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Synthesis of Substituted Furoates from Acrylates and Aldehydes by Pd(OAc)$_2$/HPMoV/CeCl$_3$/O$_2$ System

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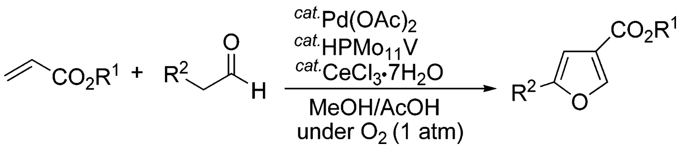

A new synthetic method of substituted furoates from acrylates and aldehydes was developed by Pd(OAc)$_2$ combined with molybdovanadophosphoric acid and Lewis acid under atmospheric dioxygen. The reaction was found to proceed through the palladium-catalyzed acetalization of acrylates with methanol followed by the reaction of the resulting acetals with aldehydes.

Introduction

Furan rings widely occur as key structural units in numerous important products, which are utilized in pharmaceuticals, essential oils and cosmetics, dyes and photosensitizers, fungicides, etc.[1] More specifically, furan carboxylates are important precursors of pesticides such as pyrethroid. Frequently used methods for the synthesis of furan derivatives are the intramolecular cyclization of 1,4-diketones (Paal−Knorr method)[1b] and the condensation between *β*-ketoesters and α-haloketones (Feist−Bénary reaction).[1c] Recently, a variety of transition-metal-catalyzed reactions have been developed for the synthesis of furan derivatives and heterocyclic compounds.[2] For instance, Pd(II)[3]- and Au[4]-catalyzed cycloisomerizations of 2-en-4-yn-1-ols are reported to lead to substituted furan derivatives. A furan carboxylate such as benzyl 5-methyl-3-furoate is known to be an attractive synthetic intermediate of resmethrin and is prepared through three steps from *δ*-phenyl levulic ester.[5] Similar furoates are derived from unsaturated lactone[6] and methyl levulinate dimethyl acetal.[7] However, most of these methods suffer from several drawbacks such as the use of uncommon chemicals, troublesome procedures, and/or the necessity of several reaction steps.

We have now developed a novel, direct route to 5- and 2,5-substituted 3-furoates (**3**), which are highly useful compounds in the pharmaceutical industry and pesticide chemistry, from acrylates (**1**) or acetyl acetones with aldehydes (**2**) under the influence of catalytic amounts of Pd(II), H$_4$PMo$_{11}$VO$_{40}$•28H$_2$O (HPMo$_{11}$V), and Lewis acid-like CeCl$_3$[8] (eq 1). It is important to note that the substituted furoates (**3**) can be directly synthesized through a catalytic process from very cheap chemicals such as acrylates and aldehydes. Therefore, this method provides a proficient and convenient synthetic route to substituted furoates.

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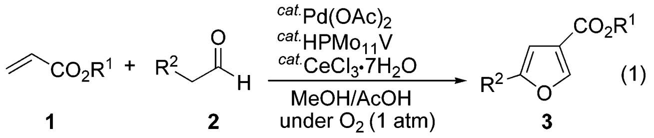
(8) Trisannelation, of acrylates to 1,3,5-benzenetricarboxylates using Pd(OAc)$_2$/HPMoV/CeCl$_3$/O$_2$ catalyst system has been reported recently, see: Tamaso, K.; Hatamoto, Y.; Sakaguchi, S.; Obora, Y.; Ishii, Y. *J. Org. Chem.* **2007**, *72*, 3603.

10.1021/jo701635f CCC: $37.00



Results and Discussion

The reaction of methyl acrylate (**1a**) with propanal (**2a**) was chosen as a model reaction and carried out under various reaction conditions (Table 1). To a mixture of $\mathrm{Pd(OAc)_2}$ (0.2 mmol), $\mathrm{HPMo_{11}V}$ (15 μmol), and $\mathrm{CeCl_3{\cdot}7H_2O}$ (0.2 mmol) in methanol/acetic acid solution, was added **1a** (1 mmol) and **2a** (6 mmol) in acetic acid over a period of 3.5 h by using a syringe pump under O_2 (1 atm); the reaction mixture stirred at 70 °C for an additional 4.5 h to give methyl 5-methyl-3-furoate (**3a**) in 90% yield (entry 1). When a mixture of **1a** and **2a** in acetic acid was added all at once to the catalytic solution, the yield of **3a** somewhat decreased (entry 2). Removal of either $\mathrm{HPMo_{11}V}$ or $\mathrm{Pd(OAc)_2}$ from the catalytic system resulted in sluggish reaction and recovery of the starting materials (entries 3 and 4). The reaction in the absence of $\mathrm{CeCl_3}$ produced polymeric products (entry 5). Furoate **3a** was not obtained by the reaction in methanol or acetic acid alone, but the addition of water to acetic acid produced **3a** in 38% yield (entry 6). These observations suggest that three metals which constitute a catalytic system and a mixed solvent are needed to promote the present reaction. When the amounts of catalysts were halved, the yield of **3a** (74%) was slightly decreased (entry 7). No reaction took place under argon atmosphere in the absence of O_2, because of difficulty of regenerating Pd(II) from the reduced Pd(0) (entry 9). Several Lewis acids such as $\mathrm{AlCl_3}$, $\mathrm{FeCl_3}$, $\mathrm{InCl_3}$, $\mathrm{SmCl_3}$, and $\mathrm{YbCl_3}$ were examined. $\mathrm{FeCl_3}$, $\mathrm{YbCl_3}$, and $\mathrm{SmCl_3}$ gave **3a** in 36%, 39%, and 10% yields, respectively, but $\mathrm{AlCl_3}$ and $\mathrm{InCl_3}$ led to a complex mixture of undesired polymeric products. $\mathrm{Yb(OTf)_3}$ and *p*-TsOH were found to be inert in the present reaction.

On the basis of these results, the furoate synthesis was examined by a combination of various aldehydes with electron-deficient alkenes (Table 2). The reaction of **2a** with several alkyl acrylates (**1b**−**1e**) afforded the corresponding alkyl furoates (**3b**−**3e**) in fair to good yields (entries 1−4).

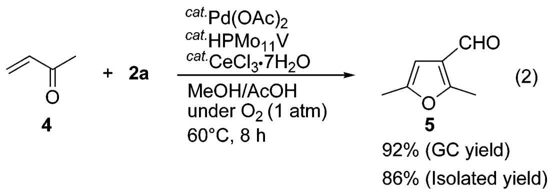
The reaction was successfully extended to several substrates other than acrylates. Acetyl acetone (**1f**) reacted with **2a** to form 2,5-dimethyl-3-acetylfuran (**3f**) in excellent yield (94%) (entry 5). 3,5-Heptanedione (**1g**) was less reactive, and the reaction at 90 °C for 15 h gave 2-ethyl-5-methyl-3-propionyl furan (**3g**) in moderate yield (entry 6). Cyclic ketones such as 1,3-cyclohexanedione (**1h**) afforded 2-methyl-6,7-dihydro-5*H*-benzofuran-4-one (**3h**) in moderate yield. It is important to note that dimethyl acetal of **1a**, methyl 3,3-dimethoxypropionate (**1i**), reacted with **2a** to afford **3a** in quantitative yield as discussed later (entry 10). The Pd(II)-catalyzed acetalization of **1a** is known to lead to acetal **1i**.[9] We reported that **1a** easily undergoes the acetalization to form **1i** in quantitative yield by $\mathrm{Pd(OAc)_2}$ combined with molybdovanadophosphate.[10]

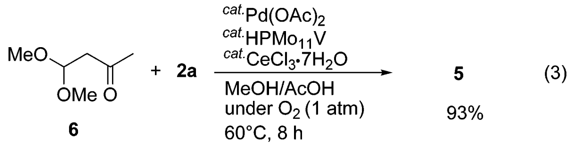
In addition, when methyl vinyl ketone (**4**) was allowed to react with **2a** under similar catalytic reaction conditions, 2,5-dimethyl-3-furaldehyde (**5**) was obtained exclusively in 92% yield (eq 2). Similarly, the reaction of the dimethyl acetal of **4**, 4,4-dimethoxy-2-butanone (**6**), with **2a** gave **5** in 93% yield (eq 3).

TABLE 1. Reaction of 1a with 2a by $\mathrm{Pd(OAc)_2}$ Combined with $\mathrm{HPMo_{11}V}$ and $\mathrm{CeCl_3}$ under Various Conditions[a]

entry	$\mathrm{Pd(OAc)_2}$/ mmol	HPMoV/ μmol	$\mathrm{CeCl_3}$/ mmol	conv/ %	yield/ %[b]
1	0.2	15	0.2	>99	90
2[c]	0.2	15	0.2	>99	83
3	0	15	0.2	5	nd[d]
4	0.2	0	0.2	34	3
5	0.2	15	0	50	nd[d]
6[e]	0.2	15	0.2	94	38
7	0.1	7.5	0.1	77	74
8[f]	0.1	7.5	0.1	80	74
9[g]	0.2	15	0.2	21	nd[d]
10[h,i]	0.2	15	0.2	>99	51
11[j]	0.2	15	0.2	>99	>99(91)

[a] A mixture of **1a** (1 mmol) and **2a** (6 mmol) in AcOH (0.5 mL) was added to a solution of $\mathrm{Pd(OAc)_2}$, $\mathrm{HPMo_{11}V}$, and $\mathrm{CeCl_3{\cdot}7H_2O}$ in MeOH (1.0 mL) and AcOH (4.5 mL) over a period of 3.5 h at 70 °C followed by stirring an additional 4.5 h at that temperature. [b] GLC yields based on **1a**. The number in parenthesis shows isolated yield. [c] A mixture of **1a** and **2a** was added all at once to the catalytic solution without using syringe pump. [d] Not detected by GLC. [e] H_2O (1.0 mL) was used in place of MeOH. [f] **1a** (1 mmol) in AcOH was added to a solution of **2a** (3 mmol), $\mathrm{Pd(OAc)_2}$, $\mathrm{HPMo_{11}V}$, and $\mathrm{CeCl_3{\cdot}7H_2O}$ in MeOH (1 mL) and AcOH (4.5 mL) over a period of 2 h followed by stirring an additional 6 h. [g] Under Ar. [h] **2a** (3 mmol) was used. [i] Trimethyl 1,3,5-benzenetricarboxylate (1.3%) was formed. [j] **2a** (7 mmol) was used.





It is rather difficult to explain clearly the reaction pathway for the formation of furoates from acrylates and aldehydes catalyzed by Pd(II) and Lewis acid. A plausible reaction path is shown in Scheme 1. It is reasonable to assume that the Pd(II)-catalyzed acetalization of acrylate **1a** with methanol is a key step to give acetal **1i** and/or **1i′** which is a synthetic equivalent of **1i**. In fact, as shown in entry 10 in Table 2, the reaction using **1i** in place of **1a** with **2a** proceeded smoothly to give **3a** in quantitative yield. The aldol-type condensation of the resulting **1i** or **1i′** with **2a** by $\mathrm{CeCl_3}$ affords an α,β-unsaturated carbonyl condensate (**A**) on which subsequent enolization by Pd(II) followed by intramolecular cyclization produces methyl furoate **3a** through Pd−H elimination from a dihydrofuran intermediate (**B**). The fact that the reaction of **1a** with benzaldehyde (**2d**) lacking α-hydrogen was completed at the stage of the formation of the condensate, methyl α-formylcinnamate (**3k**), corresponding to the condensate **A** suggests that the above-mentioned reaction pathway is probable (entry

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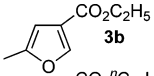
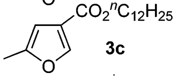
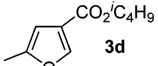
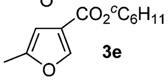
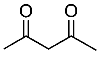
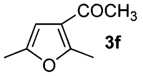
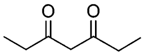
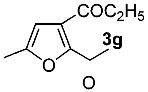
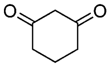
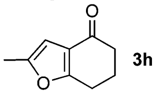
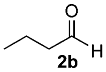
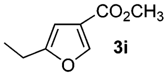
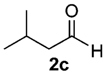
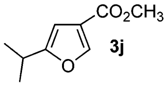
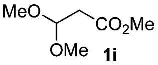
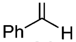
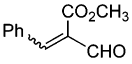
[9] Hosokawa, T.; Yamanaka, T.; Itotani, M.; Murahashi, S.-I. *J. Org. Chem.* **1995**, *60*, 6159 and refs cited therein.

[10] Yokota, T.; Fujibayashi, S.; Nishiyama, Y.; Sakaguchi, S.; Ishii, Y. *J. Mol. Catal. A: Chem.* **1996**, *114*, 113.

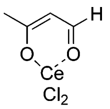
TABLE 2. Furoate Synthesis from 1 and Aldehydes (2)[a]

Entry	1	2	Product (3)	Yield (%)[b]
1[c]	$R^1 = C_2H_5$ (**1b**)	 **2a**	 **3b**	86 (80)
2	$R^1 = {}^{n}C_{12}H_{25}$ (**1c**)	**2a**	 **3c**	66
3[d]	$R^1 = {}^{i}C_4H_9$ (**1d**)	**2a**	 **3d**	77(66)
4[c]	$R^1 = {}^{c}C_6H_{11}$ (**1e**)	**2a**	 **3e**	54
5[c,d,e]	 **1f**	**2a**	 **3f**	94 (87)
6[f]	 **1g**	**2a**	 **3g**	55
7[c]	 **1h**	**2a**	 **3h**	59
8	$R^1 = CH_3$ (**1a**)	 **2b**	 **3i**	83(76)
9	**1a**	 **2c**	 **3j**	12
10	 **1i**	**2a**	**3a**	>99
11[g]	**1i**	**2a**	**3a**	87
12[h]	**1a**	 **2d**	 **3k**	89[i]

[a] A mixture of **1** (1 mmol) and **2** (7 mmol) in AcOH (0.5 mL) was added to a solution of $Pd(OAc)_2$ (0.3 mmol), $HPMo_{11}V$ (23 μmol), and $CeCl_3{\cdot}7H_2O$ (0.3 mmol) in MeOH (1.0 mL) and AcOH (4.5 mL) over a period of 3.5 h at 80 °C, followed by stirring an additional 4.5 h at that temperature. [b] GLC yields based on **1**. The numbers in parentheses show isolated yields. [c] $Pd(acac)_2$ was used instead of $Pd(OAc)_2$. [d] **2a** (10 mmol) was used. [e] Reaction was carried out at 60 °C. [f] The reaction was carried out at 90 °C for 15 h. [g] **1i** (1 mmol) in AcOH (0.5 mL) and MeOH (0.5 mL) was added to a solution of **2a** (3 mmol), $Pd(OAc)_2$ (0.1 mmol), $HPMo_{11}V$ (7.5 μmol), and $CeCl_3{\cdot}7H_2O$ (0.1 mmol) in MeOH (1.0 mL) and AcOH (4.5 mL). [h] The reaction was carried out at 60 °C for 2 h, and **2d** (60 mmol) was used. [i] E:Z = 33:67.

12). Finally, the reduced Pd(0) was reoxidized to Pd(II) by the action of the $HPMo_{11}V/O_2$ reoxidation system.[11]

The reaction of **4** with **2a** seemed to proceed in a similar reaction pathway through the Ce enolate (**7**) as a transient intermediate.



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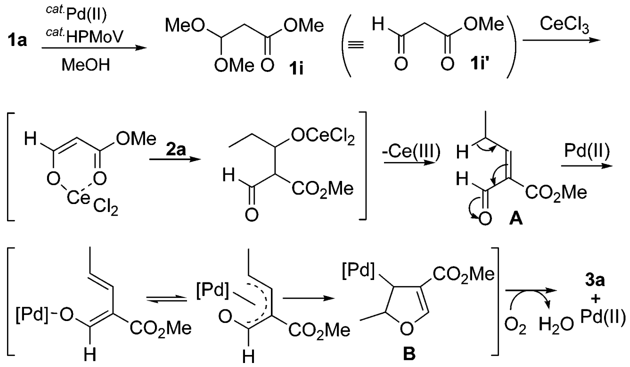
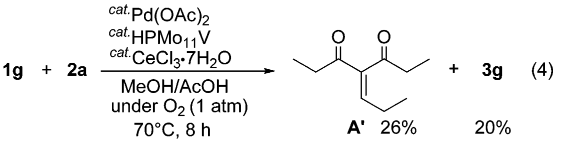
In the aforementioned reaction pathway, the condensate **A** is thought to be a precursor to the furoate **3a**. Thus, the reaction of **1a** with **2a** to obtain the condensate **A** was examined under various conditions, but we failed in isolating the **A**. However, the reaction of **1g** with **2a** to obtain an alternative condensate **A′** was carried out (eq 4). As expected, 4-propylidene-3,5-heptanedione (**A′**), which is assumed to be a precursor to furan derivative **3g**, was obtained in 26% yield along with furan **3g** (20%). The isolated **A′** is then subjected to react under the influence of $Pd(OAc)_2/HPMo_{11}V$ to give **3g** in 43% yield (eq 5). However, the cyclization of **A′** to **3g** was not induced by $CeCl_3{\cdot}7H_2O$ alone in the absence of $Pd(OAc)_2$ and $HPMo_{11}V$. This shows that the palladium species was an essential component for the furoate formation.

SCHEME 1. A Plausible Reaction Path[a] for the Formation of 3a from 1a and 2a



[a] Schemes in the brackets show a conceivable path.



(4)

$$\mathbf{A'} \xrightarrow[\text{AcOH, under } O_2 \text{ (1 atm), 70°C, 8 h}]{cat.\,Pd(OAc)_2,\ cat.\,HPMo_{11}V} \mathbf{3g}\ \ 43\% \qquad (5)$$

In conclusion, we have developed a direct route to substituted furans, which are very attractive compounds in organic synthesis, from cheap starting materials such as acrylates and aldehydes by using Pd(II) and $CeCl_3$ as key catalysts. This reaction would provide a very convenient synthetic route to various polysubstituted furoate derivatives.

Experimental Section

Compounds **3a**,[12] **3b**,[6] **3f**,[13] **3g**,[14] **3h**,[15] **3k**,[16] and **5**[17] were reported previously.

Experimental Procedures. A Typical Reaction was Carried out as Follows (Table 1, entry 11). To a solution of $Pd(OAc)_2$ (45 mg, 0.20 mmol, 20 mol %), $H_4PMo_{11}VO_{40}{\cdot}28H_2O$ ($HPMo_{11}V$)

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(38 mg, 15 μmol, 1.5 mol %), and $CeCl_3 \cdot 7H_2O$ (75 mg, 0.20 mmol, 20 mol %) in a mixed solvent of methanol (1.0 mL) and acetic acid (4.5 mL) was added a solution of **1a** (86 mg, 1 mmol) and **2a** (407 mg, 7 mmol) in acetic acid (0.5 mL) over a period of about 3.5 h by using a syringe pump under O_2 (1 atm), and the mixture was stirred at 70 °C for an additional 4.5 h. After the reaction, GLC and GC−MS analyses were performed. The conversions and yields of products were estimated from the peak areas, based on the GC internal standard technique. Solvent was removed under reduced pressure, neutralized with sodium bicarbonate, and extracted with diethyl ether (50 mL). The product, methyl 5-methyl-3-furoate (**3a**), was isolated as a pure form by Kugelrohr distillation in 91% yield.

Reaction of Methyl Vinyl Ketone (4) with Propanal (2a) in the Presence of $Pd(OAc)_2/HPMo_{11}V/CeCl_3$ (eq (2)). To a solution of $Pd(OAc)_2$ (67 mg, 0.30 mmol, 30 mol %), $H_4PMo_{11}VO_{40} \cdot 28H_2O$ ($HPMo_{11}V$) (50 mg, 23 μmol, 2.3 mol %), and $CeCl_3 \cdot 7H_2O$ (112 mg, 0.30 mmol, 30 mol %) in acetic acid (4.5 mL) was added a solution of **4** (70 mg, 1 mmol) and **2a** (581 mg, 10 mmol) in acetic acid (0.5 mL) over a period of about 4.5 h by using a syringe pump under O_2 (1 atm), and the mixture was stirred at 60 °C for an additional 3.5 h. After the reaction, GLC and GC−MS analyses were performed. The conversions and yields of products were estimated from the peak areas, based on the GC internal standard technique. Solvent was removed under reduced pressure, neutralized with sodium bicarbonate, and extracted with diethyl ether (50 mL). The product, 2,5-dimethyl-3-furaldehyde (**5**), was isolated as a pure form by Kugelrohr distillation in 86% yield.

Reaction of 4,4-Dimethoxy-2-butanone (6) with Propanal (2a) in the Presence of $Pd(OAc)_2/HPMo_{11}V/CeCl_3$ (eq (3)). To a solution of $Pd(OAc)_2$ (67 mg, 0.30 mmol, 30 mol %), $H_4PMo_{11}VO_{40} \cdot 28H_2O$ ($HPMo_{11}V$) (50 mg, 23 μmol, 2.3 mol %), and $CeCl_3 \cdot 7H_2O$ (112 mg, 0.30 mmol, 30 mol %) in acetic acid (4.5 mL) was added a solution of **6** (132 mg, 1 mmol) and **2a** (581 mg, 10 mmol) in acetic acid (0.5 mL) over a period of about 4.5 h by using a syringe pump under O_2 (1 atm), and the mixture was stirred at 60 °C for an additional 3.5 h. GLC and GC−MS analyses of the reaction mixture showed that **5** was formed in 93% yield.

Reaction of 4-Propylidene-3,5-heptadione (A′) in the Presence of $Pd(OAc)_2/HPMo_{11}V$ (eq (5)). To a solution of $Pd(OAc)_2$ (67 mg, 0.30 mmol, 30 mol %) and $H_4PMo_{11}VO_{40} \cdot 28H_2O$ ($HPMo_{11}V$) (50 mg, 23 μmol, 2.3 mol %) in acetic acid (4.5 mL) was added a solution of 4-propylidene-3,5-heptadione (**A′**) (168 mg, 1 mmol) in acetic acid (0.5 mL) over a period of about 2.5 h by using a syringe pump under O_2 (1 atm), and the mixture was stirred at 70 °C for an additional 5.5 h. GLC and GC−MS analyses of the reaction mixture showed that **3g** was formed in 43% yield.

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Supporting Information Available: Experimental procedures and spectral data of **3**, **5**, and **A′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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