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Trisannelation of Acrylates to 1,3,5-Benzenetricarboxylates by a $Pd(OAc)_2$/HPMoV/$CeCl_3$/O_2 System

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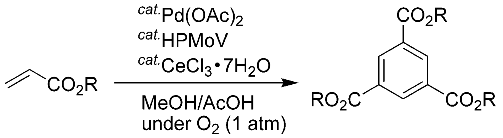
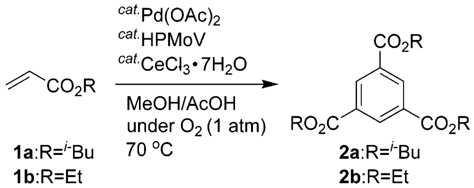


A new type of trisannelation reaction of acrylates through acetal formation was developed by $Pd(OAc)_2$ combined with molybdovanadophosphoric acid ($HPMo_8V_4$) and Lewis acid under atmospheric dioxygen. Thus, the reaction of isobutyl acrylate in the presence of $Pd(OAc)_2$, $HPMo_8V_4$, and $CeCl_3$ under O_2 (1 atm) in MeOH/AcOH afforded isobutyl 1,3,5-benzenetricarboxylate in fair yield. The reaction was found to proceed through the palladium-catalyzed acetalization of acrylate with methanol followed by the trisannelation reaction of the resulting acetal promoted by $CeCl_3$.

Dimerization of acrylates is a well-known synthetic method to obtain bifunctional dicarboxylates, which are highly useful compounds as polymer materials. This type of dimerization reaction has been extensively studied by using various transition metal complexes such as Co,[1] Ni,[2] Ru,[3] Rh,[4] and Pd.[5] In contrast to numerous studies on the dimerization of acrylates, however, there has been little study on the trisannelation reaction of acrylates. To the best of our knowledge, the synthesis of benzenetricarboxylates by trisannelation of acrylates has never been studied, although the cyclotrimerization of alkynes is known to lead to polysubstituted benzene derivatives.[6] For instance, the Ru-catalyzed cyclotrimerization of ethyl propiolate is reported to give a 4:1 mixture of triethyl 1,2,4- and 1,3,5-benzenetricarboxylates, but the regioselectivity of these two isomers is usually difficult to control by this method.[7] Triethyl 1,3,5-benzenetricarboxylate[8] was prepared by a stoichiometric reaction of ethyl 3-ethoxyacrylate with benzyltrimethylammonium ethoxide.[9] Jacobsen et al. showed the formation of triethyl 1,3,5-benzenetricarboxylate in the course of the distillation of the dimer of ethyl 3-ethoxyacrylate in the presence of $NaHSO_4$ or *p*-TsOH.[10] We have now found that a novel regioselective trisannelation reaction of acrylates to 1,3,5-benzenetricarboxylates is promoted by $Pd(OAc)_2$ combined with molybdovanadophosphoric acids in the presence of a small amount of Lewis acids in a mixed solvent of methanol and acetic acid (eq 1).



(1)

Table 1 shows the result of the reaction of isobutyl acrylate (**1a**) by $Pd(OAc)_2$ combined with $H_7PMo_8V_4O_{40}$•$23H_2O$ ($HPMo_8V_4$) and $CeCl_3$•$7H_2O$ under several reaction conditions.

A typical reaction was carried out as follows: To a solution containing $Pd(OAc)_2$ (0.10 mmol, 3.3 mol %), $HPMo_8V_4$ (0.023 mmol, 0.77 mol %), and $CeCl_3$•$7H_2O$ (0.20 mmol, 6.7 mol %) in a mixed solvent of methanol (2 mL) and acetic acid (3 mL) was added **1a** (3 mmol) in acetic acid (0.3 mL) and methanol (0.2 mL) over a period of 3.5 h under O_2 (1 atm) at 70 °C, and the mixture was stirred for an additional 18 h (entry 1). The reaction afforded triisobutyl 1,3,5-benzenetricarboxylate (**2a**) in 40% yield along with unidentified polymeric products. This is the first successful direct trisannelation reaction of acrylates to 1,3,5-trisubstituted benzene derivatives through a catalytic process, although the product yield of **2a** must be optimized. It is noteworthy that the trisannelation of **1a** was catalytically achieved in a regioselective manner to give **2a** since the trimerization of terminal alkynes is difficult to carry out regioselectively. When the amount of $Pd(OAc)_2$ was increased to 5 mol %, **2a** was obtained in 56% yield (entry 2). The reaction of **1a** under these conditions for 4 h afforded **2a** (15%, entry 3). The reaction of **1a** in the absence of $CeCl_3$ under these conditions produced **2a** in poor yield (6%, entry 5). The reaction did not proceed catalytically under an argon atmosphere (entry

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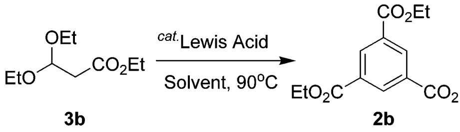
TABLE 1. **Trisannelation of 1a to 2a by the $Pd(OAc)_2/HPMo_8V_4/CeCl_3/O_2$ System under Several Reaction Conditions**[a]

entry	$Pd(OAc)_2$ (mmol)	HPMoV (μmol)	$CeCl_3$ (mmol)	conv (%)	yield[b] (%)
1	0.10	23	0.20	83	40
2	0.15	23	0.20	97	56 (55)
3[c]	0.15	23	0.20	23	15
4	0.15	30	0.20	97	35
5[d]	0.15	23	0	16	6
6[e]	0.15	23	0.20	no reaction	
7[f]	0.15	23	0.20	28	4
8[g]	0.15	23	0.20	93	19
9[h]	0.15	23	0.20	56	n.d.[i] (16)[j]

[a] To a solution of AcOH (3 mL) and MeOH (2 mL) containing $Pd(OAc)_2$, $HPMo_8V_4$, and $CeCl_3 \cdot 7H_2O$ was added **1a** (3 mmol) in AcOH (0.3 mL)/MeOH (0.2 mL) at 70 °C over a period of 3.5 h and stirred for additional 18 h. [b] GLC yields. The number in parentheses shows isolated yield. [c] Reaction time was 4 h. [d] Reaction was performed in the absence of $CeCl_3 \cdot 7H_2O$. [e] Reaction was performed under Ar. [f] AcOH (5 mL) was used without MeOH. [g] Water (2 mL) was used in place of MeOH. [h] MeOH (5 mL) was used without AcOH. [i] Not detected. [j] Yield of **3a**.

6). When methanol was removed from a mixed solvent, the conversion became very low (entry 7). However, the use of water instead of methanol afforded **2a** to some extent (19%, entry 8). No trisannelation was induced in the reaction in methanol alone, and isobutyl 3,3-dimethoxypropionate (**3a**) was obtained in 16% yield (entry 9). These results show that a mixed solvent of methanol and acetic acid is needed to obtain trisannelation product **2a**. The fact that the acetal **3a** is formed in the early stage of the reaction may provide powerful evidence that **2a** is formed through **3a**. Previously, we have reported that the acetalization of ethyl acrylate (**1b**) in ethanol is achieved by a $Pd(OAc)_2$/molybdovanadophosphate/hydroquinone system under O_2 to afford ethyl 3,3-diethoxypropionate (**3b**) in quantitative yield.[11]



(2)

TABLE 2. **Trisannelation of 3b to 2b by Several Lewis Acids under Various Conditions**[a]

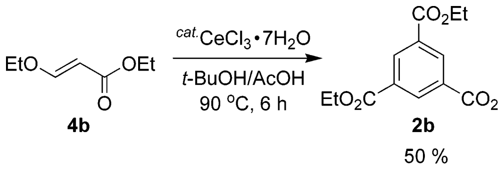
entry	solvent (mL)	Lewis acid	yield[b] (%)
1[c]	*t*-BuOH/AcOH (3/2)	$CeCl_3$	63
2	*t*-BuOH/AcOH (3/2)	$CeCl_3$	78 (70)
3	AcOH (5)	$CeCl_3$	41
4	*t*-BuOH (5)	$CeCl_3$	56
5[d]	*t*-BuOH (5)	$CeCl_3$	7
6	*t*-BuOH/AcOH (3/2)	$GdCl_3$	58
7	*t*-BuOH/AcOH (3/2)	$SmCl_3$	49
8	*t*-BuOH/AcOH (3/2)	$AlCl_3$	12
9	*t*-BuOH/AcOH (3/2)	$ZrCl_4$	13
10	*t*-BuOH/AcOH (3/2)	H_2SO_4	n.d.[e]
11	*t*-BuOH/AcOH (3/2)	TsOH[f]	n.d.[e]

[a] **3b** (3 mmol) was allowed to react in the presence of $CeCl_3$ (0.3 mmol) at 90 °C for 6 h. [b] GLC yields. The number in parentheses shows isolated yield. [c] Reaction time was 2 h. [d] Reaction was performed at 70 °C. [e] Not detected. [f] *p*-Toluenesulfonic acid.

Thus, the trisannelation of acetal **3b**, available from commercial source, was examined under the influence of a Lewis acid in a mixed solvent of *t*-BuOH and acetic acid under various reaction conditions (eq 2, Table 2).

As expected, the trisannelation of the acetal **3b** was achieved by $CeCl_3$ in a mixed solvent of *t*-BuOH[12] and acetic acid at 90 °C for 2 h to give triethyl 1,3,5-benzenetricarboxylate (**2b**) in a considerable yield (63%, entry 1). When the reaction was prolonged to 6 h, **2b** was obtained in 78% yield (entry 2). The reaction was induced to some extent in either acetic acid or *t*-BuOH alone (entries 3 and 4), but the reaction was slow at a temperature below 70 °C (entry 5). Among Lewis acids examined, lanthanide metal chlorides were found to be more efficient than normal metal chlorides. $CeCl_3$ was the best Lewis acid followed by $GdCl_3$ and $SmCl_3$ (entries 6 and 7). Use of $AlCl_3$ and $ZrCl_4$ resulted in **2b** in low yields (entries 8 and 9). No trisannelation was induced by protic acids such as TsOH and H_2SO_4 (entries 10 and 11).

On the basis of these results, a plausible reaction path for the trisannelation of **1a** to **2a** is outlined in Scheme 1. The reaction is initiated by the Pd(II)-catalyzed acetalization of acrylate **1a** to **3a**, and the resulting acetal **3a** is believed to be converted to 3-methoxy acrylate (**4a**) through a Ce acetal (**A**) as a transient intermediate. It seems rather difficult to presume the subsequent reaction paths involved in the annulation. However, we can make a proposal about the trisannelation which seems to agree with the experimental data. The Michael-type addition of **A** to **4a** affords an adduct (**B**) on which subsequent addition to **4a** followed by annelation leads to **2a**. Indeed, **4b** prepared independently was allowed to react in the presence of $CeCl_3$ in a mixed solvent of *t*-BuOH and AcOH (3:2) at 90 °C to give **2b** in 50% yield (eq 3). These results led to a conceivable reaction sequence which involved the formation of acetal **3a** promoted by the Pd(II) catalyst followed by trisannelation of the resulting **3a** to **2a** induced by $CeCl_3$.



(3)

In conclusion, we have developed a novel trisannelation reaction of acrylates through acetals to benzenetricarboxylates **2a** and **2b** by using a $Pd(OAc)_2/HPMo_8V_4/CeCl_3$ system under O_2 in a mixed solvent of methanol and acetic acid. In addition, acetal **3b** derived from ethyl acrylate was found to undergo trisannelation by Lewis acids to give **2b** in good yield.

Experimental Section

A typical reaction procedure of the reaction with **1a** was carried out as follows (Table 1, entry 2): To a solution containing $Pd(OAc)_2$ (0.10 mmol, 3.3 mol %), $HPMo_8V_4$ (0.023 mmol, 0.77 mol %), and $CeCl_3 \cdot 7H_2O$ (0.20 mmol, 6.7 mol %) in a mixed solvent of methanol (2 mL) and acetic acid (3 mL) was added **1a** (3 mmol) in methanol (0.2 mL) and acetic acid (0.5 mL) over a period of 3.5 h under O_2 (1 atm) at 70 °C, and the mixture was stirred for an additional 18 h. The conversions and the yield of products were estimated from the peak areas based on the internal standard technique using GLC and showed that **2a** was obtained in 56% yield. Then, the solvent was removed under reduced pressure, neutralized with sodium bicarbonate, and extracted with ethyl

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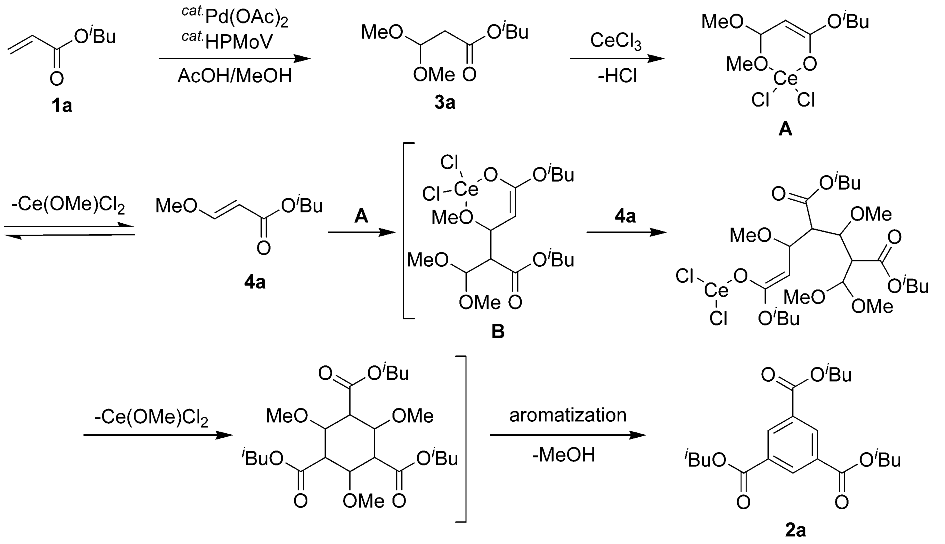
(12) *t*-BuOH was used to avoid the exchange reaction of **3b** with primary alcohols employed at higher temperature (90 °C).

SCHEME 1. A Plausible Reaction Path



acetate (20 mL). The product (**2a**) was isolated in 55% yield (207 mg) by column chromatography (230−400 mesh silica gel, *n*-hexane/ethyl acetate = 19/1).

A typical reaction procedure of the reaction with **3b** was carried out as follows (Table 2, entry 2): A mixed solvent of *tert*-BuOH (3 mL) and acetic acid (2 mL) solution of **3b** (3 mmol) and $CeCl_3 \cdot 7H_2O$ (0.30 mmol, 10 mol %) was placed in a round-bottomed flask, and the mixture was stirred at 90 °C for 6 h. The yield of the product (**2b**) was estimated from the peak areas based on the internal standard technique using GLC and showed that **2b** was obtained in 78% yield. Then, the solvent was removed under reduced pressure, neutralized with sodium bicarbonate, and extracted with ethyl acetate (20 mL). The product (**2b**) was isolated in 70% yield (205 mg) by recrystallization (H_2O/MeOH/acetone = 10/3/1).

Compounds **3b** and **4b** are commercially available. Products **2a**,[13] **2b**,[14] and **3a**[15] were known compounds and have been reported previously.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectral data of **2a** and **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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