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Application of silica gel-supported polyphosphoric acid (PPA/SiO₂) as a reusable solid acid catalyst to the synthesis of 3-benzoylisoxazoles and isoxazolines

Ken-ichi Itoh^{a,*}, Tadashi Aoyama^b, Hiroaki Satoh^b, Yuki Fujii^b, Hiroshi Sakamaki^a, Toshio Takido^b, Mitsuo Kodomari^c

^a Department of Liberal Arts and Science, College of Science and Technology, Nihon University, 7-24-1, Narashinodai, Funabashi-shi, Chiba 274-8501, Japan ^b Department of Materials and Applied Chemistry, College of Science and Technology, Nihon University, Kanda Surugadai, Chiyoda-ku, Tokyo 101-8303, Japan 5 Department of Discince and Environment of Science and Technology, Nihon University, Kanda Surugadai, Chiyoda-ku, Tokyo 101-8303, Japan

^c Department of Bioscience and Engineering, College of Systems Engineering and Science, Shibaura Institute of Technology, Fukasaku, Minuma-ku, Saitama 337-8570, Japan

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Isoxazoles have played an important role in organic and medicinal chemistry. In synthetic chemistry, isoxazoles have served as a versatile building block, and they can be converted into many useful synthetic intermediates such as 1,3-diketones,¹ β -hydroxy ketones,² and γ -amino alcohols.³ In addition, since the isoxazole ring is γ -amino alcohol analogue, compounds having isoxazole ring are frequently used in agrochemicals and medicines. For example, hymexazol (3-hydroxy-5-methylisoxazole) is widely used as fungicides and plant growth regulators,⁴ and sulfamethoxazole (4-amino-N-(5-methyl-3-isoxazolyl)-benzenesulfonamide) which belongs to a family of the sulfonamides are well known as anti-infective agents.⁵ Isoxazoles are usually prepared by following methods: 1,3-dipolar cycloaddition of dipolarophiles⁶ (alkynes, alkenes and so on) with nitrile oxides from aldoximes⁷ or α nitroketones. Among them, in the case of α -nitroketones, nitrile oxides are synthesized by dehydration using acid (sulfuric acid⁸ or p-toluenesulfonic acid⁹) or base (N-methylimidazole,¹⁰ 1,4diazabicyclo[2.2.2]octane (DABCO)¹¹ and copper(II) acetate/Nmethylpiperidine (NMP)¹²). However, reagents used there are expensive, toxic, and dangerous.

Polyphosphoric acid (PPA) is a strong mineral acid which has powerful dehydrating properties and widely used for

* Corresponding author. Tel./fax: +81 80 47 467 5307.

ABSTRACT

3-Benzoylisoxazoles were synthesized by the reaction of alkynes and benzoylnitromethane using silica gel-supported polyphosphoric acid (PPA/SiO₂). This reaction provides a convenient, efficient, and reusable synthetic method of isoxazole derivatives.

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intramolecular and intermolecular acylations, heterocyclic synthesis, and acid-catalyzed reactions. For instance, in the recent reports, the cyclization reaction of *N*,*N*'-bis(oxotrifluoroalkenyl)-1,3-phenylenediamines in PPA medium gave the bis-trifluoromethy-lated 1,7-phenanthrolines and 7-aminoquinolines,¹³ the acylation of benzene and its derivatives with 2-, 3-, 4-aminobenzoic and 4-aminophenylacetic acid in PPA afforded the aminobenzophenones,¹⁴ and the reaction of tryptamine with carboxylic acid in PPA was obtained by the 1-substitued 3,4-dihydro-9*H*-β-carboline derivatives.¹⁵ However, the use of PPA has several drawbacks: since 10- to 50-fold excess is generally employed, it is difficult to pour and stir at room temperature, and necessary to carefully alkalize before the extraction.

Recently, PPA/SiO₂ has been used as an efficient heterogeneous catalyst for many organic transformations. PPA/SiO₂ has some advantages including its low cost, ease of preparation, and ease of handling. In addition, the catalyst can be easily separated from the reaction mixture by simple filtration and is reusable. Previously, we have reported the conversion of carbonyl compounds into oxathioacetals or dithioacetals using PPA/SiO₂.¹⁶ Here, we wish to report a novel and convenient method for the synthesis of isoxazole derivatives using PPA/SiO₂ as a reusable catalyst. The reaction of benzoylnitromethane and alkynes in the presence of PPA/SiO₂ yielded the corresponding 3-benzoylisoxazoles (Scheme 1).





E-mail address: k-itoh@chem.ge.cst.nihon-u.ac.jp (K.-i. Itoh).

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Scheme 1. The transformation of benzoylnitromethane to nitrile oxides via the dehydration.

At first, reaction of benzoylnitromethane **1** with 1-octyne **2a** in the presence of various acid catalysts was performed in toluene under reflux. The results were summarized in Table 1. PPA/SiO₂ was the most effective among other acids tested except TsOH and gave 3-benzoyl-5-hexylisoxazole **3a** in high yield (Table 1, entries 1–4 and 8). SiO₂ gave trace amounts of **3a** and PPA gave **3a** in

Table 1

Reaction of benzoylnitromethane ${\bf 1}$ with ${\bf 2a}$ in the presence of various catalysts in toluene



Entry ^a	Catalyst	Amount (g) of catalyst	Yield (%) of 3a ^b
1	Concd. HCl (37%)	0.1	ND ^c
2	Concd. HNO ₃ (70%)	0.1	6
3	Concd. H ₂ SO ₄ (96%)	0.1	43
4	TsOH	0.1	90
5	PPA	0.1	52
6	SiO ₂	1.0	6
7	PPA, SiO ₂	0.07, 0.5	70
8	PPA/SiO2 ^d	0.5	90
9	HClO ₄ /SiO ₂ ^e	0.25	87
10	ZnCl ₂ /SiO ₂ ^f	0.5	58
11	Amberlyst 15	0.1	75

 a 1 (0.5 mmol), 2a (0.5 mmol), catalyst and toluene (5.0 mL) were employed under reflux for 5 h.

^b Isolated yields.

^c Not detected.

^d % By weight: 10.

e 0.5 mmol/g.

f 1.5 mmol/g.

Table 2
Effects of the loading ratio (wt. %) of PPA/SiO2, reaction time and solvent on th
reaction of 1 with 2a in the presence of PPA/SiO ₂

Entry ^a	% By weight	Weight/g	Solvent	Time/h	Yield (%) of 3a ^b
1	10	0.5	Toluene	5	90
2	20	0.25	Toluene	3	90
3	20	0.25	Toluene	4	96
4	20	0.25	Toluene	5	96
5	30	0.25	Toluene	3	90
6	20	0.25	Benzene	5	51
7	20	0.25	n-Hexane	5	25
8	20	0.25	Cyclohexane	5	89
9	20	0.25	Dichloromethane	5	N.D. ^c
10	20	0.25	1,2-Dichloroethane	5	24

 a 1 (0.5 mmol), 2a (0.5 mmol), PPA/SiO_2 and solvent (5.0 mL) were employed under reflux.

^b Isolated yields.

^c Not detected.

52% yield (Table 1, entries 5 and 6), whereas the yield of **3a** was improved up to 70% when a mixture of PPA (0.07 g) and silica gel (0.5 g) was used as a catalyst (Table 1, entry 7). The yield obtained by using TsOH was nearly equal to that obtained by PPA/SiO₂ (Table 1, entry 4). Moreover, the reaction using PPA/SiO₂ gave **3a** in highest yield when compared with acidic supported reagent and solid acid (Table 1, entries 8–11).

Effects of the loading ratio (wt. %) of PPA/SiO₂, reaction time, and solvent (such as PPA was not eluted from supported reagent) on the reaction of **1** with **2a** in the presence of PPA/SiO₂ were investigated (Table 2). Among various wt. % PPA/SiO₂ tested, 20 wt. % PPA/SiO₂ ¹⁷ was the most effective and **3a** was obtained in 96% yield (Table 2, entry 4).¹⁸ The optimum reaction time was 4 h and the most suitable solvent for the reaction was toluene (Table 2, entry 3). In case of the solvents such as benzene, *n*-hexane, dichloromethane, and 1,2-dichloroethane, the yield of **3a** was also a good solvent for the reaction. However, the yield of **3a** was slightly lower than that of toluene (Table 2, entry 8).

Generally, PPA is used large excess and is thrown away as a waste after the reaction. In contrast, PPA/SiO₂ has two merits: PPA is required only as a catalytic amount and the catalyst can be reused. PPA/SiO₂ is easily recovered from the reaction mixture by filtration. The recovered PPA/SiO₂ is regenerated by washing and drying, and can be used for a subsequent reaction. The results of recycling were summarized in Table 3. As can be seen from Table 3, PPA/SiO₂ was able to recycle five times and **3a** was obtained in satisfactory yield (Table 3, entry 5).

The reaction of **1** with alkynes **2b–2h** in the presence of PPA/ SiO₂ was carried out in toluene under reflux for 4 h. These results were summarized in Table 4. In the case of terminal alkynes, the corresponding 3-benzoylisoxaozles **3b–3g** were obtained in good

Table 3

Reusability of recovered catalyst on the reaction 1 with 2a

Entry ^a	Run	Yield of $3a \ (\%)^b$
1	1	96
2	2	94
3	3	92
4	4	85
5	5	82

 a 1 (0.5 mmol), 2a (0.5 mmol), PPA/SiO_2 (20 wt. %: 0.25 g) and toluene (5.0 mL) were employed under reflux for 4 h.

^b Isolated yields.

^b Isolated vields.

Table 4Reaction of 1 with alkynes 2b-2h in the presence of PPA/SiO2 in toluene



Entry ^a	Alkyne	R ₁	R ₂	Product	Yield (%) ^b
1	2b	Н	n-C ₄ H ₉	3b	85
2	2c	Н	$CH(CH_3)_2$	3c	70
3	2d	Н	$C(CH_3)_3$	3d	66
4	2e	Н	CH ₂ Cl	3e	83
5	2f	Н	Si(CH ₃) ₃	3f	97
6	2g	Н	Ph	3g	6
7	2h	COOCH ₃	COOCH ₃	3h	65

^a 1 (0.5 mmol), alkynes 2b-2h (0.5 mmol), PPA/SiO₂ (20 wt. %: 0.25 g) and toluene (5.0 mL) were employed under reflux for 4 h.

to excellent yields except **3g** (Table 4, entries 1–6). It seems that the yield of **3g** was very low because **2g** is sluggish toward the cycloaddition with nitrile oxide from **1**. From the disubstituted al-kyne **2h**, isoxazole derivative **3h** was obtained in 65% yield (Table 4, entry 7).

The reaction with alkynes **2i**–**2j** gave the corresponding 3-benzoylisoxazoles in excellent yields, which were a mixture of 5substituted (**3i** and **3j**) and 4-substituted-3-benzoylisoxazoles (**4i** and **4j**) (Table 5). Wade and co-workers also have reported that the reaction of nitronic ester and **2i** in the presence of TsOH afforded a mixture of **3i** and **4i** in 74 and 7 yields, respectively (ratio **3i**/ **4i** = 100/10).⁸ The ratio of **3i** and **4i** was determined by ¹H NMR compared with the area ratio between 4-position of **3i** and 5-possition of **4i**. Compared with the previous work, in the present

Table 5

Reaction of 1 with alkynes 2i-2j in the presence of PPA/SiO₂ in toluene



Entry ^a	Alkyne	R ₃	Product	Yield of ${\bf 3}$ and ${\bf 4}~(\%)^b$	Ratio (3/4) ^c
1	2i 2i	COOC ₁ H ₃	3i, 4i 3i 4i	97 96	100/7
2	2 j	COOC ₂ 115	J), T J	30	100/5

 $^a~1$ (0.5 mmol), alkynes 2i-2j (0.5 mmol), PPA/SiO_2 (20 wt. %: 0.25 g) and toluene (5.0 mL) were employed under reflux for 4 h.

^b Isolated yields.

^c Ratio was determined by ¹H NMR compared with area ratio between 4-position proton of **3** and 5-position proton of **4**.

Table 6

Reaction of 1 with alkenes **5a-5k** in the presence of PPA/SiO₂ in toluene



Entry ^a	Alkene	R4	Product	Yield (%) ^b
1	5a	n-C ₄ H ₉	6a	86
2	5b	n-C ₆ H ₁₃	6b	93
3	5c	n-C ₈ H ₁₇	6c	99
4	5d	n-C ₁₀ H ₂₁	6d	99
5	5e	CH ₂ Cl	6e	93
6	5f	CH ₂ Br	6f	75
7	5g	CH ₂ OCOCH ₃	6g	87
8	5h	CH ₂ OPh	6h	99
9	5i	CH ₂ CN	6i	99
10	5j	CH ₂ Ph	6j	64
11	5k	Ph	6k	25

^a **1** (0.5 mmol), alkenes **5a–5k** (0.5 mmol), PPA/SiO₂ (20 wt. %: 0.25 g) and toluene (5.0 mL) were employed under reflux for 4 h.

^b Isolated yields.



Scheme 2. Reaction of 1 with cyclohexene 51 in the presence of PPA/SiO₂ in toluene.

Table 7

Reaction of 7 with 2a in the presence of PPA/SiO2 in solvent



Entry ^a	Solvent	Time/h	Yield (%) of 8a ^b
1	Toluene	4	15
2	Toluene	24	7
3	o-Dichlorobenzene	1	33
4	o-Dichlorobenzene	2	50
5	o-Dichlorobenzene	4	43

 a 7 (0.5 mmol), **2a** (0.5 mmol), PPA/SiO_ (20 wt. %: 0.25 g), and solvent (5.0 mL) were employed under reflux.

^b Isolated yields.

investigation the yield (total yield: 97%) and selectivity of the product (ratio **3i/4i** = 100/7) was higher (Table 5, entry 1).

In addition, reaction of **1** with alkenes **5a–5k** in the presence of PPA/SiO₂ was carried out in toluene under reflux for 4 h. The results were summarized in Table 6. The corresponding 3-benzoylisoxazolines **6a–6k** were obtained in good to excellent yields except **6k**. In the case of cyclohexene **5l**, the corresponding isoxazoline **6l** was obtained in 20% yield (Scheme 2). From the results, it seems that **5k** and **5l** are sluggish in the cycloaddition similar to **2g**.

Finally, reaction of methyl nitroacetate **7** or 1-nitropropane with **2a** in the presence of PPA/SiO₂ was carried out in toluene under reflux. Methyl 5-hexyl-3-isoxazolecarboxylate **8a** was obtained from the reaction using **7** in low yield, however, the reaction using 1-nitropropane did not give the corresponding isoxazoles. In the reaction using **7** (Table 7), when o-dichlorobenzene was used instead of toluene as the solvent, the yield of **8a** was increased up to 50% yield (Table 7, entry 4.). As can be seen from Table 7, it seems that the dehydration of **7** required high temperature compared with **1**.

In conclusion, we developed a convenient and reusable synthesis of 3-benzoylisoxazoles from benzoylnitromethane and alkynes using PPA/SiO₂. It is particularly noteworthy that this reaction affords an efficient synthetic method for isoxazoles, therefore, we continuously tried to investigate the reaction with several α -nitroketones, alkynes and alkenes.

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- 17. Preparation of PPA/SiO₂: PPA was purchased from Aldrich. PPA (4.0 g) was charged in the round-bottom flask, and CHCl₃ (100 mL) was added. After the mixture was stirred at 50 °C for 1 h, followed by SiO₂ (16.0 g, Wakogel C-200; Wako Pure Chemical Ind., Ltd.) was added to the solution, and the mixture was stirred for another 1 h. CHCl₃ was removed by evaporation, and the resulting solid was dried in vacuo (10 mmHg) at room temperature for 3 h.
- 18. (a) Typical procedure: A mixture of α -nitroketones (0.5 mmol), alkynes (0.5 mmol) and PPA/SiO₂ (20 wt. %, 0.25 g) was stirred in toluene (5.0 mL) under reflux for 4 h. After the reaction, the used supported reagents were removed by filtration. The filtrate was evaporated to leave crude product, which was purified by column (ethyl acetate/n-Hexane = 1:5). (b) Gram-scale reaction: The reaction of 1 (6.0 mmol), 2a (6.0 mol) and PPA/SiO₂ (20 wt. %, 3.0 g) in toluene (60 mL) under reflux for 4 h gave 3a in 84% yield.