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SHORT COMMUNICATION

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Substituted 3(2*H*)-Furanones by a Tandem Michael Addition/Palladium-Catalyzed Ring-Closing Protocol

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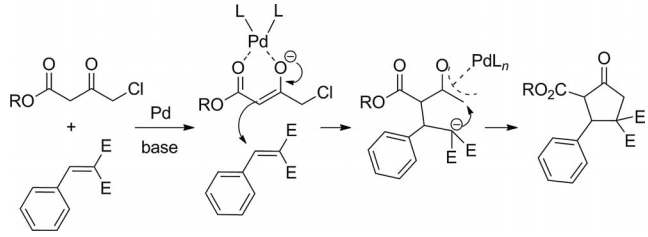
A novel palladium-catalyzed route for the synthesis of substituted 3(2*H*)-furanones from activated alkenes and 4-chloroacetoacetate was developed. The first step of the tandem reaction is the Michael addition of an acetoacetate to the alkene followed by palladium-catalyzed ring closure of the adduct to form the furanone. The reaction was extended to a number of substituted alkenes, and the corresponding substituted 3(2*H*)-furanones were obtained in good to excellent yields.

Introduction

Catalytic tandem reactions are powerful tools for synthetic organic chemists because multiple bonds can be formed in one pot.[1] Michael addition is one of the most important carbon–carbon bond-forming reactions, and it has been widely explored over the last two decades.[2] It is known that Pd^0 can undergo oxidative addition to bonds α to a carbonyl group, and this leads to the formation of oxa-π-allylpalladium complexes, but only a few reports are known for the oxidative addition to α-halo ketones.[3] In this communication, we disclose a simple route to substituted 3(2*H*)-furanones by a tandem Michael addition/palladium-catalyzed ring-closing process.

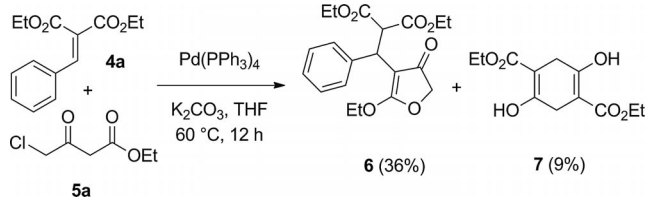
We recently developed a completely new framework for liquid crystalline materials, namely, the perhydroazulene (HAZ) unit.[4] The reported (linear) synthetic route to this core was, though high yielding, too long and required too many separation steps. We were therefore interested in devising new synthetic routes towards the perhydroazulenedione core structure with a smaller number of steps and overall higher efficiency. Our first aim was to find a new method to fuse the cyclopentanone unit to the cycloheptenone core. For the intended cyclopentanone annulation, we chose 4-chloroacetoacetate, which can be viewed as a β-diketone with a leaving group at the γ-carbon atom. We were interested in its reactivity towards activated alkenes under palladium catalysis, and we hoped that this reaction would result in cyclopentanone annulation of the alkene (Scheme 1).



Scheme 1. Our intended route for cyclopentanone annulation.

Results and Discussion

Our preliminary studies involved substituted styrene **4a** and ethyl 4-chloroacetoacetate (**5a**) as substrates. When these were allowed to react in the presence of $Pd(PPh_3)_4$ (5 mol-%) and K_2CO_3 (1.0 equiv.) in THF at 60 °C, substituted 3(2*H*)-furanone **6** was obtained in 36% yield, contrary to our expectation of a substituted cyclopentanone (Scheme 2). Diethyl 1,4-dihydroxycyclohexa-1,4-diene-2,5-dicarboxylate (**7**) was obtained as a side product in 9% yield.



Scheme 2. Pd-catalyzed synthesis of 3(2*H*)-furanone.

A number of synthetic routes to 3(2*H*)-furanones have been reported in the literature, as these molecules form the core structure of many natural products and pharmaceutically important compounds (Figure 1).[5] Some of these strategies involve acid-catalyzed transformations of substituted α-hydroxy-1,3-diketones,[5g,5i] synthetic manipulations of substituted furans,[6] cyclization of allenic hydroxy-

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ketones under basic conditions,[7] and transition-metal (Au,[8] Pt,[9] Pd,[10] Hg[11])-catalyzed strategies. Recently, two asymmetric routes to 3(2*H*)-furanones were reported by Lu et al.[12] and Yan et al.,[13] and these methods involved an organocatalyzed reaction between 4-haloacetoacetate esters and nitrostyrene.

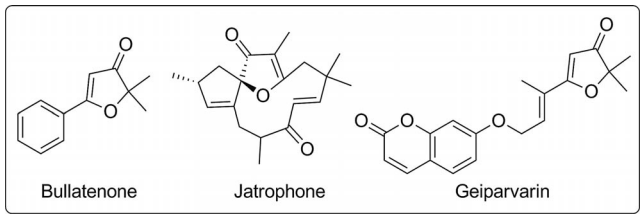
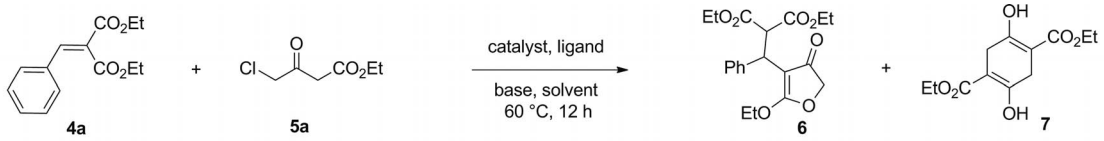


Figure 1. Bioactive molecules with the 3(2*H*)-furanone moiety.

Hence, the current interest in the 3(2*H*)-furanone ring system prompted us to investigate the scope of the transformation. Table 1 describes our efforts towards optimizing various reaction parameters with **4a** and **5a** as model substrates. The yield of furanone **6** almost doubled when 2.0 equiv. of base was used (Table 1, entry 1). Next, screening of the base revealed that K_2CO_3 was more effective than either Na_2CO_3 or Cs_2CO_3 (Table 1, entries 1–3). When Et_3N was employed as the base, the side product was formed in higher amounts (Table 1, entry 4). We then focused on finding the best catalyst/ligand combination. The catalysts tested were $Pd(PPh_3)_4$ and $Pd_2(dba)_3{\cdot}CHCl_3$, and the ligands tested were 1,2-bis(diphenylphosphanyl)ethane (dppe), 1,1′-bis(diphenylphosphanyl)ferrocene (dppf), and P(*o*-furyl)$_3$. The combination of $Pd(PPh_3)_4$ and P(*o*-furyl)$_3$ afforded the furanone in 76% yield (Table 1, entry 7). We went on optimizing other parameters such as the solvent and temperature. Among the solvents tested, THF, CH_3CN, dioxane, and DMF, the highest yield of 81% for **6** was obtained in dioxane (Table 1, entries 7, 12–14). When a solution of substrates **4a** and **5a** was stirred in the presence of $Pd(PPh_3)_4$/P(*o*-furyl)$_3$/K_2CO_3 in dioxane at room temperature, 91% of **7** was obtained after 24 h. Thus, the addition process can be switched between products **6** and **7** by changing only the temperature.

Two control experiments were carried out to establish whether palladium was the active catalyst. The first reaction was performed without the catalyst/ligand and only in the presence of base (Table 1, entry 16). The second reaction was carried out in the presence of $Pd(PPh_3)_4$/P(*o*-furyl)$_3$ without base (Table 1, entry 17). The first reaction afforded almost equal amounts of **6** (46%) and **7** (38%). The second reaction yielded only trace amounts of the desired product. Thus, we can confirm that palladium was catalyzing the reaction by comparing the first control experiment and the reaction depicted in entry 13 of Table 1. Analysis of the results reveals that under palladium catalysis the yield of

Table 1. Optimization studies.[a]



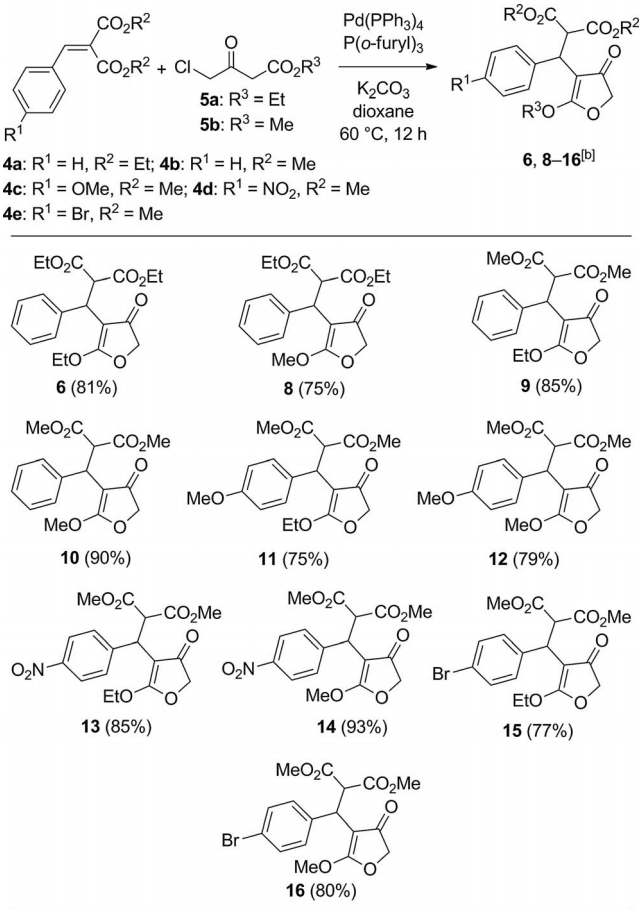
Entry	Catalyst	Ligand	Base	Solvent	Yield **6** [%][b]	Yield **7** [%][b]
1	$Pd(PPh_3)_4$	–	K_2CO_3	THF	66	13
2	$Pd(PPh_3)_4$	–	Na_2CO_3	THF	46	23
3	$Pd(PPh_3)_4$	–	Cs_2CO_3	THF	26	11
4	$Pd(PPh_3)_4$	–	Et_3N	THF	10	51
5	$Pd(PPh_3)_4$	dppe	K_2CO_3	THF	36	21
6	$Pd(PPh_3)_4$	dppf	K_2CO_3	THF	52	12
7	$Pd(PPh_3)_4$	P(*o*-furyl)$_3$	K_2CO_3	THF	76	5
8	$Pd_2(dba)_3{\cdot}CHCl_3$	–	K_2CO_3	THF	70	5
9	$Pd_2(dba)_3{\cdot}CHCl_3$	dppe	K_2CO_3	THF	64	9
10	$Pd_2(dba)_3{\cdot}CHCl_3$	dppf	K_2CO_3	THF	56	13
11	$Pd_2(dba)_3{\cdot}CHCl_3$	P(*o*-furyl)$_3$	K_2CO_3	THF	70	6
12	$Pd(PPh_3)_4$	P(*o*-furyl)$_3$	K_2CO_3	CH_3CN	51	11
13	**$Pd(PPh_3)_4$**	**P(*o*-furyl)$_3$**	**K_2CO_3**	**dioxane**	**81**	**5**
14	$Pd(PPh_3)_4$	P(*o*-furyl)$_3$	K_2CO_3	DMF	10	66
15[c]	$Pd(PPh_3)_4$	P(*o*-furyl)$_3$	K_2CO_3	dioxane	trace	91
16	–	–	K_2CO_3	dioxane	46	38
17	$Pd(PPh_3)_4$	P(*o*-furyl)$_3$	–	dioxane	trace	–

[a] Reaction conditions: **4a** (1.0 equiv.), **5a** (1.0 equiv.), catalyst (5 mol-%), ligand (10 mol-%), base (2.0 equiv.), solvent (2 mL), 60 °C, 12 h. [b] Isolated yield. [c] Reaction performed at r.t., 24 h.

3(2*H*)-furanone **6** was doubled. Under the influence of the catalyst, the Michael addition thus occurs much faster and thereby prevents the dimerization of **5a** to form product **7**.

The scope of the new protocol was next investigated under optimized conditions [alkene (1.0 equiv.), 4-chloroacetoacetate (1.0 equiv.), $Pd(PPh_3)_4$ (5 mol-%), P(*o*-furyl)$_3$ (10 mol-%) K_2CO_3 (2.0 equiv.), dioxane, 60 °C, 12 h]. In all cases, investigated styrenes **4a**–**e** reacted with 4-chloroacetoacetates **5a** and **5b**, and this led to the corresponding substituted 3(2*H*)-furanones in good to excellent yield (Table 2). We also checked if electronic effects could influence the reaction by introducing both electron-donating (i.e., **4c**) and electron-withdrawing (i.e., **4d**) substituents on the phenyl ring. It was found that the 3(2*H*)-furanones were formed in slightly better yields with styrene **4d** bearing a nitro group on the phenyl ring. Notably, in all the cases the side product was formed in negligible amounts (≤5%).

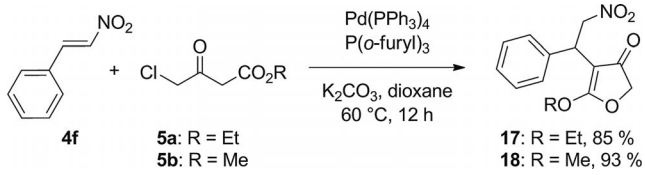
Table 2. Generalization of the furanone-forming process.[a]



[a] Reaction conditions: **4** (1.0 equiv.), **5** (1.0 equiv.), $Pd(PPh_3)_4$ (5 mol-%), P(*o*-furyl)$_3$ (10 mol-%), K_2CO_3 (2.0 equiv.), dioxane (2 mL), 60 °C, 12 h. [b] Isolated yield.

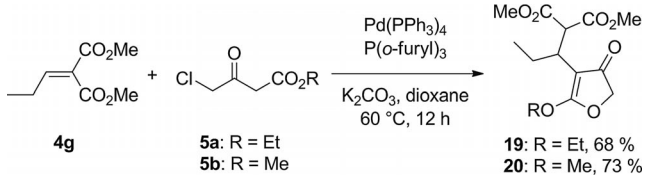
The structure of furanones **6** and **8**–**16** follows from the usual spectroscopic data (see the Supporting Information). In the case of **13** (product formed by the reaction of **4d** with **5a**), the connectivity was additionally established qualitatively by X-ray structure determination, but severe disorder of the substituents prevented satisfactory refinement.

Under the optimized conditions, the reactions of **5a** and **5b** were also attempted with *trans*-β-nitrostyrene (**4f**). Both reactions afforded corresponding 3(2*H*)-furanones **17** and **18** in excellent yields (Scheme 3).



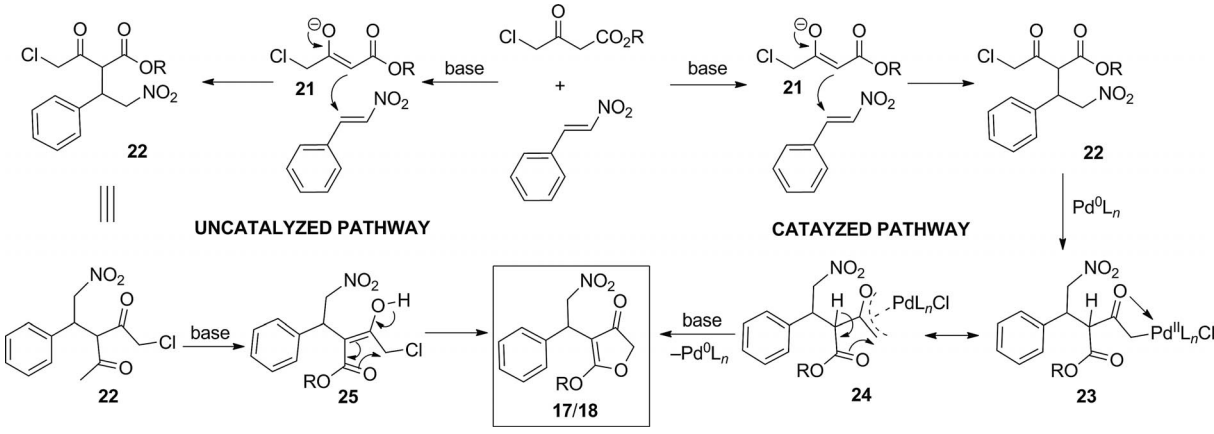
Scheme 3. Pd-catalyzed synthesis of 3(2*H*)-furanones from β-nitrostyrene.

We were then interested to determine if the phenyl ring in styrene had any influence on the outcome of the reaction. Thus, we prepared activated alkene **4g** from the aliphatic aldehyde propanal. The reactions of alkene **4g** with **5a** and **5b** were attempted under the optimized conditions. From both reactions, corresponding 3(2*H*)-furanones **19** and **20** were obtained in good yields (Scheme 4).



Scheme 4. Pd-catalyzed synthesis of 3(2*H*)-furanones from alkene **4g**.

To determine if the first step of the tandem process, that is, the Michael addition, was palladium catalyzed, we carried out two reactions with **4f** and methylacetoacetate. The first reaction was done under basic conditions [K_2CO_3 (1.0 equiv.), dioxane, 60 °C, 12 h], and the second reaction was performed under the optimized conditions. Both reactions afforded the Michael addition product in similar yields, and this proves that the Michael addition was uncatalyzed. Scheme 5 depicts a plausible mechanism for both the catalyzed and the uncatalyzed version of our 3(2*H*)-furanone synthesis from activated alkenes and 4-chloroacetoacetate. Both the catalyzed and uncatalyzed pathways commence with the Michael addition of the enolate to the α-carbon of the activated double bond to form intermediate **22**. In the next step of the catalyzed route, we believe that Pd^0L_n then undergoes oxidative addition to the C–Cl bond in intermediate **22** to form **23**. This species can subsequently give rise to oxy-π-allyl palladium intermediate **24**.[3] This step is followed by abstraction of the acidic proton by the base, which forces the ester enolate to attack the carbon end of **24** towards the ring closure to yield the 3(2*H*)-furanone.



Scheme 5. Mechanism for the formation of 3(2*H*)-furanones.

Conclusions

In conclusion, we have introduced a new methodology for the synthesis of substituted 3(2*H*)-furanones by the reaction of activated alkenes with 4-chloroacetoacetates under palladium catalysis. The reaction could be tuned to the formation of either 3(2*H*)-furanone or diethyl 1,4-dihydroxycyclohexa-1,4-diene-2,5-dicarboxylate derivatives by changing the temperature. The reaction proceeds through a catalyzed tandem Michael addition/ring-closing pathway to afford different 3(2*H*)-furanones in good to excellent yields. The products have multiple points of functionalization, which are currently being studied for different synthetic manipulations, and the results of these investigations will be reported in due course.

Experimental Section

General Experimental Procedure for the Preparation of Substituted 3(2*H*)-Furanones: Styrene (1.0 equiv.), $Pd(PPh_3)_4$ (5 mol-%), P(*o*-furyl)$_3$ (10 mol-%), and K_2CO_3 (2.0 equiv.) were placed in a Schlenk tube. The reaction flask was degassed and flushed with argon (3×). To this mixture, under an atmosphere of argon, was added dioxane (2 mL) followed by 4-chloroacetoacetate (1.0 equiv.); the mixture was stirred at 60 °C for 12 h. After completion of the reaction, the mixture was diluted with dichloromethane (20 mL) and washed with water (2 × 20 mL) and saturated brine (20 mL) solution. The organic layer was then dried with anhydrous magnesium sulfate, and the solvent was evaporated in vacuo. The residue was chromatographed on flash silica gel (ethyl acetate/pentane) to afford the product in good to excellent yields (see Tables 1 and 2).

Supporting Information (see footnote on the first page of this article): General methods, experimental procedures, and characterization data for all new compounds.

Acknowledgments

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