

CS Comb Sci. Author manuscript; available in PMC 2013 December 11.

Published in final edited form as:

ACS Comb Sci. 2012 July 9; 14(7): 403-414. doi:10.1021/co300040q.

Solution-Phase Synthesis of a Highly Substituted Furan Library

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Abstract

$$R^{1}$$
 R^{3}
 R^{2}
 R^{4}
 R^{1}
 R^{3}
 R^{2}
 R^{3}

A library of furans has been synthesized by iodocyclization and further diversified by palladium-catalyzed coupling processes. The key intermediate 3-iodofurans have been prepared by the electrophilic iodocyclization of 2-iodo-2-alken-1-ones in the presence of various nucleophiles in good to excellent yields under mild reaction conditions. These 3-iodofurans are the key components for library generation through subsequent elaboration by palladium-catalyzed processes, such as Suzuki–Miyaura, Sonagashira, Heck, aminocarbonylation and carboalkoxylation chemistry to afford a diverse set of 2,3,4,5-tetrasubstituted furans.

Keywords

solution-phase parallel synthesis; multisubstituted furans; 3-iodofurans; iodocyclization; electrophiles; nucleophiles

^{*}Corresponding Author: larock@iastate.edu. Phone: (515) 294-4660. Fax: (515) 294-0105. Supporting Information. Synthetic methods, spectral assignments, and copies of ¹H and ¹³C NMR spectra for all previously unreported starting materials and products. This material is available free of charge *via* the Internet at http://pubs.acs.org.

INTRODUCTION

Combinatorial chemistry and high-throughput screening (HTS) for drug discovery have made it possible to synthesize and/or screen large repositories of chemically diverse scaffolds in search of small molecules that disrupt or regulate macromolecular function. 1, 2 Highly substituted furans are frequently found as subunits in many bioactive natural products and pharmaceutically important substances and they are also important building blocks in organic synthesis. 3–11 Selected simple biologically active furan derivatives are shown in Figure 1. (+)-Furodysin (I) and (+)-furodysinin (II) are two sesquiterpenes isolated from pantropical marine sponges of the genus Dysidea. 12 Their absolute configurations has been established by the synthesis of their (-)-isomers from (+)-9-bromocamphor. ¹³ Interestingly, (-)-furodysinin was found in the Mediterranean D. tupha¹⁴ and both (-)furodysin (III) and (-)-furodysinin (IV) have been shown to occur in D. herbacea. 15 The pinguisane class have attracted interest because of their biological activity and rare carbon skeleton. 16 Two examples of pinguisanes are pinguisone (V) and norpinguisone (VI), which exhibit antifeedant and antifungal activity respectively. 17, 18 The hugely successful drug molecule Ranitidine (VII) (trade name Zantac), ¹⁹ is a histamine H₂-receptor antagonist that inhibits stomach acid production. It is commonly used in the treatment of peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD). Ranitidine is also known to give false positives for methamphetamine on drug tests. 19-21

For these reasons, the efficient synthesis of multiply substituted furans continues to attract the interest of synthetic chemists. Numerous heteroannulation protocols, including transition metal-catalyzed reactions, leading to multisubstituted furans have been reported. P. 22–35 Among the variety of oxygen-containing compounds that can be subjected to cyclization, unsaturated alcohols or ketones are substrates of major interest. And Previously, we found that analogous 2-(1-alkynyl)-2-alken-1-ones, which are easily prepared from simple, readily available starting materials, can be very efficiently coupled with a wide variety of nucleophiles using either catalytic amounts of AuCl₃38 or iodine 40, 42, 43 as an electrophile to afford functionally-substituted furans (Scheme 1).

Electrophilic iodocyclization is one of the most powerful methods for the efficient synthesis of a variety of functionalized carbocycles and heterocycles under mild conditions. 4,39, 42, 44 Furthermore, we have demonstrated that the resulting iodine-containing products are very useful templates for further diversification by a variety of C–C, C–N, and C–O bondforming processes and are thus valuable building blocks for combinatorial chemistry. 45–51

Herein, in an extension of our previous studies,⁴⁰ we wish to report the synthesis of a solution phase furan library using this methodology and subsequent elaboration of the resulting multisubstituted 3-iodofurans **2** by various palladium-catalyzed couplings to generate 2,3,4,5-tetrasubstituted furans **3**. To synthesize a library with greater chances for biological activity, the multisubstituted furan template **3** has been evaluated computationally for its drug-like properties on the basis of Lipinski's "rule of five".⁵²

RESULTS AND DISCUSSION

We hypothesized that our previously described iodocyclization process⁴⁰ should readily afford 2,3,4,5-tetrasubstituted furans **3** as key intermediates to compounds of biological interest (Scheme 2). The alkynes $\mathbf{1}\{I-I3\}$ were prepared by the palladium/copper-catalyzed Sonogashira coupling of appropriate starting 2-iodo-2-alken-1-ones⁵³ with various terminal alkynes. Heteroatoms were included in the acetylenes to impart drug-like, hydrogen bond donor or acceptor properties to the 2,3,4,5-tetrasubstituted furans **3**. The results are summarized in Scheme 3.

Accordingly, a set of tetrasubstituted 3-iodofurans $2\{1-34\}$ were efficiently prepared by electrophilic cyclization of the corresponding alkynes 1 in the presence of various nucleophiles including water, primary alcohols, acetic acid, and various diols using I_2 for only 0.5 h under ambient conditions. The results of this iodocyclization process are summarized in Table 1 and Figure 2. All of the reactions were monitored by thin layer chromatography and the products purified by column chromatography. All compounds 2 were characterized by 1H and ^{13}C NMR spectroscopy (see the Supporting Information for the experimental details).

These iodocyclization products 2 are the key components for library generation through subsequent elaboration by palladium-catalyzed processes, such as Suzuki-Miyaura, Sonagashira, Heck, aminocarbonylation and carboalkoxylation reactions, affording a diverse set of 2,3,4,5-tetrasubstituted furans 3 (Scheme 4). Out of the numerous possible combinations, our efforts have been guided by using Lipinski's rule of five and the commercial availability of boronic acids 4, terminal alkynes 5, styrenes 6, amines 7, and alcohols 8 (Figure 3). The purity of the reaction mixtures has been analyzed by thin layer chromatography (TLC), liquid chromatography-mass spectrometry (LC-MS), and high performance liquid chromatography (HPLC). This data has been used to populate a virtual library of all theoretically possible products, giving roughly 8,000 unique potential compounds in a combinatorial fashion.

The results for the palladium-catalyzed coupling processes performed on the multisubstituted furans $3\{1-158\}$ are summarized in Tables 2–6. Various boronic acids 4 for the Suzuki-Miyaura coupling of the multisubstituted 3-iodofurans 2 were chosen on the basis of their commercial availability and their ability to give the desired products 3{1-27,52–60,78–81,123–128} (Method A, Scheme 4). Sonogashira coupling of the 3iodofurans 2 with various terminal alkynes 5 provides the corresponding alkyne products 3{28-40,61-71,82-93,104-110,129-139} (Method B, Scheme 4). No reaction took place when the acetoxy-containing iodofurans $2\{19-21\}$ were subjected to these reaction conditions. The combination of DMF/water as the solvent and (S)-prolinol as the base was more effective than the use of Et₂NH and organic solvents, such as DMF (Scheme 5).⁵⁴ Olefin-containing furan products $3\{41-43\}$ also have been prepared by the Heck coupling of 3-iodofurans 2 with a small styrene sublibrary 6 (Method C, Scheme 4). Amide-containing products 3{72,94–96,140–141} have been prepared by the palladium-catalyzed aminocarbonylation of 3-iodofurans 2 using one atmosphere of carbon monoxide and the amines 7 (Method D, Scheme 4). In addition, carboalkoxylation of the 3-iodofurans 2 using one atmosphere of carbon monoxide and various alcohols 8 in the presence of a palladium catalyst afforded the ester-containing furan products 3{44–51,73–77,97–103,111–122,142– 164 (Method E, Scheme 4). These processes have been performed in parallel on approximately a 35–45 mg scale, starting from the 3-iodofurans 2. All of the crude furan products 3 were isolated by either column chromatography or preparative HPLC.

We have used Lipinski's rule of five as a general guide for bioavailability, because compounds with poor bioavailability face more of a challenge in becoming successful clinical candidates. The distributions of molecular weight, clogP, hydrogen donors, hydrogen acceptors, and rotatable bonds for the synthesis library derived from $3\{1-164\}$ are shown in Figure 4. The molecular weight (less than 500), clogP (less than 5), number of hydrogen bond donors (less than 5 H) and acceptors (less than 10 H), and the number of rotatable bonds (less than 10) have been calculated for each of the library members using the SYBYL program. As can be seen by viewing the data, most of the key parameters for members of the library within the range of those predicted for biologically active furan candidates.

CONCLUSIONS

In summary, we have designed a novel multisubstituted furan library, which has been rapidly constructed by solution-phase synthesis utilizing iodocyclization and palladium-catalyzed couplings. Various substituent 3-iodofurans 2 have been easily prepared through the iodocyclization of 2-(1-alkynyl)-2-alken-1-ones using I_2 as the electrophile in the presence of various nucleophiles. The multisubstituted furans 3 have been synthesized by palladium-catalyzed couplings, such as Suzuki-Miyaura, Sonogashira, Heck, aminocarbonylation and carboalkoxylation chemistry, on a diverse set of 3-iodofuran 2 building blocks, which has provided about 20+ mg pure samples of each library compound. The elaborated multisubstituted furan 3 library members have been added to the collection of the Kansas University NIH Center for Chemical Methodologies and Library Development (KU CMLD) and will be submitted to the National Institutes of Health Molecular Library Screening Center Network (MLSCN) for evaluation by a broad range of assays. We expect this basic methodology to find extensive application in the fields of combinatorial chemistry, diversity-oriented synthesis and drug discovery.

EXPERIMENTAL PROCEDURES

General Procedure for Sonogashira Coupling to Form the 2-(1-Alkynyl)-2-alken-1-ones 1{1-13}

The desired products **1** were prepared by a literature procedure. ⁴² The appropriate 2-iodo-2-alken-1-one ⁵³ (10.0 mmol), 2 mol % $PdCl_2(PPh_3)_2$, 2 mol % CuI and the terminal alkyne (15.0 mmol) were added to THF (50 mL) at 0 °C and then diisopropylamine (3.0 equiv) was added. The reaction mixture was stirred for 1 h at 0 °C and allowed to warm to room temperature to complete the reaction, which was monitored by TLC analysis. After the reaction was over, the resulting mixture was diluted with EtOAc (2 × 200 mL). The separated organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using ethyl acetate/hexanes as the eluent to afford the corresponding 2-(1-alkynyl)-2-alken-1-ones **1**.

Alkyne [1{1}]—The product was obtained as a pale red solid (92% yield): mp = 99–100 °C (uncorrected); 1 H NMR (400 MHz, CDCl₃) δ 2.41–2.47 (m, 2H), 2.66–2.73 (m, 2H), 3.77 (s, 3H), 6.84 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.77 (t, J = 2.9 Hz, 1H); 13 C NMR (100 MHz, CDCl₃) δ 27.3, 34.0, 55.2, 78.8, 95.6, 113.9 (×2), 114.4, 129.9, 133.2 (×2), 159.9, 164.6, 205.6.

General Procedure for I2-Induced Cyclization to the 3-lodofurans 2{1-34}

The iodofurans **2** were prepared by a modified literature procedure. $^{40, 42}$ To a mixture of the 2-(1-alkynyl)-2-alken-1-one **1** (2.0 mmol), I_2 (4.0 mmol), and NaHCO₃ (4.0 mmol) was added a solution of the appropriate diol (8.0 mmol) in MeCN (20 mL). The resulting mixture was stirred at room temperature for 0.5 h, unless otherwise specified. The reaction was monitored by TLC to establish completion. The mixture was diluted with EtOAc (250 mL). The excess I_2 was removed by washing with satd aq $Na_2S_2O_3$. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under a vacuum to yield the crude product, which was purified by flash chromatography on silica gel using EtOAc/hexanes as the eluent to afford the 3-iodofurans **2**

3-lodofuran [2{1}]—The product was obtained as a pale yellow oil (42% yield): ${}^{1}H$ NMR (400 MHz, CDCl₃) δ 1.87 (d, J = 5.5 Hz, 1 H), 2.28–2.35 (m, 1 H), 2.66–2.73 (m, 1 H), 2.85–2.94 (m, 1 H), 2.98–3.05 (m, 1 H), 3.84 (s, 3 H), 5.08 (br s, 1 H), 6.95 (d, J = 8.9 Hz, 2

H), 7.83 (d, J = 8.9 Hz, 2 H); 13 C NMR (100 MHz, CDCl₃) δ 24.0, 38.7, 55.5, 57.1, 69.8, 114.0 (×2), 123.8, 127.8 (×2), 134.1, 156.0, 159.6, 160.5; HRMS calcd for C₁₄H₁₃IO₃ [M]⁺, 355.9909, found 355.9919.

General procedure for Suzuki-Miyaura coupling to prepare furans 3{1-27, 52-60, 78-81, 123-128}

To a 4 dram vial was added the 3-iodofuran **2** (0.2 mmol), boronic acid (0.3 mmol), K_2CO_3 (0.5 mmol) and 10 mol % Pd(PPh₃)₄ in 20:5:1 toluene/ethanol/H₂O (20 mL). The solution was vigorously stirred for 5 min at room temperature, flushed with argon, and then heated to 80 °C for 12 h. Upon cooling to room temperature, the resulting reaction mixture was extracted with EtOAc. The crude product was purified by column chromatography on silica gel using ethyl acetate/hexanes as the eluent to afford the heteroatom ring-containing furans **3**.

Heteroatom ring-containing furan [3{1}]—The product was obtained as slightly yellow solid (74% yield): 1 H NMR (400 MHz, CDCl₃) δ 2.33–2.38 (m, 1 H), 2.65–2.71 (m, 1 H), 2.86–3.04 (m, 2 H), 3.43 (s, 3 H), 3.80 (s, 3 H), 4.44 (s, 2 H), 5.17 (d, J = 6.6 Hz, 1 H), 6.82 (d, J = 8.8 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 7.42 (d, J = 8.8 Hz, 2 H), 7.49 (d, J = 8.0 Hz, 2 H); 13 C NMR (100 MHz, CDCl₃) δ 23.6, 39.6, 55.4, 58.6, 69.6, 74.8, 114.1 (×2), 118.7, 124.7, 128.2 (×2), 128.3 (×2), 128.9 (×2), 130.6, 133.1, 136.9, 153.4, 159.2, 160.3; HRMS calcd for C₂₂H₂₂O₄ [M+H]⁺, 350.1518, found 351.1530.

General procedure for Sonogashira coupling to prepare furans 3

Method A (using Et₂NH and DMF): the 3-iodofurans 2 (0.2 mmol), the alkynes 5 (0.24 mmol), 3 mol % PdCl₂(PPh₃)₂, 6 mol % CuI, DMF (1.5 mL) and Et₂NH (1.5 mL) were mixed in a 0.5–2.0 mL Biotage microwave vial equipped with a magnetic stirrer. The vessel was placed in the microwave reactor and irradiated to ramp the temperature from room temperature to 100 °C and then held at that temperature for 20 min. The mixture was then cooled down and diluted with EtOAc. The combined organic layers were dried over MgSO₄, concentrated, and purified by either column chromatography or preparative HPLC to afford the corresponding furans $3\{28-40, 61-71, 82-93, 104-105, 129-139\}$.

Method B (using (*S*)-prolinol and DMF/H₂O): to a 4 dram vial was added the 3-iodofurans $2\{19-21\}$ (0.2 mmol), alkynes 5 (0.24 mmol), 5 mol % PdCl₂(PPh₃)₂, 10 mol % CuI, (*S*)-prolinol (0.6 mmol), and DMF-H₂O (v/v, 5:1, 1.2 mL). The solution was stirred at room temperature, flushed with argon, and then heated to 70 °C for 3 h. Upon cooling to room temperature, the reaction mixture was extracted with EtOAc. The combined organic layers were dried over MgSO₄, concentrated, and purified by preparative HPLC to afford the corresponding furans $3\{106-110\}$.

Alkyne-containing furan [3{105}]—The product was obtained as a pale yellow oil that solidified upon standing to an ivory solid (63% yield): 1 H NMR (400 MHz, CDCl₃) δ 0.93 (t, J = 7.3 Hz, 3H), 1.57–1.66 (m, 2H), 2.35–2.46 (m, 1H), 2.59–2.69 (m, 1H), 2.75–2.98 (m, 3H), 3.00 (s, 6H), 3.46–3.57 (m, 1H), 3.71 (s, 3H), 4.86 (d, J = 6.9 Hz, 1H), 6.72 (d, J = 8.9 Hz, 2H), 7.41–7.56 (m, 2H), 7.90 (d, J = 8.9 Hz, 2H); 13 C NMR (100 MHz, CDCl₃) δ 11.0, 23.5, 23.8, 32.4, 36.2, 40.5 (×2), 70.9, 76.1, 90.8, 97.4, 112.1 (×2), 119.6, 126.2 (×2), 128.6, 128.7, 129.6, 132.3, 132.4, 150.3, 159.7, 161.0; HRMS calcd for $C_{24}H_{27}N_3O_2$ [M+H]⁺, 389.2103, found 390.2172.

General procedure for Heck coupling to prepare the furans 3{41-43}

To a 4 dram vial was added the appropriate 3-iodofuran **2** (1.0 mmol), the styrene **6** (1.2 mmol), 5 mol % Pd(OAc)₂, *n*-Bu₄NI (1.0 mmol), Na₂CO₃ (2.5 mmol) and DMF (1.5 mL). The solution was stirred at room temperature and flushed with argon, and then heated to 80 °C until TLC revealed complete conversion of the starting material. The solution was allowed to cool and diluted with EtOAc. The combined organic layers were dried over MgSO₄, concentrated, and purified by either column chromatography or preparative HPLC to afford the olefin-containing furans **3**.

Olefin-containing furan [3{41}]—The product was obtained as a pale yellow oil that solidified upon standing to an ivory solid (43% yield): 1 H NMR (400 MHz, CDCl₃) δ 1.78 (d, J = 5.5 Hz, 1 H), 2.30 (s, 3 H), 2.34–2.45 (m, 1 H), 2.62–2.74 (m, 1 H), 2.91–3.05 (m, 2 H), 3.86 (s, 3 H), 5.32 (br s, 1 H), 6.99 (d, J = 8.8 Hz, 2 H), 7.05 (d, J = 8.4 Hz, 2 H), 7.07–7.18 (m, 2 H), 7.46 (d, J = 8.4 Hz, 2 H), 7.53 (d, J = 8.8 Hz, 2 H); HRMS calcd for $C_{24}H_{22}O_{5}$ [M+H]⁺, 390.1467, found 391.1480.

General procedure for aminocarbonylation to prepare furans 3{72, 94-96, 140-141}

A mixture of the appropriate 3-iodofurans **2** (0.8–1.2 mmol), 10 mol % Pd(OAc)₂, 20 mol % PPh₃, TEA (2.0 equiv), and the amine (1.5 equiv) in DMF (1.0 mL) was flushed with an atmosphere of carbon monoxide for 2 min. The solution was stirred at room temperature and then heated to 80 °C until TLC revealed complete conversion of the starting material. Then, the solution was allowed to cool and diluted with EtOAc. The separated organic layer was washed with water and brine, dried over MgSO₄, and concentrated *in vacuo*. The crude product was purified by either column chromatography or preparative HPLC to afford the corresponding amide-containing furans **3**.

General procedure for carboalkoxylation to prepare furans 3{44–51, 73–77, 97–103, 111–122, 142–164}

A stirred mixture of the appropriate 3-iodofuran **2** (0.10 mmol), 10 mol % $Pd(OAc)_2$, 20 mol % PCy_3 , TEA (0.40 mmol), and excess R4OH (0.50–1.0 mmol) in DMF (2.0 mL) was charged in a 50 mL long flask at room temperature. The mixture was flushed with CO gas for 2 min, and the flask was fitted with a balloon of CO gas. The reaction mixture was heated at 110 °C with vigorous stirring. Upon cooling to room temperature, the resulting reaction mixture was extracted with EtOAc (2 × 20 mL). The separated organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using ethyl acetate/hexanes as the eluent to afford the ester-containing furans **3**.

Ester-containing furan [3{111}]—The product was obtained as a pale yellow oil that solidified upon standing to an ivory solid (53% yield): 1 H NMR (400 MHz, CDCl₃) δ 1.77–2.02 (m, 3H), 2.03–2.11 (m, 1H), 2.04 (s, 3H), 2.54–2.63 (m, 1H), 2.73–2.81 (m, 1H), 3.75 (s, 3H), 3.85 (s, 3H), 6.17 (br s, 1H), 6.94 (d, J = 8.9 Hz, 2H), 7.85 (d, J = 8.9 Hz, 2H); 13 C NMR (100 MHz, CDCl₃) δ 18.3, 21.5, 23.1, 29.3, 51.6, 55.5, 65.5, 111.3, 113.7 (×2), 117.2, 122.7, 130.2 (×2), 154.0, 157.7, 160.6, 164.3, 170.5; HRMS calcd for $C_{19}H_{20}O_{6}$ [M+H]⁺[– $C_{2}H_{4}O_{2}$], 344.1260, found 285.1116.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources

Financial support of this work was provided by the National Institute of General Medical Sciences (GM070620 and GM079593) and the National Institutes of Health Kansas University Center of Excellence for Chemical Methodologies and Library Development (GM069663).

We thank Johnson Matthey, Inc. and Kawaken Fine Chemicals Co. Ltd. for donations of palladium catalysts; and Frontier Scientific and Synthonix for donations of boronic acids.

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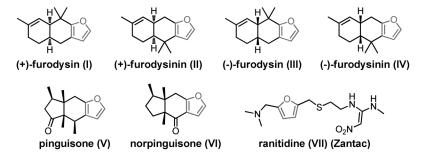


Figure 1. Examples of Significant Furan-Containing Natural Products and Pharmaceuticals

Figure 2. 3-Iodofuran Library $2\{1-34\}$

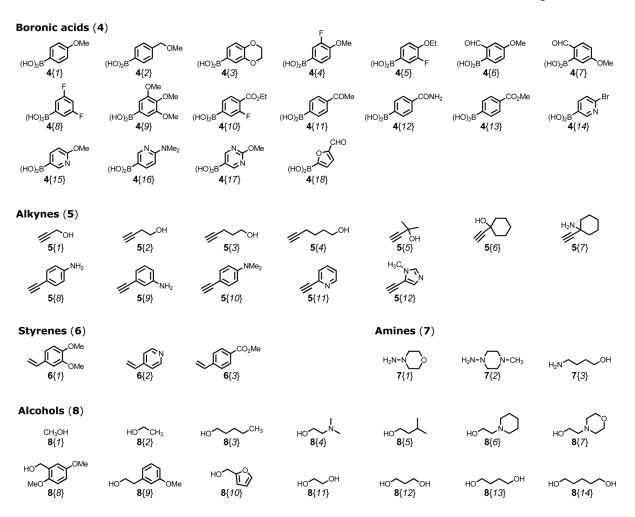


Figure 3.
Sublibraries of Boronic Acids 4, Terminal Alkynes 5, Styrenes 6, Amines 7, and Alcohols 8

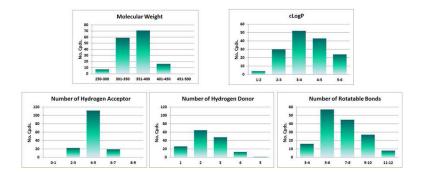


Figure 4.Distribution of physicochemical and structural properties across the library entries

$$R^1$$
 R^3
 E^+
 R^2
 R^3
 R^3
 R^4
 R^2
 R^3
 R^3
 R^3
 R^3
 R^3
 R^3
 R^3

E = H (cat. AuCl₃); NuH = ROH, enol, ArH

E = I; NuH = ROH, RCO₂H, H₂O

E = PhSe; NuH = ROH

Scheme 1.

Efficient Synthesis of Multisubstituted Furans by Electrophilic Cyclization of 2-(1-Alkynyl)-2-alken-1-ones in the Presence of Various Nucleophiles

Scheme 2.
Library Design for the Tetrasubstituted Furans 3

Scheme 3. Preparation of 2-(1-Alkynyl)-2-alken-1-ones $\mathbf{1}\{I-I3\}$

Scheme 4.

Library Generation of Various Tetrasubstituted Furans **3** from the 3-Iodofurans 2^a a *Method A* (Suzuki–Miyaura coupling), $3\{1-27,52-60,78-81,123-128\}$: 10 mol % Pd(PPh₃)₄, K₂CO₃ (2.5 equiv), boronic acid **4** (1.5 equiv), toluene/EtOH/H₂O (20/5/1), 80 °C; *Method B* (Sonogashira coupling), $3\{28-40,61-71,82-93,104-105,129-139\}$: 3 mol % PdCl₂(PPh₃)₂, 6 mol % CuI, alkynes **5** (1.2 equiv), Et₂NH, DMF, 100 °C, 20 min, using microwave irradiation; $3\{106-110\}$: 5 mol % PdCl₂(PPh₃)₂, 10 mol % CuI, (S)-prolinol (3.0 equiv), alkynes **5** (1.2 equiv), DMF/H₂O (v/v, 5:1), 70 °C; *Method C* (Heck coupling), $3\{41-43\}$: 5 mol % Pd(OAc)₂, n-Bu₄NI (1.0 equiv), Na₂CO₃ (2.5 equiv), styrenes **6** (1.2 equiv), DMF, 80 °C; *Method D* (aminocarbonylation), $3\{72,94-96,140-141\}$: CO (1 atm), 10 mol % PdCl₂(PPh₃)₂, PPh₃ (0.2 equiv), amines **7** (1.5 equiv), DMF, Et₃N (2.0 equiv), 80 °C; *Method E* (carboalkoxylation), $3\{44-51,73-77,97-103,111-122,142-164\}$: CO (1 atm), 10 mol % Pd(OAc)₂, 20 mol % PCy₃, TEA (4.0 equiv), R³OH **13** (5–10 equiv), DMF, 110 °C.

Scheme 5. Sonogashira Coupling Using the Acetoxy-Containing 3-Iodofurans $2\{19-21\}$ to Form Alkyne-Containing Furans $3\{106-110\}$

Table 1

Library Data for the 3-Iodofurans $2\{1-34\}^a$

R^{1} \sim \sim R^{3}	\\	Nu 2 {1-34}
l ₂ , NuH	NaHCO ₃ MeCN, r.t.	
	.x }	1{7-13}

entry	alkyne 1	NuH	iodofuran 2	yield (%) b	entry	alkyne 1	NuH	iodofuran 2	yield (%) b
1	1{1}	H_2O	2{1}	42	18	1{3}	n -C $_3$ H $_7$ OH	2{18}	49
2	1 {2}	H_2O	2{2}	53c	19	1{8}	CH_3COOH	2{19}	85
8	1{3}	H_2O	2{3}	78	20	1{1}	СН3СООН	2{20}	82
4	1{4}	H_2O	2{4}	68	21	1{5}	СН3СООН	2{21}	77
S	1{5}	H_2O	2{5}	73	22	1{7}	СН3СООН	2{22}	69
9	1{6}	H_2O	2{6}	47	23	1{1}	$HO(CH_2)_2OH$	2{23}	98
7	1{7}	H_2O	2{7}	89	24	1{3}	$HO(CH_2)_2OH$	2{24}	99
∞	1{3}	CH_3OH	2{8}	53	25	1{4}	$HO(CH_2)_2OH$	2{25}	83
6	1{8}	CH_3OH	2{9}	73	26	1{8}	$HO(CH_2)_2OH$	2{26}	82
10	1{6}	CH_3OH	2{10}	59	27	1{7}	$HO(CH_2)_2OH$	2{27}	82
11	1{7}	CH_3OH	2{11}	77c	28	1{9}	$HO(CH_2)_2OH$	2{28}	87
12	1{9}	CH_3OH	2{12}	87	29	1{10}	$HO(CH_2)_2OH$	2{29}	68
13	1{2}	C_2H_5OH	2{13}	73	30	1{11}	$HO(CH_2)_2OH$	2{30}	82
14	1{8}	C_2H_5OH	2{14}	77	31	1{12}	$HO(CH_2)_2OH$	2{31}	81
15	1{5}	C_2H_5OH	2{15}	87	32	1{13}	$HO(CH_2)_2OH$	2{32}	84
16	1{7}	C_2H_5OH	2{16}	99	33	1{4}	$HO(CH_2)_4OH$	2{33}	77
17	1{9}	C_2H_5OH	2{17}	82	34	1{4}	HO(CH ₂) ₅ OH	2{34}	99

^aUnless otherwise noted, all of the reactions have been carried out using NaHCO3 (2.0 equiv), the nucleophile (4.0 equiv) and I₂ (2.0 equiv) in MeCN (0.1 M conc.) at room temperature for 0.5 h.

b Isolated yields after column chromatography.

 $^{^{\}mathcal{C}}$ An inseparable mixture was obtained. This material decomposes quickly in solution.

Cho et al. Page 20

Table 2

Library Data for Compounds $3\{I-5I\}$

product 3	u	\mathbb{R}^3	building blocks method ion HRMS	method	ion HRMS	calcd for HRMS	found HRMS purity $(\%)^d$ yield $(\%)^b$	purity $(\%)^{\mathcal{G}}$	yield $(\%)^p$
3{1}	-	4-MeOC ₆ H ₄	4{2}	A	[M+H] ⁺	350.1518	351.1530	76	745
3{2}	_	$4-\mathrm{MeOC_6H_4}$	4 { <i>5</i> }	Ą	$[M+H]^+$	396.1373	397.1388	66	<i>f</i> 99
3 {3}	_	$4-\mathrm{MeOC}_6\mathrm{H}_4$	4{17}	٧	[M+H] ⁺	338.1267	339.1351	<	62
3{4}	1	3-thiophenyl	4{9}	Ą	$[M+H]^+$	372.1031	373.1043	66	58 <i>f</i>
3{5}	1	3-thiophenyl	4{10}	A	[M+H] ⁺	372.0832	373.0903	76	19
3{6}	-	3-thiophenyl	4{16}	Ą	$[M+H]^+$	326.1089	327.1175	82	41
3{7}	1	$4-\mathrm{Me}_2\mathrm{NC}_6\mathrm{H}_4$	4{4}	Ą	$[M+H]^+$	367.1584	368.1592	66	52
3{8}	2	C_6H_5	4 { <i>I</i> }	Ą		348.1362		1	f19
3{6}	7	C_6H_5	4{9}	٧	[2M+H] ⁺	380.1623	761.3345	<	72
3{10}	2	C_6H_5	4 { <i>II</i> }	Ą	$[M]^+$	348.1362	348.1372	1	81^{f}
3{11}	2	C_6H_5	4{18}	٧	[M+Na] ⁺	308.1049	331.0943	86	61
3{12}	2	$3-\mathrm{MeOC}_6\mathrm{H}_4$	4 { <i>4</i> }	∢	$[M+H]^+[-H_2O]^C$	368.1424	385.1464	66	77
3{13}	2	$3-MeOC_6H_4$	4{6}	A	$[M+H]^{+}[-H_{2}O]$	378.1467	361.1430	<	39
3{14}	2	$3-MeOC_6H_4$	4{7}	Ą	$[M+H]^{+}[-H_{2}O]$	378.1467	361.1431	84	26
3{15}	2	$3-\mathrm{MeOC}_6\mathrm{H}_4$	4 { <i>II</i> }	Ą	$[M+H]^+$	362.1519	363.1598	86	75
3{16}	2	$3-MeOC_6H_4$	4 {13}	Ą	[M+H] ⁺	378.1467	379.1553	66	61
3{17}	2	$3-MeOC_6H_4$	4 { <i>1</i> 4}	A	[M+H] ⁺	399.0470	400.0532	<	13
3{18}	7	$3-\mathrm{MeOC_6H_4}$	4 { <i>15</i> }	Ą	[M+H] ⁺	351.1471	352.1545	<	£88
3{19}	2	$3-MeOC_6H_4$	4{17}	Ą	[M+H] ⁺	352.1423	353.1506	78	41
3 {20}	2	$3-MeOC_6H_4$	4{18}	A	[M+H] ⁺	338.1143	339.1222	62	24
3{21}	2	$3,5-(MeO)_2C_6H_3$	4{8}	Ą	$[M+H]^+$	386.1330	387.1343	76	56
3{22}	7	3-thiophenyl	4{3}	∢	[M+H]+	354.0926	355.0939	86	61

,			;						4
product 3	=	K.	building blocks	method	10n HKMS	calcd for HKMS	found HKMS	purity (%) ⁴	yield (%)
3 {23}	2	3-thiophenyl	4 { <i>4</i> }	A	[M+H] ⁺	344.0882	345.0891	76	53
3{24}	2	3-thiophenyl	4{6}	٧	$[M+H]^+[-H_2O]$	354.0926	337.0890	>66	26
3{25}	2	3-thiophenyl	4 { <i>1</i> 4}	Α	$p_{+}[\mathrm{H+M}]$	374.9929	377.9978	88	23
3{26}	2	3-thiophenyl	4{15}	A	$[M+H]^+$	327.0929	328.0996	92	36
3{27}	7	3-thiophenyl	4{18}	Α	[M+Na] ⁺	314.0613	337.0500	83	12
3{28}	_	4-MeOC ₆ H ₄	5 {2}	В	[M+H] ⁺	298.1205	299.1275	66<	26
3{29}	-	3-thiophenyl	5 {2}	В	[M+H] ⁺	274.0664	275.0742	27	ж
3{30}	_	3-thiophenyl	5 { <i>9</i> }	В	$[M]^+$	321.0823	321.0831	91	f19
3{31}	2	3-MeOC ₆ H ₄	5{1}	В	$[M+H]^+$	298.1205	299.1340	<	787
3 {32}	2	3-MeOC ₆ H ₄	5 {2}	В	[M+H] ⁺	312.1362	313.1434	76	17
3{33}	2	$3-\mathrm{MeOC}_6\mathrm{H}_4$	5 {5}	В	$[M+H]^+$	326.1518	327.1650	<	81 <i>f</i>
3{34}	2	$3-\mathrm{MeOC}_6\mathrm{H}_4$	5 { <i>6</i> }	В	$[M+H]^{+}[-H_{2}O]$	366.1831	349.1793	<	62
3{35}	2	$3-\mathrm{MeOC}_6\mathrm{H}_4$	5{7}	В	$[M+H]^+$	365.1991	366.2099	<	23
3{36}	2	$3-\mathrm{MeOC_6H_4}$	5{8}	В	$[M+H]^+$	359.1521	360.1620	79	38
3{37}	2	$3-MeOC_6H_4$	5 {10}	В	$[M+H]^+$	387.1834	388.1902	84	14
3{38}	2	$3-MeOC_6H_4$	5{11}	В	$[M+H]^+$	345.1365	346.1444	94	12
3{39}	7	$3,5-({ m MeO})_2{ m C}_6{ m H}_4$	2 { <i>0</i> }	В	$[M+H]^{+}[-H_{2}O]$	396.1937	379.1900	98	51
3{40}	2	3-thiophenyl	5 {5}	В	$[M+H]^{+}[-H_{2}O]$	302.0977	285.0938	>99	3
3{41}	1	$4 ext{-MeOC}_6 ext{H}_4$	6 {3}	C	[M+H]+	390.1467	391.1480	72	43f
3{42}	2	$3-MeOC_6H_4$	6 { <i>I</i> }	C	$[M+H]^+$	406.1780	407.1876	<	56
3{43}	7	3-thiophenyl	6 { <i>I</i> }	C	[M+H] ⁺	323.0980	324.0988	78	28
3{44}	-	3-thiophenyl	8 {3}	H	$[\mathrm{M+NH_4}]^+$	320.1082	338.1432	66<	15
3{45}	-	3-thiophenyl	8(5)	Ţ	[M+H]+[H-O]	320 1092	303 1043	007	£00

.R³ -OR⁴ 1}	found HRMS	359.2002	302.1160	285.1115	360.1814
Rt OH 31445	calcd for HRMS found HRMS	358.1893	302.1154	316.1311	359.1733
3(21-43)	method ion HRMS	$[M+H]^+$	$[\mathrm{M}]^{\scriptscriptstyle +}$	$[M+H]^+[-CH_4O]^e$	[M+H] ⁺
3428		田	Щ	Щ	Щ
3(1-27)	building blocks	8{4}	8{11}	8 {2}	8{4}

4-Me₂NC₆H₄

product 3 3{46}

Cho et al.

53f

99

400.2121 369.1418

399.2046

[M+H]⁺ [M+H]⁺

ш ш ш

8{4} **8**{6}

7

3{50}

3{51}

3-MeOC₆H₄
3-MeOC₆H₄
3-MeOC₆H₄
3-MeOC₆H₄

3{47} 3{48} 3{49}

73f

96 6

yield $(\%)^{b}$

purity $(\%)^a$

 $^{a}\mathrm{UV}$ purity determined at 214 nm after preparative HPLC.

 $\frac{b}{b}$ Isolated yield after preparative HPLC.

 $^{C} {\rm Isotope:} \ [\mathrm{A+(-17)}]$

dIsotope: [A+2]

^eIsotope: [A⁺(-31)]

^fsolated yield after column chromatography. Isolated desired products 3 were characterized by ¹H and ¹³C NMR spectroscopy (see the Supporting Information).

Cho et al. Page 23

Table 3

Library Data for Compounds 3{52-77}

product 3	u	R³	building blocks	method	ion HRMS	calcd for HRMS	found HRMS	purity $(\%)^a$	yield $(\%)^{b}$
3{52}	2	4-MeOC ₆ H ₄	4{2}	Α	$[M+H]^+[-CH_4O]$	378.1831	347.1636	95	,999
3 {53}	2	$4-\mathrm{MeOC_6H_4}$	4 {3}	A	[M+H] ⁺	392.1624	393.1683	<	58
3{54}	2	$4-\mathrm{MeOC_6H_4}$	4 { <i>4</i> }	A	$[M+H]^+$	382.1580	383.1592	66	52
3 {55}	2	$4-\mathrm{MeOC_6H_4}$	4{6}	A	$[M+H]^+$	392.1624	393.1695	84	20
3{56}	2	$4-\mathrm{MeOC_6H_4}$	4 {8}	A	$[M+H]^+$	370.1380	371.1390	66	61
3{57}	2	$4-\mathrm{MeOC_6H_4}$	4{13}	Ą	$[M+H]^+$	392.1624	393.1713	95	17
3 {58}	2	3.5 -(MeO) $_2$ C $_6$ H $_4$	4{15}	A	$[M+H]^+$	395.1733	396.1745	96	38
3{59}	2	$4-\mathrm{Me}_2\mathrm{NC}_6\mathrm{H}_4$	4 {2}	Ą	$[M+H]^+[-CH_4O]$	391.2147	360.1955	69	52
3{60}	2	$4-\mathrm{Me}_2\mathrm{NC}_6\mathrm{H}_4$	4 { <i>18</i> }	Α	[M+Na] ⁺	365.1627	388.1609	92	12
3{61}		4-Me ₂ NC ₆ H ₄	5 {2}	В	[M+H] ⁺	325.1678	376.1744	99	28
3 { <i>6</i> 2}	1	$4-\mathrm{Me}_2\mathrm{NC}_6\mathrm{H}_4$	5{4}	В	$[M+H]^+$	353.1991	354.2057	81	55 _C
3 { <i>63</i> }	-	$4-\mathrm{Me}_2\mathrm{NC}_6\mathrm{H}_4$	5 {5}	В	[M+H] ⁺	339.1834	340.1904	92	61
3{64}	2	$4-\mathrm{MeOC_6H_4}$	5{1}	В	$[M+H]^+$	312.1362	313.1434	<	12
3 {65}	2	$4-\mathrm{MeOC_6H_4}$	5{4}	В	$[M+H]^+$	354.1831	355.1899	<	16
3{66}	2	$4-\mathrm{MeOC_6H_4}$	5 {5}	В	$[M+H]^+$	340.1675	341.1763	66	27
3{67}	2	$4-\mathrm{MeOC_6H_4}$	5{6}	В	$[M+H]^+$	380.1988	381.2058	66	22
3{68}	2	3.5 -(MeO) $_2$ C $_6$ H $_4$	5 {2}	В	$[M+H]^+$	392.1736	393.1749	66	28
3{69}	7	3-thiophenyl	5{1}	В	$[M+H]^+$	288.0820	289.0907	66	77 <i>c</i>
3 {70}	2	$4-\mathrm{Me}_2\mathrm{NC}_6\mathrm{H}_4$	5 {2}	В	[M+H] ⁺	339.1834	340.1902	16	51
3{71}	2	$4-\mathrm{Me}_2\mathrm{NC}_6\mathrm{H}_4$	5{4}	В	$[\mathrm{M+H}]^+[\mathrm{-CH_4O}]$	367.2147	336.1952	<i>L</i> 9	43
3{72}	2	$4-{ m MeOC_6H_4}$	7 {2}	D	[M+H] ⁺	399.2158	400.2166	93	36

	ınd	
.R³ -OR⁴ 7}	calcd for HRMS found HRMS	316.1541
A S(73-77)	d for HRMS	315.1471
Me N(H)R		
OMe R ⁴ 3{61-71}	method ion HRMS	[M+H] ⁺
爱~~	method	田
OMe (1) R4	building blocks	8{1}

Cho et al.

yield (%)

product 3 n R ³	п	R³	building blocks method ion HRMS	method		calcd for HRMS found HRMS purity $(\%)^d$	found HRMS	purity (%) <i>a</i>
3{73}	1	$4-\mathrm{Me}_2\mathrm{NC}_6\mathrm{H}_4$	8{1}	E	$[M+H]^+$	315.1471	316.1541	34
3{74}	-	$4-\mathrm{Me}_2\mathrm{NC}_6\mathrm{H}_4$	8 {2}	Щ	[M+H] ⁺	329.1627	330.1693	66<
3{75}	2	$4-\mathrm{MeOC_6H_4}$	8 {2}	ш	$[M+H]^+$	330.1467	331.1529	66
3{76}	2	$4-\mathrm{Me}_2\mathrm{NC}_6\mathrm{H}_4$	8{1}	田	$[M+H]^+$	329.1627	330.1694	68
3{77}	2	$4-\mathrm{Me}_2\mathrm{NC}_6\mathrm{H}_4$	8 {2}	Щ	$[M+H]^+[-CH_4O]$	343.1784	312.1588	69

25 25 14

 $^{\rm a}{\rm UV}$ purity determined at 214 nm after preparative HPLC.

 b Isolated yield after preparative HPLC

^CIsolated yield after column chromatography. Isolated desired products 3 were characterized by ¹H and ¹³C NMR spectroscopy (see the Supporting Information).

Cho et al. Page 25

Table 4

Library Data for Compounds 3{78–105}

product 3	п	\mathbb{R}^3	building blocks	method	ion HRMS	calcd for HRMS	found HRMS	purity $(\%)^{\mathcal{Q}}$	yield $(\%)^{b}$
3{78}	-	3-thiophenyl	4{2}	A	[M+H]+	354.1290	355.1298	95	p£9
3{79}	_	3-thiophenyl	4 { <i>6</i> }	Ą	$[M+H]^+$	368.1082	369.1141	98	21 <i>d</i>
3{80}	_	3-thiophenyl	4 { <i>1</i> 8}	Ą	$[M+H]^+$	328.0769	329.0850	76	9
3{81}	2	3-thiophenyl	4{17}	Ą	[M+H] ⁺	356.1195	357.1254	66	p89
3{82}	-	3-thiophenyl	5{1}	В	[M+H] ⁺	288.0820	289.0828	96	48
3{83}	-	3-thiophenyl	5{4}	В	$[M+H]^{+}[-C_{2}H_{6}O]^{C}$	330.1290	285.0941	66<	19
3{84}	-	3-thiophenyl	5 {5}	В	$[M+H]^+$	316.1133	317.1202	66	55
3{85}	2	$4\text{-MeOC}_6\text{H}_4$	5 {2}	В	$[M+H]^+$	340.1675	341.1734	<	23 <i>d</i>
3{86}	2	$4-MeOC_6H_4$	5 {5}	В	$[M+H]^+$	354.1831	355.1901	<	39
3{87}	2	$4\text{-MeOC}_6\text{H}_4$	5{11}	В	[M+Na] ⁺	373.1678	396.1560	76	26
3{88}	2	$4-\mathrm{Me}_2\mathrm{NC}_6\mathrm{H}_4$	5{4}	В	$[M+H]^+$	381.2304	382.2365	72	30
3{89}	2	$4-\mathrm{Me}_2\mathrm{NC}_6\mathrm{H}_4$	5{7}	В	$[M+H]^+$	406.2620	407.2629	83	22
3{90}	2	$3-MeOC_6H_4$	5{1}	В	$[M+H]^+$	326.1518	327.1603	89	14
3{91}	2	$3-MeOC_6H_4$	5{4}	В	$[M+H]^+$	368.1988	369.2079	76	17
3{92}	2	$3-\mathrm{MeOC_6H_4}$	5{7}	В	$[M+H]^+$	393.2304	394.2380	96	28
3 {93}	2	3-thiophenyl	5 {5}	В	[M+H] ⁺	330.1290	331.1366	98	25
3{94}	2	4-MeOC ₆ H ₄	7{I}	D	[M+H] ⁺	400.1998	401.2061	85	9
3{95}	2	$4\text{-MeOC}_6\text{H}_4$	7 {2}	Д	$[M+H]^+$	413.2315	414.2388	<	56
3{96}	2	$4-\mathrm{MeOC}_6\mathrm{H}_4$	7{3}	О	[M+H] ⁺	387.2046	388.2115	96	31
3{97}	-	3-thiophenyl	8 { <i>I</i> }	闰	[M+H] ⁺ [-C ₂ H ₆ O]	292.0769	247.0418	66<	62
3{98}	-	3-thiophenyl	8 {8}	Ш	[M+H]+	428.1294	429.1366	86	12

Cho et al.

			S(78-81)	3{82-93}	R4 OE: 3(94-96)	3(97-103) 3(10)	OPr Ref		
product 3 n R ³	п	R³	building blocks method ion HRMS	method	ion HRMS	calcd for HRMS $$	found HRMS	purity (%) <i>a</i>	yield $(\%)^{b}$
3{66}	-	3-thiophenyl 8 {9}	8 [9]	ш	$[M+H]^{+}[-C_{2}H_{6}O]$	412.1344	367.0993	92	∞
3{100}	2	$4-MeOC_6H_4$	8{1}	ш	$[M+H]^{+}[-C_{2}H_{6}O]$	330.1467	285.1119	<	78
3{101}	2	$4-MeOC_6H_4$	8 {2}	ш	[M+Na]+	344.1624	367.1498	76	p29
3{102}	2	$4-Me_2NC_6H_4$ 8 { <i>I</i> }	8 { <i>I</i> }	ш	$[\mathrm{M+H}]^+[\mathrm{-CH_4O}]$	343.1784	312.1580	92	39
3 {103}	2	2 $4-\text{Me}_2\text{NC}_6\text{H}_4$ 8 {2}	8 {2}	ш	[M+H] ⁺	357.1940	358.1995	87	99
3{104}	-	1 $4-\text{Me}_2\text{NC}_6\text{H}_4$ 5 {4}	5{4}	В	[M+H] ⁺	381.2303	382.2389	74	∞
3{105}	-	$4-Me_2NC_6H_4$ 5 {12}	5 {12}	В	$[M+H]^+$	389.2103	390.2172	16	p£9

 $^d\mathrm{UV}$ purity determined at 214 nm after preparative HPLC.

 b Isolated yield after preparative HPLC.

 c Isotope: [A⁺(-45)]

disolated yield after column chromatography. Isolated desired products 3 were characterized by ¹H and ¹³C NMR spectroscopy (see the Supporting Information).

Table 5

Cho et al.

Library Data for Compounds $3\{106-122\}$

product 3	u	\mathbb{R}^3	building blocks method	method	ion HRMS	calcd for HRMS found HRMS	found HRMS	purity (%) ^a yield	yield
3{106}	-	4-MeOC ₆ H ₄	5 {2}	В	$[M+H]^+$	340.1311	341.1320	66<	
3{107}	-	$4\text{-MeOC}_6\text{H}_4$	2 { <i>0</i> }	В	$[M+H]^{+}[-C_{2}H_{4}O_{2}]$	394.1780	335.1642	66	
3 {108}	_	$4-MeOC_6H_4$	5{7}	В	[2M+H] ⁺	393.1940	787.3894	86	
3 {109}	2	$4-MeOC_6H_4$	\${0}	В	$[M+H]^{+}[-C_{2}H_{4}O_{2}]$	408.1937	349.1797	86	
3{110}	2	$3-\mathrm{MeOC}_6\mathrm{H}_4$	5 { <i>9</i> }	В	[2M+H] ⁺	401.1627	803.3313	66<	
3{111}	2	4-MeOC ₆ H ₄	8{1}	闰	$[M+H]^{+}[-C_2H_4O_2]$	344.1260	285.1116	86	
3{112}	2	4-MeOC ₆ H ₄	8 {2}	Щ	[M+Na]+	358.1416	381.1305	86	
3 {113}	7	$4\text{-MeOC}_6\text{H}_4$	8{5}	ш	$[M+Na]^+$	400.1886	423.1766	<	
3{114}	7	$4-MeOC_6H_4$	8 { <i>6</i> }	Щ	$[\mathrm{M+NH_4}]^+$	464.1835	482.2159	95	
3{115}	2	$4-MeOC_6H_4$	8{7}	Щ	[M+Na]+	443.1944	466.1744	96	
3{116}	7	$3-MeOC_6H_4$	8{1}	Щ	$[M+H]^{+}[-C_{2}H_{4}O_{2}]$	344.1260	285.1116	86	
3{117}	2	$3-MeOC_6H_4$	8 {2}	Щ	[M+Na]+	358.1416	381.1312	69	
3{118}	2	3-thiophenyl	8{1}	Щ	$[M+H]^{+}[-C_{2}H_{4}O_{2}]$	320.0718	261.0576	86	
3{119}	2	3-thiophenyl	8 {2}	田	$[M+H]^{+}[-C_{2}H_{4}O_{2}]$	334.0875	275.0731	<	
3 {120}	2	3-thiophenyl	8{3}	Щ	[M+Na]+	376.1344	399.1223	66<	
3{121}	2	3-thiophenyl	8{7}	Щ	[M+Na]+	419.1403	442.1203	76	
3{122}	2	3-thiophenyl	8(9)	闰	$[M+NH_4]^+$	440.1294	458.1622	86	

 $^{\it a}{\rm UV}$ purity determined at 214 nm after preparative HPLC.

^CIsolated yield after column chromatography. Isolated desired products 3 were characterized by ¹H and ¹³C NMR spectroscopy (see the Supporting Information).

Cho et al. Page 28

 $^{\it b}$ Isolated yield after preparative HPLC

ACS Comb Sci. Author manuscript; available in PMC 2013 December 11.

Cho et al. Page 29

Table 6

Library Data for Compounds 3{123-164}

				HOUNG (S) 1289 3 16	HOUTH RT HO 31729-1399	HO-UM 3(140-141)	HO4700 3(142-160)	P. P		
product 3	п	н	\mathbb{R}^3	building blocks	method	ion HRMS	calcd for HRMS	found HRMS	purity (%) <i>a</i>	yield $(\%)^{b}$
3{123}	-	2	4-MeOC ₆ H ₄	4{6}	A	[M+H]+	408.1573	409.1588	86	23
3{124}	_	2	$4-\mathrm{MeOC_6H_4}$	4{17}	А	[M+H]+	382.1529	383.1538	92	41
3 {125}	2	5	C_6H_5	4{11}	Α	[M] ⁺	418.2144	418.2156	66	46^{C}
3{126}	2	4	C_6H_5	4{18}	Α	[M+Na] ⁺	380.1624	403.1515	66	29
3{127}	2	2	$4-\mathrm{Me}_2\mathrm{NC}_6\mathrm{H}_4$	4{12}	А	[M+H]+	420.2049	421.2125	95	53
3{128}	2	7	$4-\mathrm{Me}_2\mathrm{NC}_6\mathrm{H}_4$	4{17}	А	[M+H] ⁺	409.2001	410.2076	65	47
3{129}	-	2	4-MeOC ₆ H ₄	5{4}	В	[M+H] ⁺	370.1780	371.1851	76	46
3 {130}	-	2	$4-\mathrm{MeOC_6H_4}$	5 {5}	В	[M+H]+	356.1634	357.1693	66	41
3 {131}	-	2	$4-\mathrm{MeOC_6H_4}$	5 { <i>6</i> }	В	[M+H] ⁺	396.1937	397.1997	86	7
3 {132}	-	2	$4-\mathrm{Me}_2\mathrm{NC}_6\mathrm{H}_4$	5 {2}	В	[M+H] ⁺	355.1784	356.1801	>66	23
3 {133}	2	2	C_6H_5	5 {2}	В	$[M+H]^+$	326.1518	327.1530	66	J9L
3{134}	2	2	C_6H_5	5 { <i>6</i> }	В	$[\mathrm{M+NH_4}]^+$	380.1988	398.2320	<	58
3 {135}	2	2	$4-\mathrm{MeOC_6H_4}$	5 {2}	В	[M+H] ⁺	356.1624	357.1683	<	∞
3{136}	2	2	$4-\mathrm{MeOC_6H_4}$	5 {5}	В	[M+H] ⁺	370.1780	371.1842	91	31
3{137}	7	2	$4-\mathrm{Me}_2\mathrm{NC}_6\mathrm{H}_4$	5 {5}	В	[M+H] ⁺	383.2097	384.2105	86	46
3{138}	2	2	$4-\mathrm{Me}_2\mathrm{NC}_6\mathrm{H}_4$	5 {12}	В	[M+H] ⁺	405.2052	406.2061	65	12
3{139}	2	2	$4-\mathrm{Me_2NC_6H_4}$	5{7}	В	$[M+H]^+$	422.2569	423.2581	96	23
3{140}	2	5	C_6H_5	7{3}	D	[M] ⁺	415.2359	415.2370	66	47c
3{141}	2	S	C_6H_5	7{4}	Ω	[M]	470.2781	470.2793	<	53 _C
3{142}	-	2	4-MeOC ₆ H ₄	8{11}	Э	[M] ⁺	362.1366	362.1354	66	
3 {143}	-	2	$4-\mathrm{Me}_2\mathrm{NC}_6\mathrm{H}_4$	8 { <i>1</i> }	田	[M]	345.1576	345.1583	66	73c

Me Fr	3(161-164)
12 - 12 - 12 - 12 - 12 - 12 - 12 - 12 -	3(142-160)
HO AN HIJR	3(140-141)
	3(129-139)
4 B	128)

Cho et al.

product 3	п	Ħ	\mathbb{R}^3	building blocks method ion HRMS	method	ion HRMS	calcd for HRMS	found HRMS	purity $(\%)^a$	yield $(\%)^{b}$
3{144}	-	2	4-Me ₂ NC ₆ H ₄	8{9}	Э	[M]+	442.2468	442.2470	16	35
3{145}	-	2	$4-\mathrm{Me}_2\mathrm{NC}_6\mathrm{H}_4$	8{11}	Щ	[M]	375.1682	375.1691	66<	85c
3{146}	2	2	$4-\mathrm{Me}_2\mathrm{NC}_6\mathrm{H}_4$	8{1}	Ш	$[M]^+$	359.1733	359.1737	66<	19c
3{147}	2	2	$4-\mathrm{Me}_2\mathrm{NC}_6\mathrm{H}_4$	8{11}	Ш	[M] ⁺	389.1838	389.1841	66<	81c
3{148}	2	2	$4-\mathrm{Me}_2\mathrm{NC}_6\mathrm{H}_4$	8{12}	田	[M]	403.1995	403.2002	76	77c
3{149}	2	2	$3-\mathrm{MeOC_6H_4}$	8{1}	田	[M]	346.1416	346.1423	66<	72 ^c
3{150}	2	2	$4-\mathrm{MeOC_6H_4}$	8{1}	田	[M]	346.1416	346.1423	66	81c
3{151}	2	2	$4-\mathrm{MeOC_6H_4}$	8{11}	Ш	$[M]^+$	376.1522	376.1534	66<	. 19c
3{152}	2	2	$4-\mathrm{MeOC_6H_4}$	8 {12}	Щ	$[M]^+$	390.1679	390.1688	66<	74c
3{153}	2	2	$4-\mathrm{MeOC_6H_4}$	8{13}	Ш	$[M]^+$	404.1835	404.1838	66<	.88c
3{154}	2	2	$4-\mathrm{MeOC_6H_4}$	8{14}	Ш	[M] ⁺	418.1992	418.2005	66	72c
3{155}	2	2	3-thiophenyl	8{1}	田	[M] ⁺	308.0718	308.0725	66	71c
3{156}	2	2	3-thiophenyl	8{1}	田	[M] ⁺	322.0875	322.0880	66	.88c
3{157}	2	2	3-thiophenyl	8{11}	Э	[M]	352.0981	352.0985	66<	78
3{158}	2	7	$4-NCC_6H_4$	8{12}	Ш	[M]	385.1525	385.1534	86	299
3{159}	2	2	1-cyclohexenyl	8{1}	Щ	[M]	320.1624	320.1632	ı	71c
3{160}	2	2	1-cyclohexenyl	8{11}	田	[M]	350.1729	350.1737	ı	82c
3{161}	1	2	C_6H_5	8{11}	Щ	[M] ⁺	348.1573	348.1580	1	37c
3{162}	1	2	$4-\mathrm{MeOC_6H_4}$	8{1}	田	[M] ⁺	348.1573	348.1580	66	82^{c}
3 {163}	1	7	$4-\mathrm{MeOC_6H_4}$	8 {11}	Щ	[M]	378.1679	378.1686	66	82c
3{164}		2	$4 ext{-MeOC}_6 ext{H}_4$	8{14}	田	[M]+	420.2148	420.2158	66<	82 _C

 $^{^{}a}\mathrm{UV}$ purity determined at 214 nm after preparative HPLC.

 $^{^{}b}$ Isolated yield after preparative HPLC.

^CIsolated yield after column chromatography. Isolated desired products 3 were characterized by ¹H and ¹³C NMR spectroscopy (see the Supporting Information).