Published in final edited form as:

ACS Comb Sci. 2011 May 9; 13(3): 272–279. doi:10.1021/co100088q.

A Highly Substituted Lactone/Ester-Containing Furan Library by the Palladium-Catalyzed Carbonylation of Hydroxyl-Substituted 3-lodofurans

Chul-Hee Cho and Richard C. Larock*

Department of Chemistry, Iowa State University, Ames, Iowa 50011

Abstract

Highly substituted lactone- and ester-containing furans have been prepared by the efficient palladium-catalyzed intramolecular cyclocarbonylation or intermolecular carboalkoxylation, respectively, of hydroxyl-containing 3-iodofurans, readily prepared by the iodocyclization of 2-(1-alkynyl)-2-alken-1-ones in the presence of various diols.

Introduction

Furans represent an important class of heterocyclic compounds as they are prevalent in many biologically active natural products, as well as numerous pharmacologically interesting compounds. Among these, heteroatom-substituted furans represent an important subclass, both as synthons and as functionalized heterocycles of biological interest. Thus, the design and discovery of synthetic methods that provide access to highly substituted furans is an active area of investigation. 4–9

Transition metal-catalyzed carbonylation reactions are of broad applicability, in terms of both basic research and commercial applications. $^{10-11}$ This chemistry has been widely employed in organic synthesis, because it can be utilized on a wide variety of substrates to produce a wide range of carbonyl products and it generally proceeds smoothly under low pressures of carbon monoxide (eq 1). $^{12-13}$ Similarly, the palladium-catalyzed cyclocarbonylation/lactonization of organic halides is very useful synthetic methodology that has become an important tool in organic synthesis. $^{14-18}$ For example, we have reported that the coupling of o-iodophenols, internal alkynes, and carbon monoxide efficiently affords 3,4-disubstituted coumarins (eq 2). $^{19-20}$ Similarly, we have prepared coumestans and coumestrol by iodocyclization and subsequent palladium-catalyzed intramolecular lactonization using an acetoxy group as the nucleophile (eq 3). 21

(Het',Ar
$$-X$$
 + NuH $\frac{CO (1 \text{ atm.})}{\text{cat Pd(0')}}$ O | II |

X = Br

Nu = OH OR NRR

(1)

^{*}To whom correspondence should be addressed. Phone: (515) 294-4660. larock@iastate.edu.

$$R^2$$
 R^2 R^2

(2)

(3)

(4)

Recently, we have developed an efficient synthesis of tetrasubstituted 3-iodofurans through the electrophile-induced cyclization of 2-(1-alkynyl)-2-alken-1-ones in the presence of various nucleophiles (eq 4).^{5,22} These multisubstituted 3-iodofurans provide an ideal intermediate for further useful structure elaborations by a variety of C–C, C–O, C–N and C–S bond forming processes.^{22–29} Thus, the carbon-halogen bond can be utilized for a variety of palladium-catalyzed reactions, including Suzuki-Miyaura,³⁰ Sonogashira,³¹ Buchwald-Hartwig,^{32–33} and Heck¹² reactions to name just a few.

As a continuation of our interest in the development of attractive strategies for the synthesis of highly substituted furans, ²² we envisioned that hydroxyl-substituted 3-iodofurans, readily available by iodocyclization in the presence of diols, should prove valuable as building blocks for combinatorial chemistry by intramolecular cyclocarbonylation, as well as intermolecular carboalkoxylation (Scheme 1).

Herein, we report an efficient method for the palladium-catalyzed intramolecular cyclocarbonylation and intermolecular carboalkoxylation of various hydroxyl-substituted 3-iodofurans to give lactone- and ester-containing furan products, respectively. The hydroxyl substituents present in the latter substrates can be critical for receptor binding *in vitro* due to their hydrophilicity and, thus, lipophobic nature.³⁴ According to calculations using Lipinski's rules,³⁵ terminal hydroxyl-containing furans should be good drug candidates. Intramolecular cyclocarbonylation would also appear to provide an interesting set of lactones of potential biological interest. We anticipate that this chemistry should find broad applications in synthetic organic chemistry, as well as the pharmaceutical sciences.

Results and Discussion

We hypothesized that our previously described iodocyclization process should readily afford the requisite iodofurans for intramolecular cyclocarbonylation and intermolecular carboalkoxylation processes, ²² resulting in a diverse library of lactone- and ester-containing

furans, respectively. A convenient two-step approach to various hydroxyl-containing 3-iodofurans ${\bf 2}$ has been developed, which involves (i) the Sonogashira coupling of 2-iodo-2-alken-1-ones 36 with terminal alkynes and (ii) electrophilic cyclization by ${\bf I}_2$ (Scheme 2). The alkynes ${\bf 1}$ were prepared by the palladium/copper-catalyzed Sonogashira coupling of appropriate 2-iodo-2-alken-1-ones with terminal alkynes. The results are summarized in Table 1.

As the key step in our library synthesis, various hydroxyl-substituted 3-iodofurans $\mathbf 2$ were efficiently prepared by electrophilic cyclization of the corresponding alkynes $\mathbf 1$ with various alcohols as nucleophiles using I_2 for only 0.5 h at room temperature. The results of this iodocyclization process are summarized in Table 2 and Figure 1. All of the reactions were monitored by thin layer chromatography and the products purified by column chromatography.

The scope of this iodocyclization has been briefly examined. Alkynes bearing a phenyl substituent exhibited broad generality with a range of diols. With 1,2-ethanediol as the nucleophile, a high yield of iodocyclization product is obtained (Table 2, entry 1). However, when longer chain diols, such as 1,3-propanediol, 1,4-butanediol and 1,5-pentanediol, were used, somewhat lower yields were obtained (Table 2, entries 2-4). Unfortunately, none of the desired cyclized products were obtained when employing secondary diols, e.g. 1,4cyclohexanediol and 2,3-butanediol (Table 2, entries 5 and 6). Water is a suitable nucleophile, affording the cyclized product 2{7} in a high yield (Table 2, entry 7). 2-Arylethynyl-2-cyclohexen-1-ones bearing an electron-rich aromatic ring, such as those containing a methoxy group or a dimethylamino group reacted well with I₂, affording the corresponding iodofurans in good yields (Table 2; entries 8-10 and 12). Placing an electrondonating methoxy group in the position meta to the alkyne gave a 76% yield of the cyclized product 2{11} (Table 2, entry 11). When the terminus of the alkynyl moiety contained an aryl group bearing an electron-withdrawing group, such as a cyano group, the yield was even better (Table 2, entry 13). Products from a heterocyclic thiophenyl group and a cyclohexenyl group were also isolated in modest yields (Table 2, entries 14 and 15). Similarly, cyclized products from 2-arylethynyl-2-cyclopenten-1-ones and acyclic substrates have also been obtained in good yields (Table 2, entries 16–20).

During our investigation of the intramolecular cyclocarbonylation and intermolecular carboalkoxylation processes, we chose as our model system to examine the palladium-catalyzed reaction of hydroxyl-containing 3-iodofuran $2\{I\}$ under one atmosphere of carbon monoxide pressure (Scheme 3). As predicted, hydroxyl-containing 3-iodofuran $2\{I\}$ smoothly underwent intramolecular cyclocarbonylation using dppf as the ligand and triethylamine as the base in the presence of $Pd(OAc)_2$ as the catalyst and using a balloon (1 atm) of carbon monoxide to give the desired lactone $3\{I\}$ in a 71% yield. Unfortunately, the carboalkoxylation of $2\{I\}$ with 3.0 equiv of ethylene glycol and the same reagents at 110 °C for 12 h did not prove suitable for preparation of the desired diol $4\{I\}$, as only a 31% yield was obtained, alongside the cyclized by-product $3\{I\}$ (43% yield).

In preliminary studies, we examined the carboalkoxylation of hydroxyl-containing 3-iodofuran $2\{I\}$ with ethylene glycol under various conditions, including various catalysts and ligands. As we previously communicated, our brief ligand survey indicated that reaction efficiencies are highest when monodentate ligands, such as tricyclohexylphosphine (PCy₃), are used as the ligand and Pd(OAc)₂ is used as the catalyst. A 74% isolated yield of the desired product $4\{I\}$ can be obtained when 20 mol % of PCy₃ is employed (Scheme 4). When optimizing the reaction, the base and solvent were held constant, while the palladium-catalyst and ligand were varied. Thus, under our optimized conditions [10 mol % Pd(OAc)₂, 20 mol % PCy₃, TEA (4.0 equiv), and diol (5.0 equiv) in DMF at 110 °C under 1 atm of

CO], intermolecular carboalkoxylation of the hydroxyl-containing 3-iodofurans $2\{I\}$ to the corresponding ester-containing furans $4\{I\}$ is favored.

Having optimized the reaction conditions for the intramolecular cyclocarbonylation and intermolecular carboalkoxylation of various hydroxyl-containing 3-iodofurans $\bf 2$, we have further determined the scope of these two processes (Scheme 5 and Table 3). Neither electron-donating nor electron-deficient groups on the furan skeleton seriously affect the efficiency of these processes. The reaction has good substrate scope and tolerates a broad range of functional groups. The ability to readily accommodate Ph, MeOC₆H₄, Me₂NC₆H₄, NCC₆H₄, thiophenyl and cyclohexenyl groups should allow one to further functionalize these products by employing standard organic synthetic methods. During the carboalkoxylation, a trace amount of cyclized lactone by-products $\bf 3$, the intramolecular cyclocarbonylation product, have been observed. All of the structures of the compounds $\bf 3/4$ have been confirmed by $\bf 1H$ and $\bf 13C$ NMR spectroscopy after purification by flash chromatography (see the Supporting Information).

As mentioned earlier, the carboalkoxylation product $4\{I\}$ from $2\{I\}$ and 1,2-ethanediol was obtained in a 74% yield (Table 3, entry 1). The carbomethoxylation of $2\{I\}$ using methyl alcohol afforded the corresponding methyl ester in a 73% yield, but required a much longer reaction time (Table 3, entry 2). Use of a longer alkyl chain-containing monoalcohol, 1-pentanol, produced a 38% yield of the corresponding coupling product $4\{3\}$, which was also accompanied by the cyclized lactone $3\{I\}$ in a 35% yield (Table 3, entry 3). The carboalkoxylation of $2\{I\}$ using phenol afforded the desired product $4\{4\}$, but in a somewhat lower yield and this reaction required a longer reaction time (Table 3, entry 4). Similarly, using benzyl alcohol, the desired product $4\{5\}$ was isolated in a 36% yield (Table 3, entry 5). Unfortunately, the product $4\{6\}$ could not be isolated upon treatment with 1,4-cyclohexanediol (Table 3, entry 6). Only a small amount of the cyclized by-product $3\{I\}$ was observed.

We have also examined the effect of different alkyl-containing 3-iodofurans $2\{1-4\}$ on the intramolecular cyclocarbonylation/lactonization process (Table 3, entries 7–10). 3– Iodofuran-containing alcohol 2{1} gave the fastest lactonization, reaching completion in 9 h (Table 3, entry 7). The longer chain containing 3-iodofuran 2{2} afforded a slightly lower yield of the desired product $3\{2\}$ than $2\{1\}$ and some starting material $2\{2\}$ remained (Table 3, entry 8). Unfortunately, none of the desired products $3\{3\}$ and $3\{4\}$ could be obtained using longer reaction times, when starting from 2{3} and 2{4} (Table 3, entries 9 and 10). Noteworthy is the fact that the formation of long chain-containing $2\{3\}$ and $2\{4\}$ is more difficult than formation of 2{1}. We next employed this chemistry on 3-iodofurans 2{8}, 2{9}, 2{10} and 2{11} containing electron-donating substituents (Table 3, entries 11– 22). Hydroxyl-containing 3-iodofurans bearing an electron-rich methoxyphenyl ring, such as 2{8}, 2{9} and 2{11}, smoothly reacted by cyclocarbonylation to give the desired lactone products 3{5}, 3{6} and 3{8}, respectively (Table 3; entries 11, 17 and 21). As predicted, the long chain-containing 3-iodofuran $2\{10\}$ provided only a trace of $3\{7\}$, and the reaction suffered from low conversion (Table 3, entry 19). The products $4\{7-14\}$ have been produced in modest yields by carboalkoxylation using various alcohols, including methanol, 1,2-ethanediol, 1,3-propanediol, 1,4-butanediol, and 1,5-pentanediol (Table 3; entries 12–16, 18, 20 and 22). 3-Iodofurans 2{12} and 2{13} bearing electron-deficient aromatic rings have also provided the desired intramolecular cyclization products (Table 3, entries 23 and 27) and intermolecular carboalkoxylation products (Table 3, entries 24–26 and 28). Furthermore, both the thiophene-substituted iodofuran 2{14} and the cyclohexenylsubstituted iodofuran 2{15} afforded the expected products in modest yields using our standard procedures (Table 3, entries 29–33). The carbonylation of 3-iodofuran 2{7} by both the intramolecular cyclocarbonylation and intermolecular carboalkoxylation processes

has been investigated (Table 3, entries 34–36). Compound 2{7} cannot form the lactone-containing furan 3{13} due to ring strain (Table 3, entry 34). However, the carboalkoxylation of 2{7} with two different alcohols produced the desired products 4{22} and 4{23} (Table 3, entries 35 and 36). The intramolecular cyclocarbonylation and intermolecular carboalkoxylation of the cyclopentane-containing 3-iodofurans 2{16}, 2{17} and 2{18} smoothly proceeded to the desired products in modest yields (Table 3, entries 37–44). Aliphatic-substituted 3-iodofurans 2{19} and 2{20} have also been employed in this chemistry. As expected, the desired products were produced exclusively in near quantitative yields (Table 3, entries 45–49).

The hydroxyl-containing 3-iodofurans 2 produced by this chemistry should be very useful for the synthesis of a wide variety of other substituted furans (Scheme 6) as well. For example, the Sonogashira and Suzuki-Miyaura reactions have afforded the corresponding products 5 and 6 in good yields. In summary, we have developed a useful new synthetic route to lactone-containing furans 3 and ester-containing furans 4 by the palladium-catalyzed intramolecular cyclocarbonylation and intermolecular carboalkoxylation of hydroxyl-substituted 3-iodofurans 2, respectively. Various hydroxyl-containing 3-iodofurans 2 have been successfully prepared through the iodocyclization of 2-(1-alkynyl)-2-alken-1-ones by I_2 in the presence of various diols. These iodine-containing furans can also be readily elaborated to more complex products using known organopalladium chemistry. The iodine-containing furans 2 have thus proven to be very useful intermediates for further diversification by known palladium-catalyzed chemistry, and are thus valuable building blocks for combinatorial chemistry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Institute of General Medical Sciences (GM070620 and GM079593) and the National Institutes of Health Kansas University Chemical Methodologies and Library Development Center of Excellence (GM069663) for their generous financial support; Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. for donations of palladium catalysts; and Frontier Scientific and Synthonix for donations of boronic acids.

References

- Lipshutz BH. Five-Membered Heteroaromatic Rings As Intermediates In Organic Synthesis. Chem Rev. 1986; 86:795–819.
- Keay BA. Synthesis of multi-substituted furan rings: the role of silicon. Chem Soc Rev. 1999; 28:209–215.
- 3. Hou XL, Cheung HY, Hon TY, Kwan PL, Lo TH, Tong SY, Wong HNC. Regioselective syntheses of substituted furans. Tetrahedron. 1998; 54:1955–2020.
- 4. Yao T, Zhang X, Larock RC. AuCl₃-Catalyzed Synthesis of Highly Substituted Furans from 2-(1-Alkynyl)-2-alken-1-ones. J Am Chem Soc. 2004; 126:11164–11165. [PubMed: 15355093]
- 5. Yao T, Zhang X, Larock RC. Synthesis of Highly Substituted Furans by the Electrophile-Induced Coupling of 2-(1-Alkynyl)-2-alken-1-ones and Nucleophiles. J Org Chem. 2005; 70:7679–7685. [PubMed: 16149799]
- 6. Brown RCD. Developments in Furan Syntheses. Angew Chem, Int Ed. 2005; 44:850–852.
- 7. Babudri F, Cicco SR, Farinola GM, Lopez LC, Naso F, Pinto V. A novel cyclization reaction between 2,3-bis(trimethylsilyl)buta-1,3-diene and acyl chlorides with straightforward formation of polysubstituted furans. Chem Commun. 2007:3756–3758.

8. Dudnik AS, Sromek AW, Rubina M, Kim JT, Kel'in AV, Gevorgyan V. Metal-Catalyzed 1,2-Shift of Diverse Migrating Groups in Allenyl Systems as a New Paradigm toward Densely Functionalized Heterocycles. J Am Chem Soc. 2008; 130:1440–1452. [PubMed: 18173272]

- 9. Sydnes LK, Holmelid B, Sengee M, Hanstein M. New Regiospecific Synthesis of Tri- and Tetra-Substituted Furans. J Org Chem. 2009; 74:3430–3443. [PubMed: 19344132]
- 10. Ojima I, Tzamarioudaki M, Li Z, Donovan RJ. Transition Metal-Catalyzed Carbocyclizations in Organic Synthesis. Chem Rev. 1996; 96:635–662. [PubMed: 11848768]
- 11. Brennführer A, Neumann H, Beller M. Palladium-Catalyzed Carbonylation Reactions of Aryl Halides and Related Compounds. Angew Chem, Int Ed. 2009; 48:4114–4133.
- 12. Schoenberg A, Heck RF. Palladium-catalyzed formylation of aryl, heterocyclic, and vinylic halides. J Am Chem Soc. 1974; 96:7761–7764.
- Kormos CM, Leadbeater NE. Microwave-Promoted Hydroxycarbonylation in Water Using Gaseous Carbon Monoxide and Pre-Pressurized Reaction Vessels. Synlett. 2006:1663–1666.
- 14. El Ali B, Okuro K, Vasapollo G, Alper H. Regioselective Palladium(II)-Catalyzed Synthesis of Five- or Seven-Membered Ring Lactones and Five-, Six- or Seven-Membered Ring Lactams by Cyclocarbonylation Methodology. J Am Chem Soc. 1996; 118:4264–4270.
- 15. Negishi E, Copéret C, Ma S, Mita T, Sugihara T, Tour JM. Palladium-Catalyzed Carbonylative Cyclization of 1-Iodo-2-alkenylbenzenes. J Am Chem Soc. 1996; 118:5904–5918.
- Kreimerman S, Ryu I, Minakata S, Komatsu M. Lactone Synthesis Based on Atom Transfer Carbonylation. Org Lett. 2000; 2:389–391. [PubMed: 10814330]
- 17. Schiller R, Pour M, Fáková H, Kuneš J, Císařová I. Neighboring Group Effect in Pd-Catalyzed Carbonylation Terminated by Lactonization: A Need for a Protective Group and/or DMF. J Org Chem. 2004; 69:6761–6765. [PubMed: 15387600]
- 18. Fernandes TA, Carvalho RCC, Gonçalves TMD, da Silva AJM, Costa PRR. A tandem palladium-catalyzed Heck-lactonization through the reaction of ortho-iodophenols with β-substituted acrylates: synthesis of 4,6-substituted coumarins. Tetrahedron Lett. 2008; 49:3322–3325.
- Kadnikov DV, Larock RC. Synthesis of Coumarins via Palladium-Catalyzed Carbonylative Annulation of Internal Alkynes by o-Iodophenols. Org Lett. 2000; 2:3643–3646. [PubMed: 11073665]
- Kadnikov DV, Larock RC. Palladium-Catalyzed Carbonylative Annulation of Internal Alkynes: Synthesis of 3,4-Disubstituted Coumarins. J Org Chem. 2003; 68:9423–9432. [PubMed: 14629168]
- Yao T, Yue D, Larock RC. An Efficient Synthesis of Coumestrol and Coumestans by Iodocyclization and Pd-Catalyzed Intramolecular Lactonization. J Org Chem. 2005; 70:9985– 9989. [PubMed: 16292831]
- 22. Cho CH, Larock RC. A convenient synthetic route to furan esters and lactones by palladium-catalyzed carboalkoxylation or cyclocarbonylation of hydroxyl-substituted 3-iodofurans. Tetrahedron Lett. 2010; 51:3417–3421. [PubMed: 20577579]
- 23. Nicolaou KC, Bulger PG, Sarlah D. Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis. Angew Chem, Int Ed. 2005; 44:4442–4489.
- 24. Cho CH, Neuenswander B, Lushington GH, Larock RC. Parallel Synthesis of a Multi-Substituted Benzo[b]furan Library. J Comb Chem. 2008; 10:941–947. [PubMed: 18937516]
- Waldo JP, Mehta S, Neuenswander B, Lushington GH, Larock RC. Solution Phase Synthesis of a Diverse Library of Highly Substituted Isoxazoles. J Comb Chem. 2008; 10:658–663. [PubMed: 18671435]
- Cho CH, Neuenswander B, Lushington GH, Larock RC. Solution-Phase Parallel Synthesis of a Multi-substituted Benzo[b]thiophene Library. J Comb Chem. 2009; 11:900–906. [PubMed: 19569714]
- 27. Worlikar SA, Neuenswander B, Lushington GH, Larock RC. Highly Substituted Indole Library Synthesis by Palladium-Catalyzed Coupling Reactions in Solution and on a Solid Support. J Comb Chem. 2009; 11:875–879. [PubMed: 19746991]
- 28. Cho CH, Jung DI, Larock RC. A new approach to desketoraloxifene analogs from oxygen-bearing 3-iodobenzo[b]thiophenes prepared via iodocyclization. Tetrahedron Lett. 2010; 51:6485–6488. [PubMed: 21113432]

29. Cho CH, Neuenswander B, Larock RC. Diverse Methyl Sulfone-Containing Benzo[b]thiophene Library via Iodocyclization and Palladium-Catalyzed Coupling. J Comb Chem. 2010; 12:278–285. [PubMed: 20055500]

- 30. Suzuki A. Carbon-carbon bonding made easy. Chem Commun. 2005:4759-4763.
- 31. Sonogashira K, Tohda Y, Hagihara N. A convenient synthesis of acetylenes: catalytic substitutions of acetylenic hydrogen with bromoalkenes, iodoarenes and bromopyridines. Tetrahedron Lett. 1975; 16:4467–4470.
- 32. Muci AR, Buchwald SL. Practical Palladium Catalysts for C-N and C-O Bond Formation. Top Curr Chem. 2002; 219:131–209.
- 33. Hartwig JF. Carbon–heteroatom bond formation catalysed by organometallic complexes. Nature. 2008; 455:314–322. [PubMed: 18800130]
- 34. Grese TA, Cho S, Finley DR, Godfrey AG, Jones CD, Lugar CW, Martin MJ, Matsumoto K, Pennington LD, Winter MA, Adrian MD, Cole HW, Magee DE, Phillips DL, Rowley ER, Short LL, Glasebrook AL, Bryant HU. Structure–Activity Relationships of Selective Estrogen Receptor Modulators: Modifications to the 2-Arylbenzothiophene Core of Raloxifene. J Med Chem. 1997; 40:146–167. [PubMed: 9003514]
- 35. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Delivery Rev. 1997; 23:3–25.
- 36. Krafft ME, Cran JW. A Convenient Protocol for the α-Iodination of α,β-Unsaturated Carbonyl Compounds with I₂ in an Aqueous Medium. Synlett. 2005:1263–1266.

Figure 1. Hydroxyl-containing 3-Iodofurans **2** Synthesized by Iodocyclization

Scheme 1.

Scheme 2.

Scheme 3.

CO (ba con) 10 mc % Pe(CAC); 20 mc % PCy; 4{1} + 3{1} Eth 13 ceu v, (74%, (trace)

Scheme 4.

CO that ere:

TEA CMF EC 'C

R

TEA CMF EC 'C

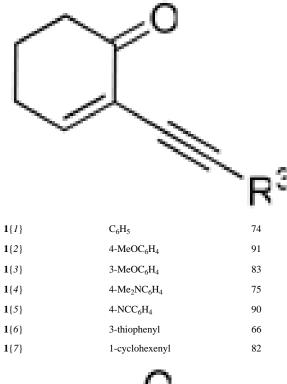
T

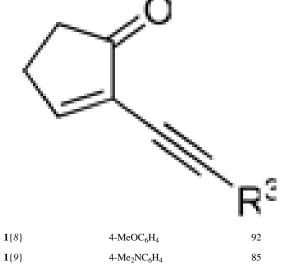
Scheme 5.

Scheme 6.

Table 1

Library Data for Compounds $1\{1-12\}$





Alkenynone 1	\mathbb{R}^3	yield (%) <i>a</i>
1{10}	3-thiophenyl	87

The desired products 1 have been characterized by $^1\mathrm{H}$ and $^{13}\mathrm{C}$

NMR spectroscopy.

 $^{^{}a}$ All yields are isolated yields after column chromatography.

Table 2

Library Data for Hydroxyl-Containing 3-Iodofurans 2^a

entry	1	HnN	product 2	product 2 yield $(\%)^b$	entry	1	NuH	product 2	product 2 yield $(\%)^b$
-	1{/}	1{ <i>1</i> } HO(CH ₂) ₂ OH	2{1}	83	11	1{3}	HO(CH ₂) ₂ OH	2{11}	9/
2	1{/}	1{ <i>I</i> } HO(CH ₂) ₃ OH	2 {2}	77	12	1{4}	HO(CH ₂) ₂ OH	2{12}	87
8	1{/}	1{ <i>I</i> } HO(CH ₂) ₄ OH	2{3}	99	13	1{5}	HO(CH ₂) ₂ OH	2{13}	68
4	1{/}	HO(CH ₂) ₅ OH	2{4}	65	14	1{6}	HO(CH ₂) ₂ OH	2{14}	82
S	1{/}	(2{5}	nr^{c}	15	1{7}	HO(CH ₂) ₂ OH	2{15}	82
		/ / / / / / / / / / / / / / / / / / / /							
)							
9	1{/}		2{6}	$\mathrm{nr}^{\mathcal{C}}$	16	1{8}	HO(CH ₂) ₂ OH	2{16}	98
		_							
		5							
		5. (:							
		\ \ \ \ \ \ \							
		_							
7	1{/}	1{ <i>I</i> } H ₂ O	2{7}	62	17	1{9}	HO(CH ₂) ₂ OH	2{17}	99
∞	1 {2}	1(2) HO(CH ₂) ₂ OH	2{8}	82	18	1 {10}	$HO(CH_2)_2OH$	2{18}	63
6	1 {2}	1{2} HO(CH ₂) ₃ OH	2{9}	<i>L</i> 9	19	1{11}	HO(CH ₂) ₂ OH	2 {19}	43
10	1 {2}	1{2} HO(CH ₂) ₅ OH	2{10}	47	20	1{12}	$HO(CH_2)_2OH$	2 {20}	84

^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.

balated yields after column chromatography. All hydroxyl-containing 3-iodofurans 2 have been characterized by ¹H and ¹³C NMR spectroscopy.

 $^{^{}c}$ Starting material $\mathbf{1}\{I\}$ decomposed.

Table 3

olecular Carboalkoxylation to 4^a

Ţ

Cho and Larock

yield (%)trace8 27 36 nr^e 77 47f trace⁸ 81 **4**{*1*-2*1*} **4**{3} **4**{*4*} **4**{5} 4{6} **4**{2} 4{8} product **3**{*I*} **3**{3} **3**{4} time (h) 24 32 12 24 24 HO(CH₂)₂OH HO(CH₂)₂OH $\mathrm{CH_3OH}_\mathcal{C}$ $CH_3OH^{\mathcal{C}}$ $PhOH^{\mathcal{C}}$ R⁴OH 4-MeOC₆H₄ 4-MeOC₆H₄ $4-MeOC_6H_4$ Ph Ph Ph ₽3 Ph Ph Ph Ph Ph ACS Comb Sci. Author manuscript; available in PMC 2012 May 9.

Page 18

		fime (b)	prq	product	yield $(\%)^b$
\mathbb{R}^3	$\mathbb{R}^4\mathrm{OH}$	cuire (II)	ю	4	
$4-\mathrm{MeOC_6H_4}$	HO(CH ₂) ₃ OH	12		4{9}	74
$4-\mathrm{MeOC_6H_4}$	$HO(CH_2)_4OH$	18		4{10}	89
$4-\mathrm{MeOC_6H_4}$	$HO(CH_2)_5OH$	18		4{11}	72
$4-\mathrm{MeOC_6H_4}$	ı	6	3{6}		28
$4-\mathrm{MeOC}_6\mathrm{H}_4$	$HO(CH_2)_2OH$	12		4{12}	92
$4-\mathrm{MeOC}_6\mathrm{H}_4$		24	3{7}		trace8
$4-MeOC_6H_4$	$HO(CH_2)_2OH$	12		4{13}	65
$3-MeOC_6H_4$	ı	6	3{8}		81
$3-MeOC_6H_4$	$ m CH_3OH^{\cal C}$	24		4{14}	72
4- Me ₂ NC ₆ H ₄		6	3{9}		83
$4- \mathrm{Me_2NC_6H_4}$	$ m CH_3OH^{\cal C}$	24		4{15}	92
4- Me ₂ NC ₆ H ₄	HO(CH ₂) ₂ OH	12		4{16}	81
4- $Me_2NC_6H_4$	$HO(CH_2)_3OH$	12		4{17}	TT
4-NCC ₆ H ₄	ı	6	3{10}		69
$4-NCC_6H_4$	$HO(CH_2)_3OH$	12		4{18}	99
3-thiophenyl	ı	6	3{11}		74
3-thiophenyl	$ m CH_3OH^{\cal C}$	24		4{19}	89
1-cyclohexenyl	ı	6	3{12}		75
1-cyclohexenyl	$ m CH_3OH^{\it c}$	24		4{20}	71
1-cyclohexenyl	HO(CH ₂),OH	12		4(21)	82

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

yield (%)

nr^e 73 62

4 {22} 4 {23}

Ϋ́

63

product

time (h)

R⁴OH

R3

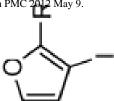
3{*13*} **3** {*13*}

12 16

HO(CH₂)₂OH

Ph Ph

ACS Comb Sci. Author manuscript; available in PMC 2012 May 9.



C	ho an	d Lar	ock																				
yield $(%)^b$	52h	<i>L</i> 9	61	73	85	89	71												37	499	55	64	28
4	4{24}	4{25}		4{26}	4{27}		4{28}	EI O KR3		`o´_	4{29–32}								4{29}		4{30}	4{31}	4{32}
product 3			3{15}			3{16}		()) ()		\	, I		_	-(o o)	3{17}		3{17}			
time (h)	24	12	6	24	12	6	24												12	6	36	24	24
R ⁴ OH	$ m CH_3OH^{\it C}$	HO(CH ₂) ₂ OH	1	$ m CH_3OH^{\it c}$	HO(CH ₂) ₂ OH	1	$ m CH_3OH^{\it c}$												HO(CH ₂) ₂ OH		$ m CH_3OH^{\cal C}$	$HO(CH_2)_2OH$	$HO(CH_2)_5OH$
R ³	4-MeOC ₆ H ₄	$4\text{-MeOC}_6\text{H}_4$	$4- \mathrm{Me_2NC_6H_4}$	$4- \mathrm{Me_2NC_6H_4}$	4- Me ₂ NC ₆ H ₄	3-thiophenyl	3-thiophenyl												Ph	$4-\mathrm{MeOC}_6\mathrm{H}_4$	$4\text{-MeOC}_6\mathrm{H}_4$	$4-MeOC_6H_4$	$4\text{-MeOC}_6\mathrm{H}_4$
						A	CS Ca	mb S	مِي ر ر	uthor	manus	scrip	t; avai	lable i	in PM	IC 20	12 M	ay 9	•				

cted to a balloon of CO, and the reaction mixture was stirred at 80 °C. ii. Intermolecular carboalkoxylation: the 3-iodofuran 2 (0.20 he 3-iodofuran 2 (0.20 mmol), 10 mol % Pd(OAc)2, 20 mol % dppf, and TEA (0.80 mmol) were stirred in DMF (2.0 mL) at room

d R⁴OH (1.00 mmol) were stirred in DMF (2.0 mL) at room temperature. The vial was purged with CO for 2 min and then connected to

Page 21

 b All yields are isolated yields after column chromatography. The desired products 3 and/or 4 have been characterized by 1 H and 13 C NMR spectroscopy.

 $^{c}10.0 \, \mathrm{Equiv}$ of the desired alcohol were used.

 $^d\mathrm{The}$ cyclized by-product $3\{I\}$ was observed in 35% yield.

"None of the desired carboalkoxylation product was observed. The starting material $2\{I\}$ decomposed.

 $f_{
m Some}$ starting material remained.

hAn inseparable mixture was obtained. $^{\it g}$ The starting material remained.