Introduction

Polysubstituted furan derivatives are essential oxygen-containing heterocycles that are embedded in a number of biologically active natural products (Figure 1). A large number of furan derivatives have shown interesting biological activities, such as anti-nociceptive, anti-diabetic, anti-allergic and anti-asthmatic, as well as cytotoxic and antitumor properties.

In addition, many substituted furans are present in dyes, essential oils, cosmetics, flavors, and fragrances. As valuable building blocks, furans are also employed in the synthesis of natural products, electrochemical polymers, and biomolecular macrocycles. Accordingly, the construction of substituted furans has attracted significant attention from chemists. Except for the classical methods, numerous efforts have been dedicated to the development of efficient synthetic methods for the preparation of diversely substituted furans. The development of general and efficient strategies for the synthesis of substituted furans from simple and readily available precursors under mild conditions is of great interest.

In particular, as important furan derivatives, furancarboxylates occur widely as structural units in a variety of synthetic and natural compounds that can be applied as pharmaceuticals and organic materials. Recently, the utilization of simple ketones or 1,3-dicarbonyl compounds as starting materials to construct furancarboxylates through cyclization has attracted increasing interest. General methods for the preparation of the furancarboxylate framework include ring modification and cyclization of acyclic precursors, most of which focus on the cyclization of alkyne- and allene-containing substrates catalyzed by transition metals. For example, Maulide and co-workers developed a method for the synthesis of polysubstituted furancarboxylates from sulfonium ylides and alkynes by gold-catalyzed cross-coupling cyclization. Other methods involve the reaction of alkynes with 1,3-dicarbonyls using dl-[Ni(Phen)_3]Cl_2/Ag_2CO_3 or SnCl_2/CuI as the catalyst. Beyond that, Deng and co-workers reported a strategy for the synthesis of polysubstituted furancarboxylates through potassium iodide (KI)/tert-butyl hydroperoxide (TBHP)-promoted tandem Michael addition/oxidative annulation from 1,3-dicarbonyl compounds and allenes under mild conditions.

Keywords
(E)-3-aryl-2-cyanoacrylates, 1,8-diazabicyclo[5.4.0]undec-7-ene, cyclization reaction, ethyl glycinate hydrochloride, furancarboxylates

Abstract

An efficient synthetic approach for the preparation of densely substituted furans starting from (E)-ethyl 3-aryl-2-cyanoacrylates and ethyl glycinate hydrochloride mediated by 1,8-diazabicyclo[5.4.0]undec-7-ene in the presence of water is investigated. The reactions are carried out under mild conditions in N,N-dimethylformamide at 95 °C. The products are cleanly obtained in 50%–57% yields, resulting in an appealing alternative for accessing polysubstituted furan-2,4-dicarboxylates. The structure of a typical product, diethyl 5-amino-3-(p-tolyl)furan-2,4-dicarboxylate, is confirmed by X-ray crystallography.

Keywords
(E)-3-aryl-2-cyanoacrylates, 1,8-diazabicyclo[5.4.0]undec-7-ene, cyclization reaction, ethyl glycinate hydrochloride, furancarboxylates

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Novel synthesis of furancarboxylate derivatives via cyclization reactions of (E)-ethyl 3-aryl-2-cyanoacrylates and ethyl glycinate hydrochloride

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Although these strategies have been well explored during the past few years, the reactions in many cases suffer from one or more drawbacks such as difficult to obtain substrates, harsh reaction conditions, and the use of noble metal catalysts. In the light of the significance of furancarboxylate systems and their diverse pharmacological properties, there has been a continuous effort to develop new, convenient, and versatile methods for synthesis of this class of compounds. Many studies have shown that glycinate derivatives are highly active and common intermediates in the synthesis of many important heterocycles.\textsuperscript{30-33} Recently, we reported a metal-free, simple, and practical synthetic approach for the synthesis of 5-amino-1H-pyrrole-2-carboxylates via the iodine-catalyzed [3 + 2] cycloaddition reaction of substituted 2-benzylidene-malonitrile and ethyl glycinate hydrochloride.\textsuperscript{34} However, to the best of our knowledge, the cyclization reaction utilizing ethyl glycinate hydrochloride has not been reported to construct furancarboxylates. Herein, we have developed a new method for the synthesis of furancarboxylates starting from 3-aryl-2-cyanoacrylates and ethyl glycinate hydrochloride in the presence of water and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

### Results and discussion

To develop optimal reaction conditions, we began our investigation by studying the cyclization reaction of ethyl (E)-2-cyano-3-(p-tolyl)acrylate (1a) and ethyl glycinate hydrochloride (2). As shown in Table 1, the reaction using a combination of DBU and water afforded the product 3a in a yield of 16% in N,N-dimethylformamide (DMF) at 120 °C (entry 1). As the volatility of water at 120 °C led to inferior results, the reaction temperature was changed to 95 °C. Gratifyingly, the yield increased to 50% under these conditions (entry 2).

Further testing revealed that on using 3 mol L\textsuperscript{-1} HCl (0.1 equiv) instead of DBU at 95 °C, no conversion was observed (entry 3). In the absence of base, using the combination of iodine and water, no reaction took place (entry 4). Next, ethyl (E)-2-cyano-3-(p-tolyl)acrylate (1a) was treated with acid (3 mol L\textsuperscript{-1} HCl or H\textsubscript{2}SO\textsubscript{4}) first, after which the procedure utilized in entry 2 was adapted; however, only 31% and 37% yields of product 3a were obtained (entries 5 and 6). The possible mechanism of the reaction implied that the oxygen of the furan skeleton is derived from water via hydrolysis of the nitrile; thus, H\textsubscript{2}O\textsubscript{2} and K\textsubscript{2}CO\textsubscript{3} were used together in dimethyl sulfoxide (DMSO) at 95 °C for the introduction of oxygen via the addition of the nitrile group to water, with the reaction yielding only 22% of product 3a (entry 7).

Further reactions using ratios of 1a/2 of 1:2.5 or 1:3 in the presence of DBU and water produced 53% and 52% yields, respectively (Table 1, entries 8 and 9). Decreasing the reaction temperature to 85 °C in the presence of DBU and water did not improve the reaction performance, with a 46% yield being obtained (entry 10).

With optimized conditions in hand, the scope of the reaction was evaluated using different ethyl (E)-3-aryl-2-cyanoacrylates (Table 2). Thus a series of ethyl (E)-3-aryl-2-cyanoacrylates was synthesized from the corresponding aldehydes using ethyl cyanoacetate according to a reported procedure.\textsuperscript{35} The (E)-3-aryl-2-cyanoacrylate was then reacted with ethyl glycinate hydrochloride (2). This transformation tolerated a variety of substituents on the phenyl ring of ethyl (E)-3-aryl-2-cyanoacrylate substrate, including MeO, Me, Br, and Cl. The aromatic heterocycle thiophene as a substrate was also tolerated under optimized reaction conditions, affording the corresponding furan-2,4-dicarboxylate 3j in a good yield (51%).

The molecular structures of diethyl 5-amino-3-aryl-furan-2,4-dicarboxylates 3a-J were elucidated from their spectroscopic analyses, with that of 3a described herein as an example. In the infrared (IR) spectrum of 3a, sharp absorption bands at 1694 and 1668 cm\textsuperscript{-1} are due to C(2)-CO\textsubscript{2}Et and C(4)-CO\textsubscript{2}Et stretching frequencies, respectively. The mass spectrum of 3a displayed the molecular ion peak at m/z=340.1165 [M+Na]+, which is in

![Figure 1. Examples of natural compounds containing a furan skeleton.](image-url)

| Entry | Selected conditions | Yield of 3a\textsuperscript{b} |
|-------|---------------------|-----------------------------|
| 1     | H\textsubscript{2}O (1.0 equiv), DBU (1.0 equiv), DMF, 120 °C | 16 |
| 2     | H\textsubscript{2}O (1.0 equiv), DBU (1.0 equiv), DMF, 95 °C | 50 |
| 3     | HCl (0.1 equiv), DMF, 95 °C | 0 |
| 4     | H\textsubscript{2}O (1.0 equiv), I\textsubscript{2} (0.1 equiv), DMF, 95 °C | 0 |
| 5     | (1) HCl (1.0 equiv), rt; (2) DBU (1.0 equiv), DMF, 95 °C | 31 |
| 6     | (1) H\textsubscript{2}SO\textsubscript{4} (1.0 equiv), rt; (2) DBU (1.0 equiv), DMF, 95 °C | 37 |
| 7     | H\textsubscript{2}O\textsubscript{2} (1.0 equiv), K\textsubscript{2}CO\textsubscript{3} (1.0 equiv), DMSO, 95 °C | 22 |
| 8     | H\textsubscript{2}O (1.0 equiv), DBU (1.0 equiv), DMF, 95 °C, n(1a/2)=1:2.5 | 53 |
| 9     | H\textsubscript{2}O (1.0 equiv), DBU (1.0 equiv), DMF, 95 °C, n(1a/2)=1:3 | 52 |
| 10    | H\textsubscript{2}O (1.0 equiv), DBU (1.0 equiv), DMF, 85 °C, n(1a/2)=1:2.5 | 46 |

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; DMF: N,N-dimethylformamide; DMSO: dimethyl sulfoxide.

\textsuperscript{b}n(1a/2) = 1:2 unless otherwise noted, reaction time: 12h.

\textsuperscript{b}Isolated yields.
agreement with the proposed structure. The 1H nuclear magnetic resonance (NMR) spectrum of 3a exhibited two doublets at 7.21 ppm (2H) and 7.15 ppm (2H) for two pairs of non-equivalent aromatic protons, and one singlet at 6.02 ppm (2H) for C(5)-NH₂. The 1H chemical shifts were entirely consistent with the protons in diethyl 5-amino-3-arylfuran-2,4-dicarboxylate 3a. The 1H-decoupled 13C NMR spectrum of 3a showed 15 distinct signals containing two sets of ethyl ester signals in agreement with the suggested structure. Two CO₂Et groups and one methyl on the aromatic ring appeared at 163.7, 161.8, and 20.3 ppm, respectively. The crystal structure of 3a is shown in Figure 2 with the relevant crystal data given in Table 3. X-ray crystallographic analysis determined that product 3a possesses four contiguous substituents at C(2), C(4), C(3), and C(5) of the furan unit, two ester groups, an aromatic ring, and an amino group. On the basis of spectroscopic evidence, the structures of compounds 3a–j were identified as diethyl 5-amino-3-arylfuran-2,4-dicarboxylates.

On the basis of these studies, a plausible mechanism is outlined in Scheme 1. The substrate ethyl glycinate hydrochloride undergoes deprotonation in the presence of the base to give ylide intermediate A, which undergoes a nucleophilic addition to (E)-3-aryl-2-cyanoacrylates to afford intermediate B, which stabilized by charge delocalization to intermediate C. Subsequent nucleophilic addition of water to the ketene imino group affords intermediate D. An intramolecular nucleophilic substitution generates dihydrofuran intermediate E by displacement of ammonia and then undergoes dehydrogenation to give the desired product 3a.

**Conclusion**

In summary, this work describes an efficient synthetic approach for the preparation of densely substituted furans starting from (E)-3-aryl-2-cyanoacrylates and ethyl glycinate hydrochloride in the presence of water. The reactions were carried out under mild reaction conditions in DMF medium at 95 °C, and the products were cleanly obtained in moderate yields. Hence, this method repre-
Experimental

General

All melting points were determined using a Yanaco melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet FTIR 5DX spectrometer. 1H NMR (400 MHz, CDCl3) and 13C NMR (100 MHz, CDCl3) spectra were obtained on Bruker A V-400 and 600 spectrometers according to a reported method,35 and other reagents and solvents were purchased from commercial suppliers and purified by standard techniques.

General procedure for the synthesis of diethyl 5-amino-3-(4-methylphenyl)furan-2,4-dicarboxylate (3b). To a mixture of ethyl (E)-3-aryl-2-cyanoacrylates 1 (1 mmol) and ethyl glycinate hydrochloride (2) (349 mg, 2.5 mmol) in DMF (5 mL) were added DBU (152 mg, 1.0 mmol) and water (1 mmol). The mixture was stirred at 95°C for 12 h. After completion of the reaction (monitored by TLC), water (15 mL) was added to the cooled reaction mixture and then extracted with ethyl acetate (2×10 mL). The organic phase was washed with water (10 mL) and brine (10 mL), and dried over anhydrous sodium sulfate. After removal of ethyl acetate, the crude product was purified by flash chromatography (EtOAc/hexanes, 1:4, silica gel) to give the desired products 3.

Diethyl 5-amino-3-(4-methylphenyl)furan-2,4-dicarboxylate (3b). Yellowish solid, yield: 57%; m.p. 171.5–172.7°C (PE/EtOAc); 1H NMR (CDCl3, 600 MHz): δ 7.22 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 5.64 (s, 2H), 4.08 (q, J = 7.2 Hz, 2H), 4.04 (q, J = 7.2 Hz, 2H), 3.83 (s, 3H), 1.06 (t, J = 7.2 Hz, 3H), 1.01 (t, J = 7.2 Hz, 3H); 13C{1H} NMR (100 MHz, DMSO-d6): δ 163.7, 161.8, 158.3, 135.0, 130.0, 127.8, 122.6, 113.2, 111.4, 91.4, 59.3, 58.7, 54.2, 13.0, 12.9; IR (KBr, cm −1): 3479, 3406, 3301, 2965, 1682, 1647, 1556, 1291, 1262, 1098, 1021, 804; HRMS (ESI): m/z [M + Na]+ calcd for C17H19NNaO6: 356.1110; found: 356.1119.

Diethyl 5-amino-3-(4-bromophenyl)furan-2,4-dicarboxylate (3c). Yellowish solid, yield: 55%; m.p. 171.0–172.2°C (PE/EtOAc); 1H NMR (CDCl3, 400 MHz): δ 7.48 (d, J = 7.8 Hz, 2H), 7.19 (d, J = 7.8 Hz, 2H), 6.12 (s, 2H), 4.13 (q, J = 6.9 Hz, 2H), 4.06 (q, J = 6.9 Hz, 2H), 1.11 (t, J = 6.9 Hz, 3H), 1.02 (t, J = 6.9 Hz, 3H); 13C{1H} NMR (100 MHz, DMSO-d6): δ 163.4, 161.8, 157.7, 133.7, 130.9, 130.3, 129.1, 120.9, 116.9, 91.2, 59.5, 58.8, 13.0, 12.9; IR (KBr, cm −1): 3445, 3347, 2965, 1682, 1647, 1556, 1291, 1262, 1098, 1021, 804; HRMS (ESI): m/z [M + Na]+ calcd for C17H19BrNNaO6: 404.0110; found: 404.0115, 406.0092.

Diethyl 5-amino-3-(m-tolyl)furan-2,4-dicarboxylate (3d). Yellowish solid, yield: 57%; m.p. 165.0–167.0°C (PE/EtOAc); 1H NMR (CDCl3, 400 MHz): δ 7.28–7.23 (m, 1H), 7.19 (d, J = 7.8 Hz, 1H), 7.15 (s, 1H), 7.13 (d, J = 7.8 Hz, 1H), 6.12 (s, 2H), 4.13 (q, J = 6.9 Hz, 2H), 4.06 (q, J = 6.9 Hz, 2H), 2.38 (s, 3H), 1.11 (t, J = 6.9 Hz, 3H), 1.02 (t, J = 6.9 Hz, 3H); 13C{1H} NMR (100 MHz, DMSO-d6): δ 165.2, 162.1, 143.7, 136.7, 130.9, 130.3, 129.6, 129.1, 128.3, 128.9, 116.9, 91.2, 59.5, 58.8, 21.0, 13.0, 12.9; IR (KBr, cm −1): 3432, 3362, 2960, 1680, 1642, 1550, 1295, 1260, 1048, 1022, 796; HRMS (ESI): m/z [M + Na]+ calcd for C17H18BrNNaO6: 340.1161; found: 340.1157.

Diethyl 5-amino-3-(o-tolyl)furan-2,4-dicarboxylate (3e). Yellowish solid, yield: 53%; m.p. 163.0–164.6°C (PE/EtOAc); 1H NMR (CDCl3, 400 MHz): δ 7.29–7.21 (m, 2H), 7.17 (d, J = 7.8 Hz, 1H), 7.15 (d, J = 7.8 Hz, 1H), 6.15 (s, 2H), 4.22 (q, J = 6.9 Hz, 2H), 4.19 (q, J = 6.8 Hz, 2H), 2.30 (s, 3H), 1.16 (t, J = 6.9 Hz, 3H), 1.12 (t, J = 6.9 Hz, 3H); 13C{1H} NMR (100 MHz, DMSO-d6): δ 164.9, 161.2, 145.7, 138.7, 130.5, 130.0, 129.6, 129.0, 128.2, 128.0, 116.9, 91.0, 59.9, 58.6, 20.8, 13.2, 12.6; IR (KBr, cm −1): 3440, 3346, 2950, 1680, 1648, 1552, 1290, 1287, 1262, 1008, 998, 822; HRMS (ESI): m/z [M + Na]+ calcd for C17H19NNaO6: 340.1161; found: 340.1158.
Diethyl 5- amino-3-(3-methoxyphenyl)furan-2,4-dicarboxylate (3f).
Yellowish solid, yield: 52%; m.p. 168.5–169.5°C (PE/EtOAc); 1H-NMR (CDCl3, 400 MHz): δ 7.56 (d, J = 7.8 Hz, 1H), 7.30–7.18 (m, 3H), 6.32 (s, 2H), 4.18 (q, J = 6.9 Hz, 2H), 4.12 (q, J = 6.9 Hz, 2H), 0.96 (t, J = 6.9 Hz, 3H); 13C{1H} NMR (100 MHz, DMSO-d6): δ 163.5, 162.0, 157.7, 133.3, 133.1, 130.7, 129.6, 125.3, 122.3, 116.2, 91.3, 59.4, 58.6, 12.8, 12.6; IR (KBr, cm−1): 3440, 3331, 2952, 1680, 1642, 1550, 1321, 1230, 1098, 1004, 992, 804; HRMS (ESI): m/z [M+Na]+ calcd for C16H15Br2NNaO5: 481.9215; found: 481.9212, 483.9192, 485.9170.

Declaration of conflicting interests
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Supplemental Material
Full details of the X-ray structure and crystal refinement of compound 3a are available online. Crystallographic data for 3a have been deposited with the Cambridge Crystallographic Data Centre with the deposition number CCDC 1923227. The data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk).

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