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Synthesis of tetrasubstituted furans by sequential SmI_2-promoted reduction and Pd-catalyzed cyclization

José M. Aurrecoechea* and Elena Pérez

Departamento de Química Orgánica, Facultad de Ciencias, Universidad del País Vasco, Apartado 644, 48080 Bilbao, Spain

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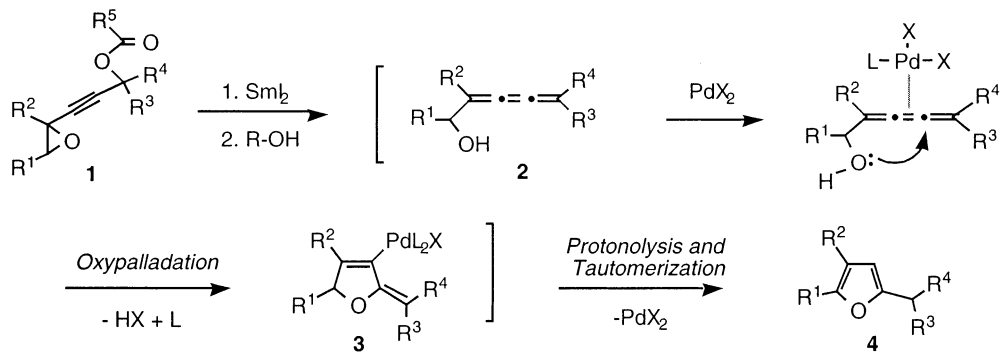
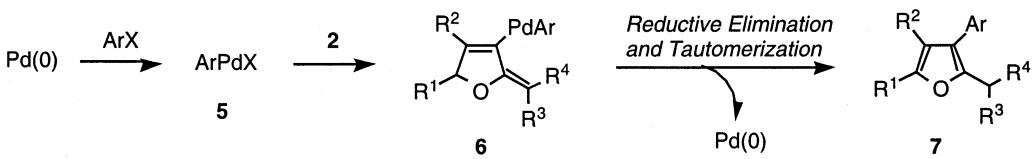
Abstract—Tetrasubstituted furans are obtained in a one-pot, two-step sequence comprising SmI_2-promoted reduction of a readily available 4,5-epoxyalk-2-ynyl ester followed by Pd(0)-promoted cyclization of the resulting 2,3,4-trien-1-ol in the presence of an aryl halide or triflate. © 2001 Elsevier Science Ltd. All rights reserved.

The synthesis of polysubstituted functionalized furans has attracted the continuous attention of the synthetic chemist due to the widespread presence of the furan nucleus in Nature[1,2] and also because of the commercial importance of its derivatives[2] and their applications as advanced synthetic intermediates.[3,4] Numerous methods have been devised for the regioselective synthesis of mono-, di- and trisubstituted furans with various substitution patterns starting from acyclic precursors or preformed furans.[5–8] In contrast, reports on the regioselective preparation of functionalized tetrasubstituted furans are more scarce.[9]

We have described a new method of synthesis of trisubstituted furans **4** that makes use of a facile SmI_2-mediated reduction of epoxypropargyl esters **1** to generate 2,3,4-trien-1-ols **2**, followed by Pd(II)-catalyzed cycloisomerization of **2** (Scheme 1).[10] The conversion **2**→**4** is facilitated by Pd(II) which presumably activates one of the triene double bonds of **2** to



Scheme 1.



Scheme 2.

* Corresponding author. E-mail: qopaufem@lg.ehu.es

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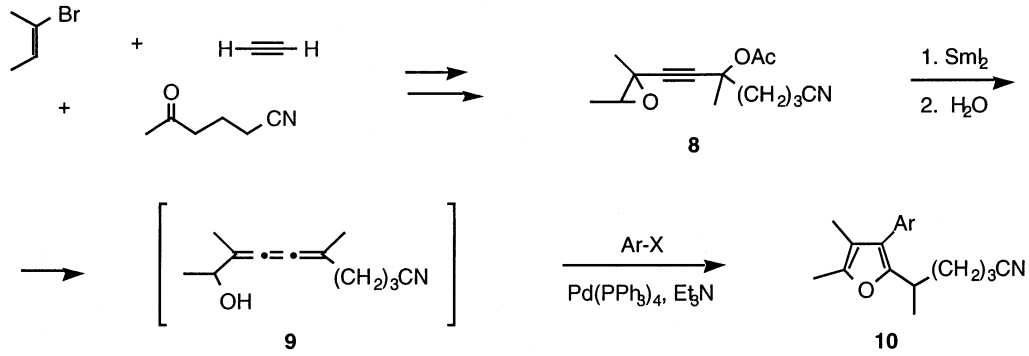
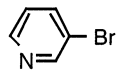
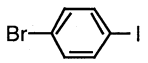
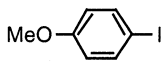
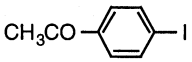
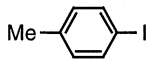


Scheme 3.

Table 1. Formation of tetrasubstituted furans **10** from **8** and Ar–X

Entry	Ar-X	T (°C)[a]	10 (% Yield)	Entry	Ar-X	T (°C)[a]	10 (% Yield)
1	PhI	60	**10a** (53)	5		80	**10d** (53)
2	PhOTf	80	**10a** (54)				
3		70	**10b** (73)	6		60	**10e** (40)[b]
4		70	**10c** (64)	7		70	**10f** (53)

[a] Temperature for the cyclization step. [b] After the reduction step, the reaction mixture was worked-up and crude triene **9** submitted to the usual cyclization conditions.

nucleophilic attack by an internal hydroxyl group. This gives a cyclized oxypalladated intermediate **3** that finally leads to furan **4** via protonolysis of the C–Pd bond and prototautomerization.

An attractive variant of this reaction would involve the use of Pd(II) complexes **5** generated in situ by oxidative addition of aryl halides or triflates to catalytic Pd(0) (Scheme 2). If complexes **5** were electrophilic enough to activate the double bond as above, then the oxypalladation process would likely be followed by reductive elimination (before or after tautomerization), leading eventually to the formation of tetrasubstituted furans **7**, with regeneration of the Pd(0) catalytic species.[†] This paper reports preliminary results on the successful application of these ideas. The similar use of in situ-generated RPdX complexes to promote the cyclization of alcohols or ketones to unsaturated systems has been previously utilized to synthesize furans with various substitution patterns.[9j,13]

Epoxyester **8** has been used as a model substrate. This is readily synthesized[10] by Sonogashira coupling between (*E*)-2-bromobutene and the propargyl alcohol derived from acetylene and 5-oxohexanenitrile, followed by acetylation and epoxidation. Treatment of **8** with 2.2 equivalents of SmI_2 in THF led, after addition of water, to the formation of a diastereomeric mixture of alcohols **9** (Scheme 3).[10] If so desired, these alcohols can be isolated (85% yield) and characterized by ^1H and ^{13}C NMR[14] after column chromatography on silica gel deactivated with Et_3N.

For furan formation, however, alcohols **9** need not be isolated. Instead, once the initial reduction step was complete, the THF solvent was stripped off and the residue was treated with water (1 equivalent), catalytic (5 mol%) $Pd(PPh_3)_4$, an aryl halide or triflate (2 equivalents) and Et_3N (5 equivalents) in DMF at 60–80°C. Starting from **8**, this one-pot sequence led to the formation of furans **10** that were isolated in moderate overall yields[‡] (Scheme 3; Table 1). Formation of **10a** was also possible directly from the samarium alkoxide precursor of **9** if water was omitted in the cyclization step. However, this led to a lower yield of **10a** (28%) and

[†] Alternative productive pathways leading to **7** can also be envisioned via initial carbopalladation of the central triene double bond[11,12] followed by palladacycle formation and reductive elimination.[9j]

[‡] Typical experimental procedure: To a solution of SmI_2 (ca. 0.1 M, 2.6 mmol) in THF (26 mL) was added via cannula a solution of **8** (1.2 mmol) in THF (3 mL) at −5°C under Ar. The mixture was stirred at the same temperature for 3.5 h. Dry air and Ar were successively bubbled through the solution, and the reaction mixture was allowed to reach rt. Removal of the solvent in vacuo afforded a residue that was dissolved in DMF (5 mL) containing H_2O (1.2 mmol). After addition of Et_3N (0.84 mL, 6.02 mmol), an aryl halide (2.40 mmol) and $Pd(PPh_3)_4$ (0.14 g, 0.12 mmol), the solution was stirred at 60–80°C until complete consumption of the trienol intermediate (13–72 h). Aqueous work-up and purification by liquid chromatography afforded furans **10**. All products were characterized by their spectral (^1H and ^{13}C NMR, IR) properties and HRMS or elemental analysis.

much longer reaction times (3 days versus 12 h). Other reaction conditions also gave inferior results. For example, the use of $Pd(OAc)_2$ in place of $Pd(PPh_3)_4$ with PhI, under otherwise the same conditions, led to the formation of trisubstituted furan **4** ($R^1=R^2=R^3=$Me; $R^4=$3-cyanopropyl)[10] in 50% yield instead of the desired **10a**. Furan **10a** was formed when $Pd(OAc)_2$ was used in conjunction with PPh_3 (15 mol% with respect to **8**), but in a diminished 33% yield (compare with entry 1 in Table 1). Under the latter conditions, the use of THF as solvent in the cyclization step led only to formation of **4** ($R^1=R^2=R^3=$Me; $R^4=$3-cyanopropyl)[10] in 25% yield.

Some interesting observations regarding the cyclization step emanate from the results presented in Table 1: (i) While aryl iodides have been mainly used in this study, the corresponding use of triflates appears promising (entry 2), and the use of a bromide has also been possible if the aryl group was electron-deficient (compare entries 3 and 5). (ii) Both electron-deficient and electron-rich aromatics have been found to participate effectively in the cyclization step. (iii) A significantly lower yield (37%) was realized in the formation of **10a** when the use of PhOTf was accompanied by LiCl (compare with entry 2). This could be taken as a reflection of the greater ability of organopalladiums **5** to activate the triene system to nucleophilic attack as their electrophilic character increases. Ligand exchange from X=OTf to X=Cl in **5** certainly renders the activating Pd complex **5** less electrophilic.

As exemplified in Scheme 3 for substrate **8**,[10] this new strategy for the synthesis of tetrasubstituted furans would take advantage of the use of convenient vinyl, acetylene, aldehyde or ketone, and aryl fragments to introduce the ring substituents. In the examples shown, α-branching at the C-2 furan substituent appears to be readily incorporated using this methodology and this stems from the choice of a ketone rather than an aldehyde fragment in the preparation of substrate **8** (Scheme 3). Some functionality is shown to be tolerated, both at the starting material preparation[10] and cyclization stages, and precedent on related SmI_2-reductions and Pd-catalyzed cyclizations indicates that this will probably be the case for a more extensive range of functional groups.

In summary, a new method is described for synthesis of tetrasubstituted furans that features the Pd(0)-catalyzed cyclization of a 2,3,4-trien-1-ol generated in situ by SmI_2-promoted reduction of a 4,5-epoxyalk-2-ynyl ester substrate. The heterocyclic ring carbon framework is provided by the strategic use of vinyl halide and acetylene fragments in the assembly of the starting material, whereas aryl and reduced-carbonyl groups are incorporated as ring substituents.

Acknowledgements

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