol ether, acid chloride, and so forth. Thereby, a mild and metal-free synthetic method for the preparation of multisubstituted furan is highly desirable for further development of this useful heterocycle.

A few previous synthetic methods with the breakage of highly strained cyclopropane or epoxide have been reported in the literature based on the cycloisomerization. All of these methods proceed by the intermediacy of A, which is more or less similar to the reactive intermediate derived from the acyclic starting material. Oxygen from the carbonyl group of the starting substrate adjacent to cyclopropane or ring-opened epoxide attacks the activated alkynic or allenic appendage with the assistance of metal catalysts such as Cu, Ag, Au, and In. However, in this study, we developed a completely different method. The suitably disposed carbonyl oxygen ended in the furan ring attacks nonactivated aziridine which is activated by BF3·OEt₂ followed by aromatization to yield furan. This strategy is depicted as B in Figure 2. The cyclization with the opening of aziridine for a new heterocyclic compound was observed in our early investigations. However, it has not been shown to make a new ring through the cyclization with the breakage of the aziridine ring in an intramolecular fashion. This extraordinary reaction pathway involving cyclization by heteroatoms at the tether of the starting material with

Figure 1. Drugs and natural products containing the 2-amino-methylfuran motif.
concomitant breakage of the highly strained ring shows a possibility to develop new methods for the preparation of various heterocycles.

The key for the success is the breaking of the aziridine ring by the nearby oxygen. Normally, most of the “activated” aziridines readily react with the incoming nucleophile at the less hindered site without any controllable regiochemical diversity. Another chemical method to make ring opening easy is to design the starting substrate with olefin for allylic activation. Even though we have studied aziridine for quite a long time, we were not able to open the “unactivated” aziridine rings with the internal oxygen so far because of the intrinsic inertness of the ring opening. Aziridine in this synthesis is “unactivated” with the electron-donating substituent at the ring nitrogen and is quite stable and inert to almost all nucleophiles. However, they have a big advantage on the regiochemical diversity, that is, their ring can be opened either at C2 or at C3 and is completely controllable by the selection of activators and nucleophiles.

RESULTS AND DISCUSSION

At first, we prepared diethyl 2-(aziridin-2-ylmethylene)malonate (2a) having suitably disposed carbonyl oxygen located near aziridine being ready to attack for the ring opening. Initially, aziridinyl malonate (2a) was treated with 1.05 equiv of BF₃·OEt₂ and sodium acetate in CH₂Cl₂ at room temperature (rt) for 4 h to expect the usual intermolecular aziridine ring-opening product 3a’. Much to our surprise, only intramolecular aziridine ring-opening product 3a was formed in 85% yields without furnishing any traces of the product arising from the intermolecular ring opening (Scheme 1).

Once the structure of furan 3a was confirmed, the same reaction was performed without using external nucleophile sodium acetate and the same results were observed as above. To improve the reaction yield for the conversion of aziridines to furan derivatives, various Lewis acids such as AlCl₃, CeCl₃, I₂, and/or FeCl₃ were screened (Table 1). Among them, only BF₃·OEt₂ and FeCl₃ yielded the expected product, and BF₃·OEt₂ was the most effective.

Several different aziridines were utilized for the intramolecular ring-opening reaction, leading to the synthesis of various aminomethylfurans in good to moderate yields (Table 2).

The optimized reaction protocol was applied for the starting materials with various substituents, that is, R¹ at the nitrogen of 2-(aziridin-2-ylmethylene)malonate and/or 1,3-dione including...
Scheme 2. Mechanism of the Formation of Furan 3a and γ-Lactone 5 from Unsaturated Ester 2a and Saturated Ester 4, Respectively

Scheme 3. Conversion of Furan 3b to Michael Adduct 6 and Polycyclic Compound 7

2-phenylethyl (2a, 2b, 2c, 2I, 2m, 2n, 2o, and 2p), benzyl (2d and 2e), i-butyl (2f, 2g, and 2h), c-hexyl (2i and 2j), and n-hexyl (2k) groups without altering the reaction yields. No difference was observed in the reaction yields by changing the alkyl esters (R3 and/or R4) of 2-(aziridin-2-ylmethylene)-malonate, whether they are methyl (2b and 2f), ethyl (2a, 2d, 2g, 2i, 2l, and 2m), or i-Pr (2c, 2e, 2h, 2j, and 2k). The same starting malonates decorated with the additional methyl (2I, R2 = Me) and i-Pr (2m, R2 = i-Pr) groups at the β-position aiming for the substituent at C4 of the furan ring yielded the expected products (3l and 3m) with the same efficiency. Under the same reaction conditions, the starting substrate (2n) bearing ester (R4 = OEt) and ketone (R3 = Me) at each side (E-/Z-mixture) also afforded the product (3n) in 80% yield. The product 3n retaining the methycarbonyl group at the C3 position of furan suggested us that the aziridine ring opening proceeded by more electron-rich ester oxygen instead of the ketone oxygen. A striking feature of this reaction was represented by the reactions with ketones, as shown in 2o (R3 and R4 = Me) and 2p (R3 and R4 = −CH2CH2CH2−) to produce furans 3o and 3p in 85 and 77% yields, respectively. The formation of these products is ascribed to the breakage of the aziridine ring by ketone oxygen. All of the reactions afforded the expected products in >75% yield with complete conservation of the starting atoms to the products, that is, with high degree of atom economy (Table 2).

A plausible mechanism of this reaction is detailed in Scheme 2. Lewis acid activates the aziridine ring (I) of the starting material 2 by coordinating with the lone pair electrons in the ring nitrogen which was observed in our earlier study.18 At this stage, the ring is highly activated toward the incoming nucleophile, that is, the suitably disposed carbonyl oxygen with the breakage of the carbon–nitrogen bond in aziridine as in I to yield II. This dominant regioselectivity is directed by the allylic activation and by the preference of 5-exo-tet cyclization according to Baldwin’s rule.15,16,19 Then, the aromatization via deprotonation of the acidic proton next to the aminomethyl substituent as in II afforded furan 3.

A corroborating evidence of this mechanism was found from the same reaction with the saturated substrate, diethyl 2-(azirin-2-ylmethylene)malonate 4, affording γ-lactone 5 instead of furan (Scheme 2). When the proton at C2 of aziridine is not acidic enough, dealkylation to form γ-lactone 5 is more dominant rather than aromatization. Therefore, furan 3 and lactone 5 from dialkyl 2-(azirin-2-ylmethylene)malonate 2a and dialkyl 2-(azirin-2-ylmethylene)malonate 4 were obtained from the similar intermediate I in the presence of Lewis acid BF3OEt2, respectively. This reaction proceeded without any metallic additives as catalysts or reagents with complete conservation of all of the starting atoms to the products, that is, as a high degree of atom-economical synthesis.

Taking advantage of this synthetic method to get highly substituted furan especially with aminomethyl appendage at C5, we treated aminomethylfuran 3b with 1.0 equiv of dimethyl acetylenedicarboxylate (DMAD) and obtained Michael addition product 6 in quantitative yields. The reaction of aminomethylfuran 3b with 2.0 equiv of DMAD afforded highly functionalized polycyclic compound 7 as a single isomer, confirmed by the NMR spectra (Scheme 3). The crystalline structure of the single stereoisomeric product 7 confirmed four new stereocenters generated from the

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stereoselective conjugate additions and cycloaddition reactions. Furthermore, it should be noted that all of the atoms in one furan and two acetylenedicarboxylates are completely retained in the adduct without the loss of any atom. On the basis of the above observation, the plausible reaction mechanism for the formation of compound 7 from amino-methylfuran 3b via Michael adduct 6 is proposed (Scheme 4).

**CONCLUSIONS**

In conclusion, we developed a new synthetic method for highly substituted furans from 2-(aziridin-2-ylmethylene)malonate and/or 1,3-diazine via aziridine ring opening by the internal carbonyl oxygen with the assistance of BF$_3$·OEt$_2$ followed by aromatization. This synthetic method is free from any metal and is highly atom-economical with all of the atoms in the starting material retained in the final product.

**EXPERIMENTAL SECTION**

**General Information.** Chiral aziridines are available from Sigma-Aldrich as reagents and from Imagene Co., Ltd. (http://www.imagene.co.kr/) in bulk quantities. All commercially available compounds were used as received unless stated otherwise. All reactions were carried out under a nitrogen atmosphere in oven-dried glassware with a magnetic stirrer. Dichloromethane was distilled from calcium hydride. Reactions were monitored by thin-layer chromatography (TLC) with 0.25 mm E Merck precoated silica gel plates (60 F254). Visualizations were monitored by thin-layer chromatography (TLC) with 0.25 mm E Merck precoated silica gel plates (60 F254). Visualizations were obtained using a RUDOLPH AUTOPOL III polarimeter. Optical rotations were obtained using a JASCO P-2000 polarimeter. Optical rotation data were reported as follows: $[\alpha]_D^{20}$ (concentration $c = \text{g/ml}$, solvent).

**General Procedure for the Synthesis of Multisubstituted Furan (3).** To a stirred solution of dialkyl 2-(aziridin-2-ylmethylene)malonate or 2-(aziridin-2-ylmethylene)-1,3-dione 2 (500 mg, 1.57 mmol) in CH$_2$Cl$_2$ (5.0 mL) was added BF$_3$·OEt$_2$ (0.20 mL, 1.65 mmol) at ambient temperature. The reaction mixture was allowed to stir for 4 h (Table 2). After completion of the reaction as confirmed by TLC (50% EtOAc/hexane), the mixture was quenched with aq NaHCO$_3$ (5.0 mL) and extracted with CH$_2$Cl$_2$ (10 × 3 mL). The combined organic layer was dried over anhydrous Na$_2$SO$_4$ and the solvent was removed in vacuo. This crude product was purified by column chromatography to provide analytically pure furan 3.

**Scheme 4. Plausible Reaction Mechanism for the Formation of Compound 7**
Isopropyl 5-[(Benzyloxy)methyl]-2-isopropoxyfuran-3-carboxylate (3e). \( R_1 = 0.60 \) (EtOAc/hexane, 50%); 1H NMR (400 MHz, CDCl3): \( \delta \) 7.35–7.27 (m, 4H), 7.26–7.20 (m, 1H), 6.39 (s, 1H), 5.18–5.08 (m, 1H), 4.94–4.84 (m, 1H), 3.76 (s, 2H), 3.64 (s, 2H), 1.77 (br s, 1H), 1.40 (d, \( J = 6.2 \) Hz, 6H), 1.29 (d, \( J = 6.3 \) Hz, 6H); 13C NMR (CDCl3, 101 MHz): \( \delta \) 162.4, 160.6, 143.4, 139.5, 128.1, 127.9, 126.7, 108.1, 94.9, 76.8, 66.6, 52.2, 44.8, 22.1, 21.7; HRMS-MALDI (m/z): [M + Na]* calcld for C19H25NO4Na, 354.1676; found, 354.1660.

Methyl 5-[(tert-Butylamino)methyl]-2-methoxyfuran-3-carboxylate (3f). \( R_1 = 0.50 \) (EtOAc/hexane, 50%); 1H NMR (400 MHz, CDCl3): \( \delta \) 6.38 (s, 1H), 4.10 (s, 3H), 3.80 (s, 3H), 3.64 (d, \( J = 0.7 \) Hz, 2H), 1.60 (br s, 1H), 1.15 (s, 9H); 13C NMR (CDCl3, 101 MHz): \( \delta \) 163.4, 161.4, 144.3, 107.9, 91.6, 58.1, 51.1, 50.6, 39.6, 28.8; HRMS-MALDI (m/z): [M + Na]* calcld for C19H25NO4Na, 264.1207; found, 264.1214.

Ethyl 5-[(tert-Butylamino)methyl]-2-ethoxyfuran-3-carboxylate (3g). \( R_1 = 0.40 \) (EtOAc/hexane, 50%); 1H NMR (400 MHz, CDCl3): \( \delta \) 6.39 (s, 1H), 4.44 (q, \( J = 7.1 \) Hz, 2H), 4.25 (q, \( J = 7.1 \) Hz, 2H), 3.64 (d, \( J = 0.7 \) Hz, 2H), 1.76 (br s, 1H), 1.45 (t, \( J = 7.1 \) Hz, 3H), 1.32 (t, \( J = 7.1 \) Hz, 3H), 1.16 (s, 9H); 13C NMR (CDCl3, 101 MHz): \( \delta \) 163.1, 161.3, 144.1, 107.7, 93.0, 68.2, 59.7, 50.7, 39.7, 28.8, 14.9, 14.3; HRMS-MALDI (m/z): [M + Na]* calcld for C19H25NO4Na, 292.1520; found, 292.1534.

Isopropyl 5-[(Cyclohexylamino)methyl]-2-isopropoxyfuran-3-carboxylate (3h). \( R_1 = 0.50 \) (EtOAc/hexane, 50%); 1H NMR (400 MHz, CDCl3): \( \delta \) 6.37 (s, 1H), 5.18–5.07 (m, 1H), 4.96–4.85 (m, 1H), 3.64 (d, \( J = 0.6 \) Hz, 2H), 1.77 (br s, 1H), 1.40 (d, \( J = 6.2 \) Hz, 6H), 1.29 (d, \( J = 6.3 \) Hz, 6H), 1.15 (s, 9H); 13C NMR (CDCl3, 101 MHz): \( \delta \) 162.7, 160.7, 144.5, 107.4, 95.3, 77.1, 66.9, 50.6, 39.7, 28.8, 22.3, 21.9; HRMS-MALDI (m/z): [M + Na]* calcld for C18H27NO4Na, 320.1833; found, 320.1848.

Ethyl 5-[(Cyclohexylamino)methyl]-2-ethoxyfuran-3-carboxylate (3i). \( R_1 = 0.40 \) (EtOAc/hexane, 50%); 1H NMR (400 MHz, CDCl3): \( \delta \) 6.38 (s, 1H), 4.43 (q, \( J = 7.1 \) Hz, 2H), 4.25 (q, \( J = 7.1 \) Hz, 2H), 3.69 (s, 2H), 2.51–2.40 (m, 1H), 1.91–1.83 (m, 2H), 1.79 (br s, 1H), 1.77–1.70 (m, 2H), 1.65–1.57 (m, 1H), 1.44 (t, \( J = 7.1 \) Hz, 3H), 1.32 (t, \( J = 7.1 \) Hz, 3H), 1.27–1.16 (m, 3H), 1.15–1.04 (m, 2H); 13C NMR (CDCl3, 101 MHz): \( \delta \) 163.1, 161.3, 144.5, 108.3, 92.8, 68.0, 59.8, 55.3, 42.8, 33.1, 26.0, 24.8, 14.9, 14.3; HRMS-MALDI (m/z): [M + Na]* calcld for C18H27NO4Na, 318.1677; found, 318.1677.

Isopropyl 5-[(Cyclohexylamino)methyl]-2-isopropoxyfur an-3-carboxylate (3j). \( R_1 = 0.60 \) (EtOAc/hexane, 50%); 1H NMR (400 MHz, CDCl3): \( \delta \) 6.63 (s, 1H), 5.17–5.07 (m, 1H), 4.89 (sep, \( J = 6.2 \) Hz, 1H), 3.68 (d, \( J = 0.6 \) Hz, 2H), 2.44 (tt, \( J = 10.3, 3.8 \) Hz, 1H), 1.89–1.81 (m, 2H), 1.77 (br s, 1H), 1.75–1.68 (m, 2H), 1.65–1.57 (m, 1H), 1.40 (d, \( J = 6.2 \) Hz, 6H), 1.29 (d, \( J = 6.3 \) Hz, 6H), 1.27–1.16 (m, 3H), 1.15–1.03 (m, 2H); 13C NMR (CDCl3, 101 MHz): \( \delta \) 162.7, 160.7, 144.1, 107.9, 95.1, 77.7, 67.9, 55.1, 42.8, 33.1, 25.9, 24.8, 22.3, 21.9; HRMS-MALDI (m/z): [M + Na]* calcld for C18H27NO4Na, 346.1990; found, 346.2002.
56.5, 43.2, 37.0, 23.8, 22.8, 22.1; HRMS-MALDI (m/z): [M + Na]+ calcd for C16H21NO4Na, 314.1363; found, 314.1373.

(R)-Ethyl 2-Oxo-5-[(1-phenylethylamino)methyl]-tetrahydro-furan-3-carboxylate (5). Procedure A. BF3·OEt2 (0.16 mL, 1.3 mmol) was added to a solution of ester 4 (160 mg, 0.5 mmol) in CH2Cl2 (4.0 mL), and the mixture was stirred for 2 h at rt. The reaction mixture was quenched with aq NaHCO3 and extracted with CH2Cl2, and the combined organic layer was dried over Na2SO4. The solvents were removed under vacuum to get a crude product, which was purified by column chromatography to yield pure lactone 5 (81 mg, 56%).

Procedure B. BF3·OEt2 (0.16 mL, 1.3 mmol) was added to a solution of ester 4 (160 mg, 0.5 mmol) in acetonitrile (4.0 mL), and the mixture was refluxed for 2.0 h at 90 °C. The reaction mixture was cooled to rt and quenched with aq NaHCO3. The reaction mixture was extracted with CH2Cl2 (3 × 10 mL), the combined organic layer was dried over Na2SO4, and the solvents were removed under vacuum to get a pure product, which was purified by column chromatography to yield pure lactone 5 (125 mg, 86%). Rf = 0.30 (EtOAc/hexane, 50%); 1H NMR (400 MHz, CDCl3): δ 7.37–7.30 (m, 4H), 7.27–7.20 (m, 1H), 4.68–4.59 (m, 0.5H), 4.55–4.46 (m, 0.5H), 4.24–4.13 (m, 2H), 3.76 (dq, J = 10.2, 6.6 Hz, 1H), 3.67 (dt, J = 10.6, 8.1 Hz, 1H), 2.81–2.71 (m, 1H), 2.61–2.53 (m, 3H), 2.12 (br s, 1H), 1.33–1.21 (m, 6H); HRMS-MALDI (m/z): [M + Na]+ calcd for C16H21NO4Na, 314.1363; found, 314.1373.

(3R,5R,5S,8aR)-Pentamethyl-6-Methoxy-2-[(1-phenyl-ethyl)-2,4a,5,6-tetrahydro-1H-6,8a-epoxyisoquinoline-3,4,5,7,8-pentacarboxylate (7). A mixture of aminomethylfur an 3b (200 mg, 0.69 mmol) and DMAD (84 μL 0.69 mmol) in a sealed tube was stirred for 1 h at 90 °C. The reaction mixture was purified by column chromatography to get pure compound 6 (288 mg, 97% yield). [α]D20 = +66.7 (c = 1.0, CHCl3); Rf = 0.40 (EtOAc/hexane, 50%); 1H NMR (400 MHz, CDCl3): δ 7.45–7.25 (m, 5H), 6.25 (s, 1H), 4.86 (s, 1H), 4.78 (q, J = 6.8 Hz, 1H), 4.02 (s, 3H), 3.96 (s, 3H), 3.92 (s, 2H), 3.76 (s, 3H), 3.64 (s, 3H), 1.64 (d, J = 6.9 Hz, 3H); 13C NMR (CDCl3, 101 MHz): δ 167.8, 166.0, 160.3, 161.0, 153.7, 138.7, 138.6, 128.6, 128.0, 127.3, 110.2, 91.5, 86.4, 58.7, 57.9, 53.0, 51.1, 50.8, 41.5, 17.0; HRMS-MALDI (m/z): [M + Na]+ calcd for C28H31NO12Na, 544.1473; found, 544.1460.

(4α,5R,5S,8aR)-Pentamethyl-6-Methoxy-2-[(1-phenyl-ethyl)-2,4a,5,6-tetrahydro-1H-6,8a-epoxyisoquinoline-3,4,5,7,8-pentacarboxylate (7). A mixture of aminomethylfur an 3b (200 mg, 0.69 mmol) and DMAD (0.17 mL, 1.4 mmol) in acetonitrile (4.0 mL), the mixture was puriﬁed by column chromatography to yield pure lactone 7 (81 mg, 56%). Rf = 0.35 (EtOAc/hexane, 50%); 1H NMR (400 MHz, CD3CN): δ 7.37–7.30 (m, 4H), 7.27–7.20 (m, 1H), 4.68–4.59 (m, 0.5H), 4.55–4.46 (m, 0.5H), 4.24–4.13 (m, 2H), 3.76 (dq, J = 10.2, 6.6 Hz, 1H), 3.67 (dt, J = 10.6, 8.1 Hz, 1H), 2.81–2.71 (m, 1H), 2.61–2.53 (m, 3H), 2.12 (br s, 1H), 1.33–1.21 (m, 6H); HRMS-MALDI (m/z): [M + Na]+ calcd for C28H31NO12Na, 544.1473; found, 544.1913.
