Heterocycle Synthesis

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An Alkyne Hydroacylation Route to Highly Substituted Furans**

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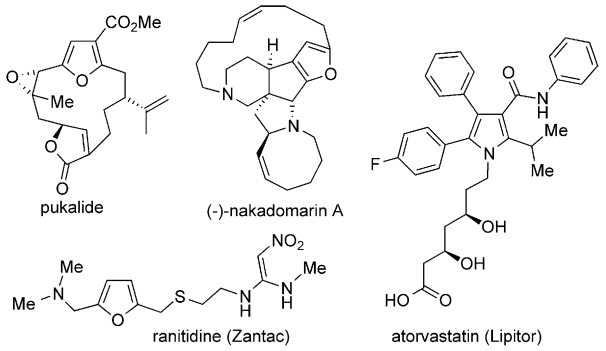
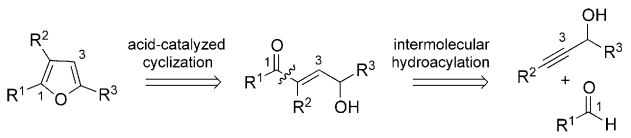
Heterocyclic compounds, such as the bioactive natural products pukalide and nakadomarin A, and the hugely successful drug molecules ranitidine (Zantac) and atorvastatin (Lipitor) are of great importance in pharmaceutical, agrochemical, and other fine-chemical applications (Scheme 1).[1] While there exists a range of methods for transforming relatively complex starting materials into substituted heterocycles, and for the functionalization of existing heterocycles, there is less precedent for methodology which involves the direct, regiodefined synthesis of highly substituted heterocycles from simple starting materials.[2] As such, new methods for the synthesis of substituted heterocycles (or their precursors) are potentially of significant value. This is particularly true if such methods do not suffer from the same drawbacks as the traditional syntheses of 1,4-dicarbonyl compounds, the classic substrates for the preparation of furans, thiophenes, and pyrroles; these syntheses are often either step- or atom-inefficient. The recent advances achieved in intermolecular alkene and alkyne hydroacylation chemistry means that these transformations are now ideal methods to exploit for the synthesis of heterocyclic molecules, because they employ simple substrates and commercially available catalyst systems, and generate no by-products because of their 100% atom-economy.[3–5] In addition, a broad range of aldehydes can now be employed, and particularly in the case of alkyne hydroacylation, significant substitution of the unsaturated component can be tolerated, thus allowing for the regioselective production of highly substituted complex molecules in one catalytic intermolecular carbon–carbon bond forming step. Herein, we demonstrate the utility of intermolecular alkyne hydroacylation in the efficient synthesis of di- and trisubstituted furans and related heterocycles.



Scheme 1. Examples of significant heterocycle-containing natural products and pharmaceuticals.

γ-Hydroxy-α,β-enones are known to undergo acid-catalyzed dehydrative cyclization to form furans, and this transformation has been exploited by several research groups,[6] most notably in the recent work from Donohoe et al.[7] The intermolecular hydroacylation of an aldehyde with readily available propargylic alcohols would permit the synthesis of γ-hydroxy-α,β-enones with 100% atom efficiency; coupling this carbon–carbon bond formation with an acid-catalyzed dehydrative cyclization would allow for the regioselective synthesis of di- or trisubstituted furans. The associated disconnection is novel for this type of heterocycle (Scheme 2).

Our initial investigations to realize the above route to furans focused on the combination of propargyl alcohol **1a** and the *S*-chelating alkyl aldehyde **2a** (Table 1). The hydroacylative union of these two substrates using a dppe-derived Rh catalyst proceeded without incident. However, attempts to achieve a dehydrative cyclization using TFA provided only a small amount of the desired furan **3a** (entry 1). Reducing the time for the cyclization event to 1 hour, and then to 10 minutes, increased the yield of furan up to 50% (entries 2 and 3). After exploring the use of several alternative acids, it was found that the use of *p*-TSA increased the yield to 66% (entries 4–7). Given the known acid sensitivity of simple alkyl-substituted furans we speculated that the purification of the furan product by chromatography on silica gel might be responsible for the moderate yields of the isolated products.[8] Accordingly, although the use of neutral alumina offered no advantage, purifications employing Florisil (magnesium silicate) or triethylamine-doped silica allowed the furan to be isolated in significantly increased yields (entries 8–10).



Scheme 2. An alkyne hydroacylation route to furans.

With the optimized conditions established, a short series of 2,5-disubstituted furans was prepared (Scheme 3). Propargylic aryl and heteroaryl substituents could be introduced

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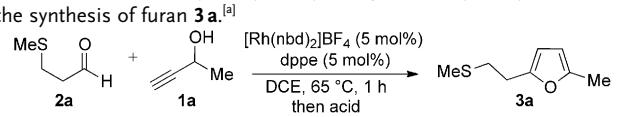
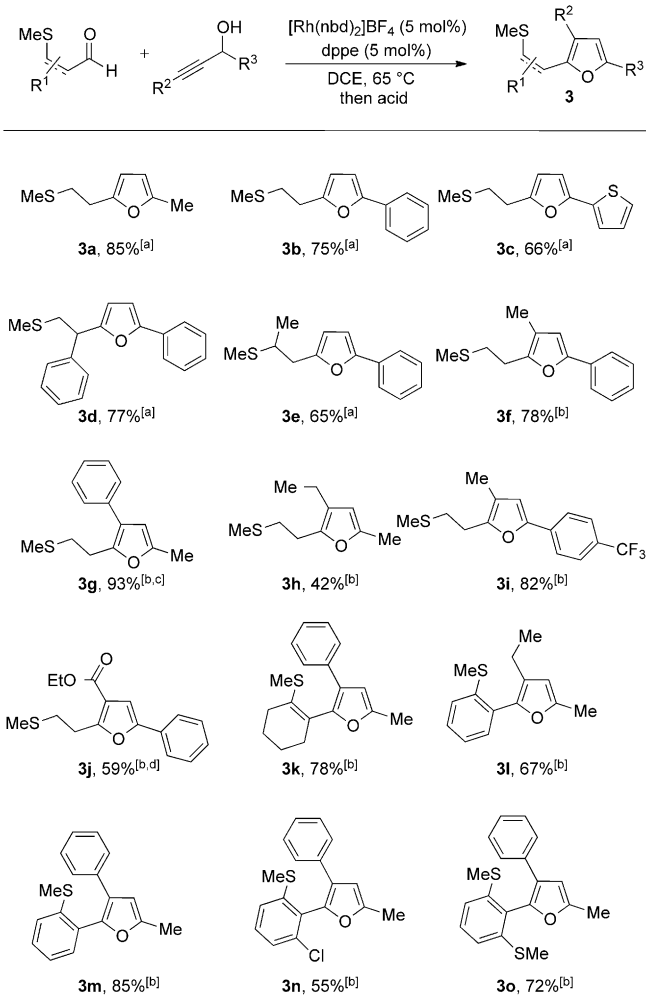
Table 1: Rhodium-catalyzed hydroacylation/acid-catalyzed cyclization for the synthesis of furan **3a**.[a]



Entry	Acid	*t*	Purification	Yield [%][b]
1	TFA (excess)	16 h	silica	trace
2	TFA (excess)	1 h	silica	29
3	TFA (excess)	10 min	silica	50
4	PPTS (10 mol%)	1 h	silica	0
5	HCl (10 mol%)	1 h	silica	8
6	*p*-TSA (10 mol%)	30 min	silica	57
7	*p*-TSA (10 mol%)	2 h	silica	66
8	*p*-TSA (10 mol%)	2 h	neutral alumina	26
9	*p*-TSA (10 mol%)	2 h	Florisil	75
10	*p*-TSA (10 mol%)	2 h	NEt_3-doped silica	85

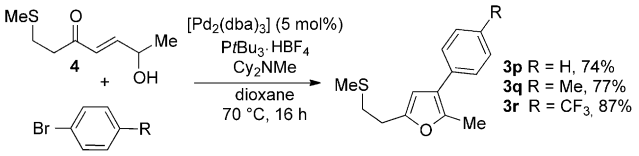
[a] Reaction conditions: **1** (0.75 mmol), **2** (1.1 equiv), $[Rh(nbd)_2]BF_4$ (0.05 equiv), dppe (0.05 equiv), DCE, 65 °C, 1 h, followed by acid (equivalents as stated) at the given conditions. [b] Yields of the isolated product. DCE = dichloroethane, dppe = 1,2-bis(diphenylphosphino)-ethane, nbd = norbornadiene, PPTS = pyridinium *para*-toluenesulfonate, *p*-TSA = *para*-toluenesulfonic acid, TFA = trifluoroacetic acid.

without incident, as could α and β branching on the aldehyde component (furans **3b–e**). We next looked to expand the process to include internal alkyne substrates, thus allowing the preparation of trisubstituted furans. The hydroacylation step employing internal alkynes proceeded efficiently, although longer reaction times were needed for the reactions to reach completion (16 h versus 1 h). The cyclization conditions that had proved to be optimal for the 2,5-disubstituted furans (10 mol% of *p*-TSA) were unsuccessful for the trisubstituted examples, with only partial conversion into the desired furan being observed. However, the use of anhydrous HCl, which produced only traces of furan in the majority of the 2,5-disubstituted examples because of product decomposition, proved to be proficient at rapidly and cleanly converting the hydroacylation products in situ into the desired trisubstituted furans in good to excellent yields. These reaction conditions were applied to the synthesis of a variety of trisubstituted furans from alkyl and aryl aldehydes, and internal propargylic alcohols. Two regioisomeric trisubstituted furans (**3f** and **3g**) were produced by simply altering the alkyne employed in the hydroacylation step. Pleasingly, modest scaling up of the reaction was also possible, with furan **3g** being obtained in an excellent 93% yield upon isolation, from a 3.0 mmol scale reaction. A trialkyl variant (**3h**) could be synthesized, but was isolated only in 42% yield; although both the hydroacylation step and the acid-catalyzed dehydrative cyclization proceeded to completion without the production of any by-products, the product degraded when purified by column chromatography, despite the use of thoroughly base-washed silica. An ester substitutent was readily incorporated (**3j**). A cyclohexenyl aldehyde was utilized to furnish furan **3k**. Aromatic aldehydes could also be readily employed, leading to furans **3l–o**. Furan **3n** includes an aryl chloride substituent, thus demonstrating the tolerance of the method towards incorporating halide substituents for potential derivatization of the products.



Scheme 3. Scope of the rhodium-catalyzed hydroacylation/acid-catalyzed cyclization synthesis of di- and trisubstituted furans. Reaction conditions: aldehyde (0.75 mmol), alkyne (1.1 equiv), $[Rh(nbd)_2]BF_4$ (0.05 equiv), dppe (0.05 equiv), DCE, 70 °C, 1 h, or 16 h followed by acid. Yields are of the isolated products. [a] *p*-TSA (10 mol%), 2 h. [b] HCl (4.0 M in dioxane, 1.0 equiv). [c] 3.0 mmol scale. [d] No acid needed for cyclization.

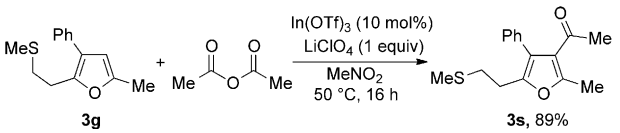
An inherent limitation with methodology that is based on employing propargylic alcohols as one of the reaction components is the inability to directly access furans bearing a substituent at the position that originated from the propargylic carbon atom (i.e., position 3 as shown in Scheme 2). To rectify this we explored the possibility of functionalizing the initially formed hydroacylation adducts before cyclization to the heterocycle. Subjecting γ-hydroxy-α,β-enone **4** to Heck-coupling conditions, as described by Donohoe et al.,[7,9] with a range of aryl bromides, provided trisubstituted furans **3p–r** in good yields (Scheme 4). The furans were isolated directly from the reactions, without the need for an additional acid-catalyzed cyclization. The utility of this set of Heck reactions is that it allows access to regioisomers not available from the initial hydroacylation/cyclization methodology, for example, compare furans **3f**, **3g**, and **3p**. Combined with the ability to employ aryl aldehydes as substrates, the methodology enables the selective intro-



Scheme 4. Functionalization of hydroacylation adducts using the Heck reaction leading to regioisomeric trisubstituted furans. dba = dibenzylideneacetone.

duction of aryl substituents to each of the four furan carbon atoms.

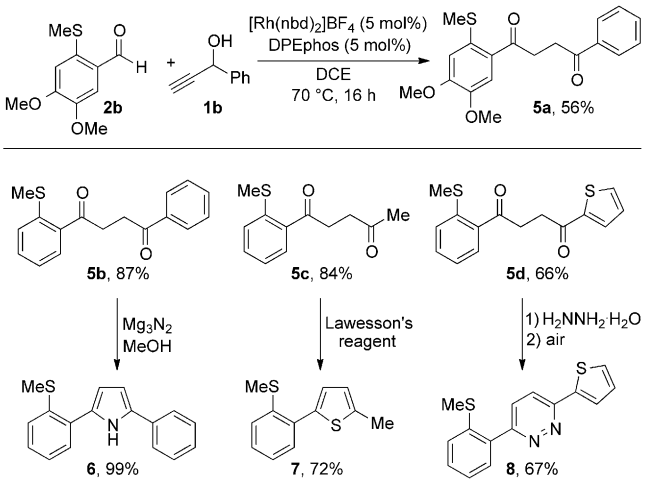
Attempts to apply the Heck chemistry to the synthesis of tetrasubstituted furans were unsuccessful. However, tetrasubstituted products could be accessed from the corresponding trisubstituted furans using In-catalyzed Friedel–Crafts chemistry. For example, treatment of furan **3g** with acetic anhydride in the presence of catalytic $In(OTf)_3$ delivered the fully substituted heterocycle in 89% yield (Scheme 5).[10] This overall process provides a concise and efficient route to fully substituted furans.



Scheme 5. Indium-catalyzed Friedel–Crafts synthesis of tetrasubstituted furan **3s**. Tf = trifluoromethanesulfonyl.

Finally, given the efficiency of the aldehyde/propargylic alcohol hydroacylative coupling it was desirable to be able to access alternative heterocycles from the same combination of substrates. However, attempts to convert the γ-hydroxy-α,β-enone products directly into pyrroles or thiophenes were unproductive. A solution to this issue was realized when an alternative catalyst system was used for the hydroacylation step: employing a DPEphos-derived catalyst for the union of aromatic aldehyde **2b** and propargylic alcohol **1b** led not to the expected γ-hydroxy-α,β-enone, but to 1,4-dicarbonyl **5a** (Scheme 6). The 1,4-dicarbonyl is presumed to originate from a Rh-catalyzed isomerization of the initially formed γ-hydroxy-α,β-enone.[11] The ability to access 1,4-dicarbonyl systems directly opened up a host of possibilities for further functionalization; Scheme 6 shows representative 1,4-dicarbonyl products (**5b–d**), together with their conversion into pyrrole,[12] thiophene,[13] and pyridazine[14] heterocycles.

In summary, we have demonstrated the applicability of a rhodium-catalyzed intermolecular hydroacylation to the synthesis of di- and trisubstituted furans in a regiocontrolled fashion; this reaction proceeds through a 100% atom-economic carbon–carbon bond forming step followed by a simple dehydrative cyclization. The Heck reaction has been utilized to further increase the scope of the methodology to access regioisomeric trisubstituted furans. An unprecedented indium-catalyzed acylation procedure for the synthesis of tetrasubstituted furans from the trisubstituted furans thus produced, has also been disclosed. In addition, we have a



Scheme 6. Rhodium-catalyzed preparation of 1,4-dicarbonyl compounds and their conversion into various heterocycles. DPEphos = bis(2-diphenylphosphinophenyl)ether.

developed an atom-efficient synthesis of 1,4-dicarbonyl compounds, from the same reaction components, and demonstrated the transformation of these products into five- and six-membered heterocycles.

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