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Development of an efficient method for preparation of 1,3,5-trihydroxyisocyanuric acid (THICA) and its use as aerobic oxidation catalyst

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Abstract—1,3,5-Trihydroxyisocyanuric acid (THICA), which serves as an efficient radical-producing catalyst from hydrocarbons, was successfully prepared by two methods. The reaction of *O*-benzylhydroxyamine with phenyl chloroformate gave formbenzyloxycarbamic acid phenyl ester of which subsequent treatment with dimethylaminopyridine (DMAP) produced 1,3,5-tribenzyloxyisocyanurate leading to THICA by hydrogenation with H_2 on Pd/C. The other method involved the direct synthesis of 1,3,5-tribenzyloxyisocyanurate from *O*-benzylhydroxyamine and diphenyl carbonate. The aerobic oxidation of *p*-methylanisole catalyzed using THICA as a key catalyst afforded *p*-anisic acid in almost quantitative yield (>99%).
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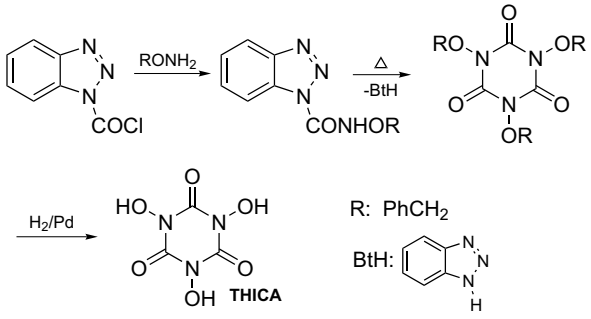
1. Introduction

In the course of the attempts to prepare esters or salts of hypothetical acid (HO–N=C=O), its trimer 1,3,5-trihydroxyisocyanuric acid (THICA) is prepared. Thus, THICA and its alkoxy derivatives, which are precursors of THICA, are prepared by several methods.[1–4] For example, 1,3,5-tribenzyloxyisocyanurate (**4**) was synthesized by the reaction of *O*-benzylhydroxyamine hydrochloride (**1**) with phosgene[1] or 1.1′-carbonyldiimidazole.[2] Alkoxy 1,3,5-trimethoxyisocyanurates are prepared by the reaction of diethyl *N*-ethoxyphosphoramidate with CO_2[3] and by the photolysis of methyl azidoformate.[4] However, these methods are insufficient as practical methods in large-scale syntheses, since the starting materials used are difficult to obtain from commercial sources. Recently, Butula and Takac have reported an alternative synthesis of THICA through three steps using 1-benzotriazolecarboxylic acid as a key compound as shown in Scheme 1.[5]



Scheme 1. A conventional preparation of THICA.

Quite recently, we have found that THICA serves as an efficient catalyst for the aerobic oxidation of methylbenzenes substituted by electron-withdrawing substituents, which are very difficult to be oxidized with O_2 under mild conditions.[6] For instance, *p*-nitrotoluene was successfully oxidized to *p*-nitrobenzoic acid (87%) under atmosphere dioxygen in the presence of THICA (5 mol%), $Co(OAc)_2$ (0.5 mol%), and $Mn(OAc)_2$ (0.05 mol%) at 130 °C. Thus, we are driven by necessity to prepare THICA by a simple method using commercially available compounds as starting materials. In this letter, we wish to report the development

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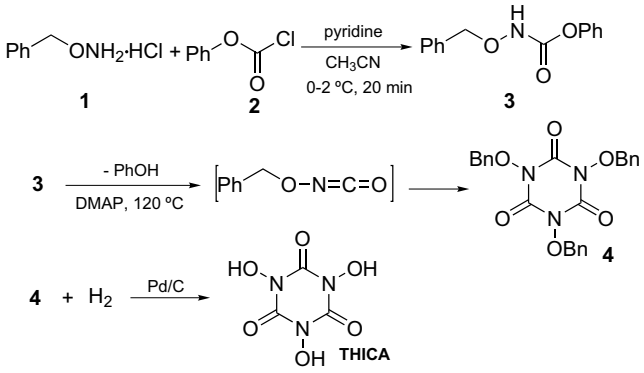


Scheme 2.

of a versatile method for the synthesis of THICA and its use as the catalyst for the aerobic oxidation of *p*-methylanisole to *p*-anisic acid.

2. Results and discussion

A new synthetic route to THICA using **1** and phenyl chloroformate (**2**) is depicted in Scheme 2. A typical reaction is carried out as follows: To a mixture of **1**, pyridine and dried CH_3CN were added dropwise **2** under N_2 at 0 °C followed by stirring at room temperature to afford formbenzyloxycarbamic acid phenyl ester (**3**). After the evaporation of solvent, the residue was treated with 4-dimethylaminopyridine (DMAP) at 120 °C to give 1,3,5-tribenzyloxyisocyanurate (**4**) in 82% yield. The hydrogenolysis of **4** on Pd/C afforded THICA in almost quantitative yield.

Thus, the reaction of **1** with **2** was examined in the presence of various bases without the isolation of **3**. It was found that the yield of **4** was considerably affected by the bases used and the reaction temperatures. These results are summarized in Table 1.

Among the bases examined, DMAP was found to be the best base followed by triethylamine (TEA) and DABCO. The reaction of **3** in the presence of 1 equiv of DMAP at 90 and 120 °C afforded **4** in 66% and 82% yields, respectively (Runs 6 and 7). Upon treatment of **3** with a strong base like DBU at 90 °C, **4** was obtained in 28% yield. However, no product was obtained by the reaction at 120 °C because of the decomposition of **3** during the reaction course. Imidazole was also effective to form **4** in moderate yield (Run 8). By the treatment of a weak base like pyridine at 90 °C, **3** was not converted into **4**. A strong base like *t*-BuOK did not promote the conversion of **3** to **4**. It seems that the basicity of bases is important to obtain **4** from **3** in satisfactory yield.

Table 1. Effect of bases and temperature for the formation of **4**[a]

Run	Base (pK_a)	Temp/°C	Yield of **4**/%
1	DBU (11.5)	90	28
2		120	Decomp.
3	TEA (10.72)	90	69
4	DABCO (8.7)	90	35
5		120	45
6	DMAP (9.65)	90	66
7		120	82
8	Imidazole (7.01)	120	42
9	Lutidine (6.90)	120	0
10	Pyridine (5.2)	90	0
11	*t*-BuOK	120	0

[a] The reaction method is shown in Experimental.

On the basis of these results, the reaction was carried out by the use of DMAP under several conditions (Table 2).

The reaction by the use of **3** isolated gave almost the same result as that by successive reaction (Run 1). Hereafter, the reaction was examined without isolation of **3**. The reaction of **3** in the presence of 0.1 and 0.5 equiv of DMAP afforded **4** in 15% and 44% yields, respectively (Runs 2 and 3). These results suggest that a stoichiometric amount of a base is needed to convert **3** to **4**, probably because of the formation of a salt with phenol liberated from **3** during the reaction. The reaction at 160 °C resulted in a decrease of **4**. Although this method was found to provide THICA in good yield, the use of phenyl chloroformate **2**, which is easily decomposed in the presence of water, is limited to the reaction under anhydrous condition. Therefore, if THICA can be synthesized by the reaction of **1** with diphenyl carbonate (DPC) instead of **2**, this method would provide a very convenient new route to THICA, since DPC is stable to water and is an easily available compound which is produced in industrial scale as a key component of polycarbonate resins. Thus, we next tried the development of a new route to THICA from **1** and DPC.

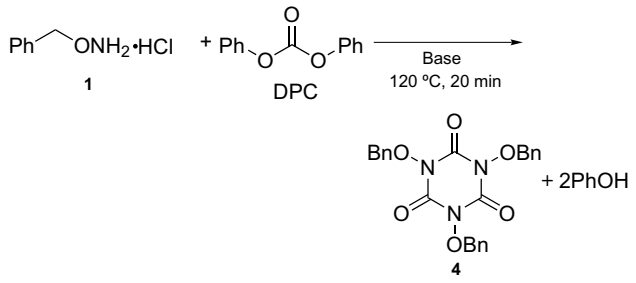
It was found that **4** can be produced by one step reaction of **1** with DPC in the presence of a base (Scheme 3). The results are shown in Table 3.

A mixture of **1** (10 mmol), DPC (10 mmol), and DMAP (10 mmol) was heated under N_2 at 120 °C for 20 min to

Table 2. Reaction of **1** with **2** using DMAP under several conditions[a]

Run	DMAP (equiv)	Yield of **4** (%)
1	1	81
2	0.1	15
3	0.5	44
4[b]	1	23

[a] The isolated **3** was reacted with DMAP.
[b] 160 °C.



Scheme 3.

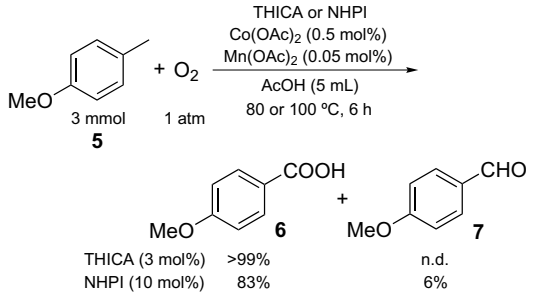
Table 3. Reaction of **1** with diphenyl carbonate (DPC) under several conditions[a]

Run	Base (equiv)	Temp (°C)	Time (min)	Yield of **4** (%)
1	DMAP (1)	120	20	50
2	DMAP (2)	120	20	70
3[b]	DMAP (2)	120	30	72
4	TEA (2)	90	20	52
5	Bu_3N (3)	90	180	67
6	—	120	No reaction	

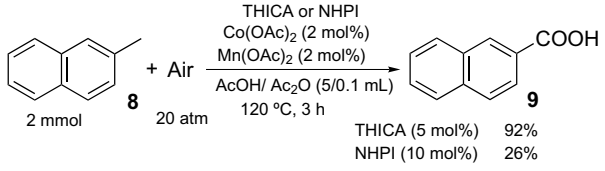
[a] The reaction method is shown in Experimental.
[b] The reaction was carried out by 100-mmol scale of **1**.

give **4** in 50% yield (Run 1). When the amount of DMAP was doubled under these conditions, the yield of **4** increased to 70% based on **1** used (Run 2). We tried the preparation of **4** in a 100-mmol scale and obtained almost the same result as that in the 10-mmol scale (Run 3). It is interesting to note that **4** can be easily prepared from **1** and DPC by a short-time reaction. The reaction using a cheap base like TEA in place of DMAP gave **4**, although the yield somewhat decreased (Run 4). It is because the reaction must be carried out at up to 90 °C due to the low boiling point (88.8 °C) of TEA. No reaction took place in the absence of a base (Run 6).

The aerobic oxidation of *p*-methylanisole (**5**) to *p*-anisic acid (**6**) by THICA was compared with that by *N*-hydroxyphthalimide (NHPI). The oxidation of **5** under dioxygen atmosphere (1 atm) in acetic acid by THICA combined with small amounts of $Co(OAc)_2$ and $Mn(OAc)_2$ at 80 °C afforded **6**, which is an important component of polyesters, in almost quantitative yield (>99%), while in the reaction using NHPI (10 mol%), **6** and *p*-methoxybenzaldehyde (**7**) were formed even at 100 °C for 10 h (Scheme 4). This shows that THICA possesses higher catalytic activity than NHPI for the aerobic oxidation of **5**. Similarly, THICA promoted the oxidation of 2-methylnaphthalene (**8**) to form the corresponding carboxylic acid **9** in excellent yield (Scheme 5).



Scheme 4.



Scheme 5.

In conclusion, we have developed a new versatile method for the synthesis of THICA, which is an efficient catalyst of the aerobic oxidation of methylbenzenes.

3. Experimental

All starting materials were commercially available and used without any purification.

3.1. Procedure for the preparation of THICA by the reaction of 1 with 2

Phenyl chloroformate (**2**) (1.57 g, 10 mmol) was added dropwise to a mixture of *O*-benzylhydroxyamine hydrochloride (**1**) (1.60 g, 10 mmol), pyridine (1.58 g, 20 mmol), and anhydrous CH_3CN (20 mL) over a period of 20 min under N_2 at 0–2 °C followed by at 25 °C for 2 h. The reaction mixture was concentrated at 30 °C followed by dilution with ethyl acetate (50 mL). The precipitate was filtered off and the filtrate was concentrated. The precipitate involving **3** was added to DMAP (1.22 g, 10 mmol) and heated to 120 °C for 20 min. After cooling to room temperature, methanol (10 mL) was added to the reactant and stirred for 20 min. The precipitate was filtered off, washed with methanol (10 mL), and dried in vacuo at 80 °C for 12 h to give **4** (1.22 g) in 82% yield. The hydrogenolysis of **4** (0.95 g, ca. 2 mmol) on Pd/C (10% Pd, 0.25 g) was carried out in dioxane (50 mL) under normal pressure of H_2 at room temperature for 3 h. The catalyst was filtered off from the reaction mixture and washed with dried dioxane (10 mL). The filtrate was evaporated under reduced pressure to give THICA (0.37 g) in almost quantitative yield. Spectral data of the resulting THICA were in agreement with those of literature values.[5] **3** could be isolated in 94% yield by the reaction of **1** with **2**.

3.2. Procedure for the preparation of 4 by the reaction of 1 with DPC

A mixture of **1** (1.60 g, 10 mmol), DPC (2.14 g, 10 mmol), and DMAP (2.44 g, 20 mmol) was heated at 120 °C for 20 min. After cooling to room temperature, methanol (10 mL) was added to the reaction mixture and stirred for 20 min. The resulting precipitate was filtered off and washed with additional methanol (10 mL). The precipitate was dried under reduced pressure at 80 °C to give **4** (1.05 g, 70% yield).

3.3. Procedure of the oxidation of 5 and 8

An acetic acid solution (5 mL) of **5** (3 mmol), THICA, $Co(OAc)_2$, and $Mn(OAc)_2$ was paced in a 50 mL pear-shaped flask with a balloon filled with O_2. The mixture was stirred at 100 °C for 6 h. The conversions and yields of products were estimated from the peak areas based on the internal standard technique using GLC. The oxidation of **8** was carried out by a similar manner as that of **5**.

Acknowledgements

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