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Facile Synthesis of 3a,6a-Dihydro-furo[2,3-b]furans and Polysubstituted Furans Involving Dearomatization of Furan Ring via Electrocyclic Ring-Closure

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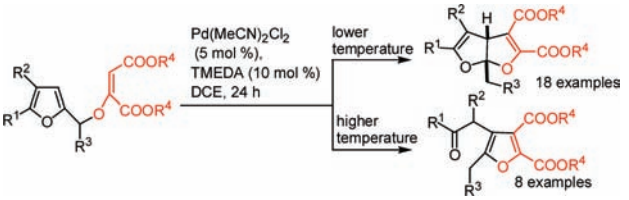
ABSTRACT



A facile and atom-economic method for the synthesis of 3a,6a-dihydro-furo[2,3-b]furan derivatives and polysubstituted furans starting from furylcarbionls has been developed. This protocol involved a domino Claisen rearrangement/dearomatizing electrocyclic ring-closure/aromatizing electrocyclic ring-opening sequence.

The transformation of readily available and stable aromatic rings into functionalized alicyclic derivatives is widely recognized as an attractive strategy for the construction of valuable synthetic intermediates when the conjugated π system is successfully broken up.[1] Of particular interest is the dearomatization of furan ring due to its lower Dewar resonance energy of 4.3 kcal mol and because furan rings contain masked functionalities of olefin, diene, enol ether, and 1,4-dicarbonyl. Accordingly, the partial dearomatization of the furan ring allows the reactivity of the remaining unsaturation to be intensively exploited. To date, there are a number of different methods that, with unequal scope, allow the dearomatization of the furan ring and have been extensively used in the synthesis of numerous bioactive molecules.[2] For example, Birch reduction of furan rings leads to 2,5-dihydrofurans.[3] Furans have been widely used as dienes and less frequently as dienophiles in cycloadditions for the construction of different bicyclic or tricyclic skeletons.[4] Oxidations of furan derivatives produce 2,5-dialkoxy-2,5-dihydrofurans,[5] 6-hydroxy-6*H*-pyran-3-one,[6] 6-hydroxy-6*H*-pyran-3-one,[7]

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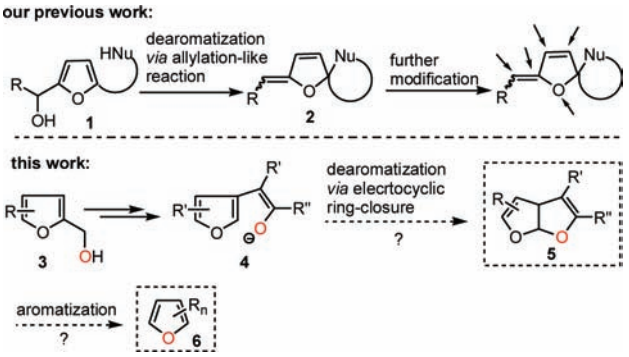
and buteno-lides.[8] Other examples include acid-catalyzed molecular rearrangement of 2-furylcarbinols into cyclopentenones[9] and nucleophilic addition to furan−chromium complexes.[10] As a consequence, the development of a new method for the dearomatization of furan rings continues to be an active and rewarding research area.

Recently, we and other groups have disclosed accesses to spiro-compounds **2** and other bioactive molecules starting from furycarbinol **1** tethered to a side chain at the α-position of its furan ring with a nucleophile (Scheme 1).[11]

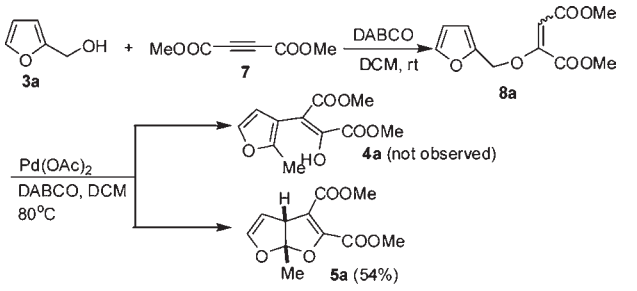
Scheme 1. Synthetic Application of Furans Characterized by Dearomatization



The key step involves the dearomatization of the furan ring through an acid-catalyzed intramolecular allylation-like reaction. These achievements encouraged us to develop more novel strategies directed toward the dearomatization of furan ring of 2-furylcarbinol and expanding its synthetic applications. Electrocyclic reaction of common conjugated poylenes (4π or 6π electron system) is a well-known method for the preparation of cyclic compounds.[12] Nevertheless, to the best of our knowledge, the dearomatizing electrocyclic reaction involving π-electrons of the aromatic ring is seldom reported. In this communication, we reported the facile synthesis of 3a,6a-dihydro-furo[2,3-b]furan derivatives **5** and polysubstituted furan **6** using 2-furylcarbinol as the starting material, which involved a domino palladium-catalyzed Claisen rearrangement/dearomatizing eletrocyclic ring-closure/aromatizing eletrocyclic ring-opening sequence.

We began by synthesizing 2-(furan-2-ylmethoxy)-but-2-enedioic acid dimethyl ester (**8a**) via the addition reaction of furfuryl alcohol (**3a**) with dimethyl 2-butynedioate (**7**) in the presence of a catalytic amount (10 mol %) of DABCO (Scheme 2).[13] After completion of the addition reaction, 5 mol % of $Pd(OAc)_2$ was added, and the reaction mixture was then heated at 80 °C for 24 h to undergo the Claisen rearrangement step.[14] Unexpectedly, no Claisen rearrangement-type product **4a** was observed.

Scheme 2. Synthesis of **5a** from **3a**



Instead, 3a,6a-dihydro-furo[2,3-b]furan **5a** was formed with a moderate yield (54%) over two steps. This unexpected result is especially interesting and useful because it provides a novel entry to 3a,6a-dihydro-furo[2,3-b]-furans, key structural units in many important pharmaceuticals and bioactive natural products.[15] Additionally, **5a** is stable enough to store on the bench for several months and can also be used as a versatile intermediate for the construction of many other useful molecules. Moreover, this transformation presented an unprecedented method for the dearomatization of five-membered

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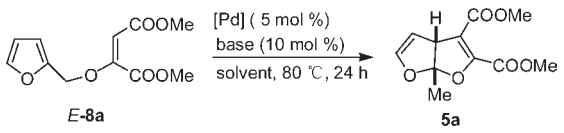
aromatic rings via electrocyclic ring-closure. Hence, our attention was piqued by the potential of this novel transformation, and we decided to optimize the reaction conditions for it.

Table 1. Optimization of Reaction Conditions[a]



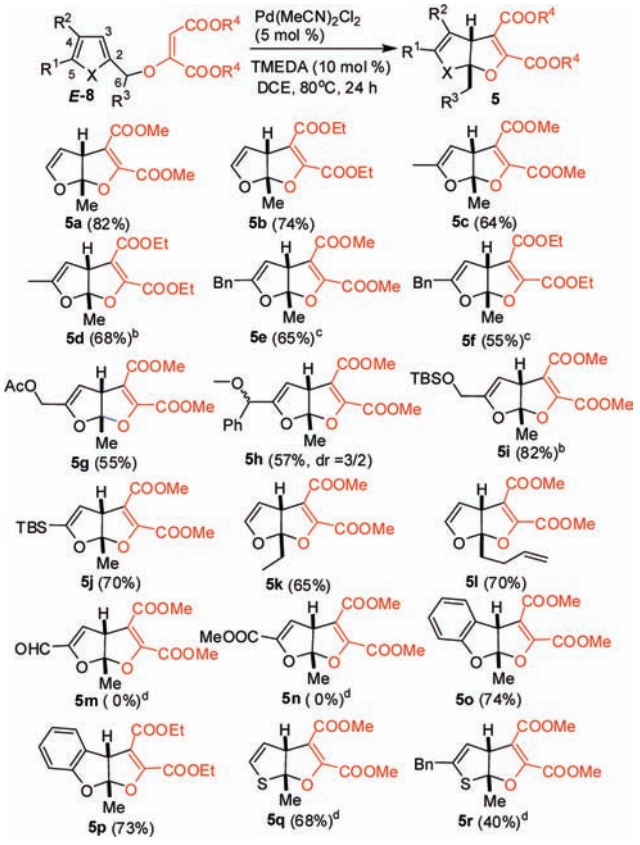
entry	[Pd]	solvent	base	yield[b] (%)
1	$Pd(OAc)_2$	DCM	DABCO	54
2	$Pd(OAc)_2$	DMF	DABCO	trace
3	$Pd(OAc)_2$	MeCN	DABCO	45
4	$Pd(OAc)_2$	THF	DABCO	28
5	$Pd(OAc)_2$	DCE	DABCO	60
6	$Pd(OAc)_2$	DCE	DMAP	52
7	$Pd(OAc)_2$	DCE	DIEA	60
8	$Pd(OAc)_2$	DCE	TMEDA	68
9	$Pd(OAc)_2$	DCE	pyridine	57
10	$Pd(OAc)_2$	DCE	dppp	57
11	$Pd(OAc)_2$	DCE	dppe	trace
12	$PdCl_2$	DCE	TMEDA	ND
13	$Pd(CF_3COO)_2$	DCE	TMEDA	14
14	$Pd(PPH_3)_4$	DCE	TMEDA	42
15	**$Pd(MeCN)_2Cl_2$**	**DCE**	**TMEDA**	**82**
16	$[Pd(MeCN)_4][BF_4]$	DCE	TMEDA	10

[a] All reactions were carried out on a 1 mmol scale. [b] Yield determined by ^1H NMR using 1,3,5-trimehylbenzene as an internal standard.

As a model reaction, *E*-**8a** was treated with a variety of bases and palladium sources in different solvents at 80 °C to optimize the reaction conditions. Initially, various solvents were screened when Pd $(OAc)_2$ was employed as the catalyst and DABCO as the base (Table 1, entries 1−5). DCE was the best one and resulted in **5a** in 60% yield. Then, different bases were examined; TMEDA was the best (Table 1, entry 8). Other nitrogen-containing bases (e.g., DIEA, pyridine, DMAP) and two diphosphines of dppp and dppe were also capable of promoting the transformation but provided lower yields than TMEDA (Table 1, entries 5−11). Finally, palladium sources were screened (Table 1, entries 12−16). The best result was obtained when $Pd(MeCN)_2Cl_2$ was employed as the catalyst (Table 1, entry 15). Thus, we concluded that the optimized combination for this reaction was to use DCE as the solvent, TMEDA (10 mol %) as the base, and $Pd(MeCN)_2Cl_2$ (5 mol %) as the catalyst. It is worth noting that under the same reaction conditions, *Z*-**8a** can also be transformed into **5a** with a yield comparable to *E*-**8a**, but a longer reaction time is needed.

To understand the generality of this transformation, we subjected a variety of *E*-**8** to provide **5** under the optimized conditions. The results are summarized in Table 2. When R^1 (substitution at the 5-position of the furan ring) was an electron-donating group such as H, TMS, or an

Table 2. Synthesis of **5**[a]



[a] All reactions were performed on a 1 mmol scale. Yields of isolated products are given. Unless otherwise noted, t = 80 °C. [b] t = 30 °C. [c] t = 60 °C. [d] t = 140 °C.

alkyl group, this transformation proceeded well, giving **5a**−**l** in moderate to good yields. Nevertheless, when R^1 was an electron-withdrawing formyl or methoxycarbonyl group, this transformation did not occur (**5m** and **5n**). These results imply that the electron-rich furan ring is helpful for the cleavage of the C6−O bond, thus facilitating the transformation. Delightedly, when the aromatic ring of *E*-**8** was a benzofuran or thiophene, these were also dearomatized and produced the furo[2,3-b]benzofuran (**5o**, **5p**) and dihydro-thieno[2,3-b]furan (**5q**, **5r**) in moderate to good yields.

Polysubstituted furan is a key structural unit in many bioactive natural products and pharmaceuticals.[16] It is also a reactive species that can be engaged in complex chemical transformations.[2] In an attempt to highlight the synthetic application of the obtained product **5**, we attempted to convert **5** into polysubstituted furan **6** via an aromatizing electrocyclic ring-opening. Much to our pleasure, **5c** can be converted into **6c** with almost a quantitative yield when heated in DCE at 100 °C for 24 h in the

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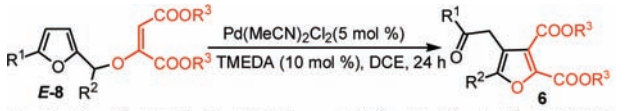
presence of TMEDA (10 mol %). Its structure was determined by single-crystal X-ray data analysis (**6t**, see the Supporting Information). We also found that during the transformation of *E*-**8c** into **5c**, when the reaction temperature was raised to 100 °C for 24 h, **6c** was exclusively obtained in 67% yield. Therefore, a series of polysubstituted furans **6** with diverse functionalities were synthesized in moderate to good yields via an one-pot procedure from *E*-**8** (Scheme 3).

Scheme 3. Synthesis of **6** from *E*-**8** (All Reactions Were Performed on a 1 mmol Scale)



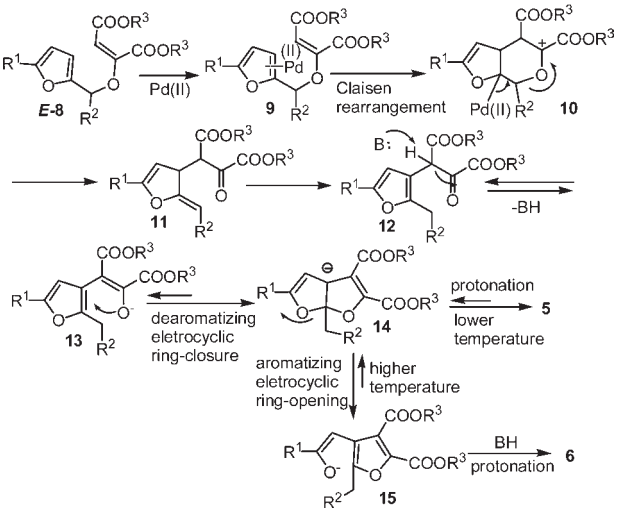
6c R^1 = Me, R^2 = H, R^3 = Me, (67%)[a] **6d** R^1 = Me, R^2 = H, R^3 = Et, (65%)[a]
6e R^1 = Bn, R^2 = H, R^3 = Me, (41)%[a] **6f** R^1 = Bn, R^2 = H, R^3 = Et, (40)%[a]
6g R^1 = $AcOCH_2$, R^2 = H, R^3 = Me, (80)%[a]
6i R^1 = $TBSOCH_2$, R^2 = H, R^3 = Me, (69%)[a]
6s R^1 = $TBSO(CH_2)_3$, R^2 = H, R^3 = Me, (57%)[b]
6t R^1 = Ph, R^2 = H, R^3 = Me, (70%)[b]

[a] 80 °C. [b] 100 °C.

On the basis of the experimental results shown above, a tentative mechanistic interpretation of the preceding observations is proposed in Scheme 4. The coordination of Pd(II) with the double bond of the furan ring of *E*-**8** formed complex **9**. The carbopalladation of the double bond of the furan ring gave rise to intermediate **10**, which underwent a Pd(II) elimination step, producing **11** and recycling the palladium catalyst. The aromatization of **11** provided **12**. After deprotonation and dearomatizing electrocyclic ring-closure steps, the carbanion **14** was formed. The protonation of **14** at lower temperature formed **5**, whereas at higher temperature, **14** was converted into **6** through two steps of aromatzing electrocyclic-opening and protonation, subsequently.

In summary, employing a readily available furylcarbinol as the starting material, we developed a facile and atom-economic method for the synthesis of 3a,6a-dihydrofuro[-2,3-b]furans and polysubstituted furans. These two structural units are found in many bioactive products and might be used as synthetic building bolcks. This

Scheme 4. Plausible Reaction Mechanism



protocol involves a palladium-catalyzed domino Claisen rearrangement/dearomatizing electrocyclic ring-closure/aromatizing ring-opening sequence. The unprecedented dearomatization of five-membered aromatic rings through electrocylic ring-closure would be helpful to expand their synthetic application as building blocks in organic synthesis. Further studies on the scope and asymmetric aspect of these reactions, as well as their application for the synthesis of natural bioactive products, are ongoing in our laboratory. The results will be reported in due course.

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Supporting Information Available. Details on general experimental methods, crystal data and structure of **6t**, and copies of ^{1}H NMR and ^{13}C NMR spectra of all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.