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Synthesis of thioamides from thiocarboxylic acids using phosphonium-type condensing reagents

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ABSTRACT

The synthesis of thioamides via the condensation reaction of thiocarboxylic acids with amines is described. Using 3-cyano-1,2,4-triazole as a favorable nucleophilic catalyst and 3-cyano-1,2,4-triazol-1-yl-tris(pyrrolidine-1-yl)phosphonium hexafluorophosphate (PyCTP) as a new phosphonium-type condensing reagent, thioamides are obtained selectively over amides, which can be attributed to the hardness of the phosphorus center of the condensing reagent.

Thioamide is a functional group in which the oxygen atom of an amide group is replaced with a sulfur atom. Thioamides have properties distinct from amides, despite their similar structures. For example, thioamides exhibit higher nucleophilicity and electrophilicity [1,2] and different hydrogen bond-forming ability [3]. Thioamides are used widely as intermediates for the synthesis of various compounds, such as heterocycles, because of their unique reactivity [2]. Furthermore, thioamide-containing peptides have found useful applications in the pharmaceutical field because of their higher tolerance to peptidases and cell permeability compared with their amide counterparts [4,5]. Thioamides are synthesized conventionally from amides using sulfurizing reagents, such as Lawesson's reagent [6,7]; however, this method is not suitable for the synthesis of compounds containing both thioamide and amide groups. In addition, the use of sulfurizing reagents has a series of operational and environmental drawbacks arising from their pungent smell. Recently, Yang *et al.* reported an ynamide-mediated strategy for the formation of thioamide bonds [8]. This strategy does not require any sulfurizing reagents and enables the site-specific incorporation of a thioamide bond into a peptide backbone in both solution and solid-phase conditions. As another approach, Hoeg-Jensen *et al.* reported a method for thioamide formation via a condensation reaction using phosphonium-type condensing reagents [9]. They found that [(6-nitrobenzotriazol-l-yl)oxy]tris (pyrrolidino)phosphonium hexafluorophosphate (PyNOP) was suitable for the condensation reaction of thioacetic acid with cyclohexylamine. Considering that a thiocarboxylic acid has two nucleophilic sites, namely, a hard oxygen atom and a soft sulfur atom according to the hard and soft acids and bases principle, they evaluated the oxygen/sulfur (O/S) selectivity in the nucleophilic attack of the thioacetic acid to the condensing reagent. As the activation of the oxygen atom by the condensing reagent is expected to afford a thioamide as a main product and a phosphine oxide as a by-product, whereas the activation of the sulfur atom produces an amide along with a phosphine sulfide derivative (Fig. 1), they determined the O/S selectivity by measuring the ratio between the phosphine oxide and the phosphine sulfide by ^{31}P NMR spectroscopy [9]. When the reaction was conducted using PyNOP, the O/S selectivity was 92%, and the ratio of the resulting thioamide to the amide was 79:21. This chemoselectivity was attributed to the hardness of the phosphorus center of the condensing reagent.

Meanwhile, our group designed another phosphonium-type condensing reagent, 3-nitro-l,2,4-triazol-l-yl-tris(pyrrolidin-1-yl) phosphonium hexafluorophosphate (PyNTP) [10], which has a prominent activity for the synthesis of phosphates [10,11], carboxylic acid esters [12], and peptide derivatives [13]. This reactivity results from the high leaving group ability of 3-nitro-1,2,4-triazole, which can act as a potent nucleophilic catalyst on its release from the phosphorus center. PyNTP can be expected to be applicable to the condensation reaction for thioamide formation, because it has a hard electrophilic center owing to the presence of 3-nitro-1,2,4-triazole. In this research, the condensation reaction of thiocarboxylic acids and amines was examined using various condensing reagents, including PyNTP, to gain further insights into the chemoselectivity of this reaction.

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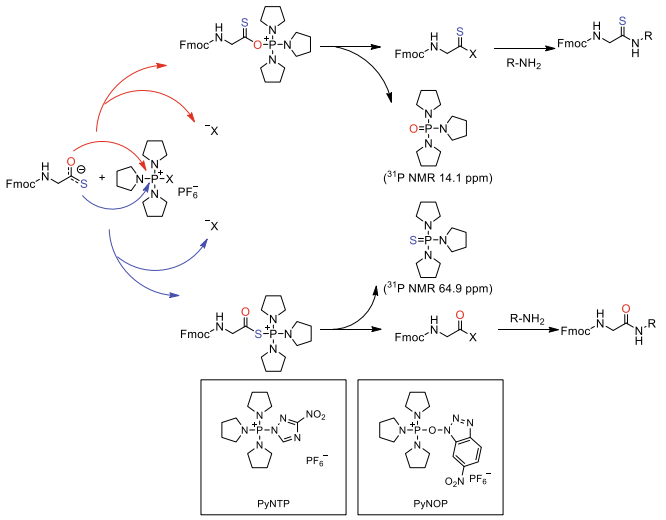
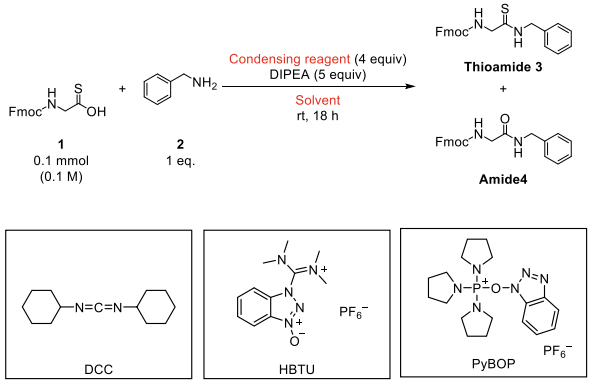


Fig. 1. Plausible mechanism for the formation of thioamide bonds using phosphonium-type condensing reagents.

First, the conditions for the condensation reaction were investigated using Fmoc-thioglycine **1** and benzylamine **2**. Compound **1** was synthesized from Fmoc-Gly-OH following a method reported previously [14] and stored as a potassium salt, because thiocarboxylic acids are known to react with atmospheric oxygen to form disulfides [15,16]. Prior to the condensation reactions, the potassium salt of the thiocarboxylic acid was transformed into a free acid by its treatment with an aqueous solution of $KHSO_4$. Various condensing reagents were examined by reacting equimolar amounts of thiocarboxylic acid **1** (0.1 M) and amine **2** in the presence of 4 equivalents of a condensing reagent in CH_2Cl_2 at room temperature (rt) for 18 h. 4 equivalents of condensing reagents were used to minimize the effect of hydrolysis of condensing reagent by water on the reaction outcome [17]. Then, the mixture was analyzed by ^{31}P NMR to establish the ratio between phosphine oxide and phosphine sulfide, and reverse-phase high-performance liquid chromatography (RP-HPLC) was performed to determine the ratio between thioamide **3** and amide **4**. The results are shown in Scheme 1 and Table 1 (entries 1–4).

When the thiocarboxylic acid and the amine were condensed in the presence of DCC or HBTU, which are used commonly for the synthesis of oligopeptides, the formation of the amide was significant, and the thioamide was hardly formed (Table 1, entries 1 and 2). In contrast, the use of benzotriazol-l-yl-oxy-tris(pyrrolidin-1-yl)phosphonium hexafluorophosphate (PyBOP), a phosphonium-type condensing reagent having 1-hydroxybenzotriazole as a leaving group, afforded the desired thioamides (Table 1, entry 3).



Scheme 1. Investigation of condensing reagents and solvents.

Furthermore, PyNTP gave the highest selectivity for thioamide formation (Table 1, entry 4).

Next, the O/S selectivity in the nucleophilic attack of thiocarboxylic acid **1** to the condensing reagent was evaluated by measuring the ratio of the resulting phosphine oxide and phosphine sulfide using ^{31}P NMR spectroscopy (Table 1, P═S (%)) using the method reported by Hoeg-Jensen *et al.* [9] Although PyNTP afforded higher selectivity than PyBOP, the O/S selectivity in the nucleophilic attack of thiocarboxylic acid **1** to PyNTP was lower than that of the analogous reaction with PyBOP (Table 1, entries 3 vs. 4). Therefore, we proposed a plausible mechanism for this reaction as shown in Fig. 2. When the oxygen atom of the thiocarboxylic acid reacts with PyNTP, an intermediate **5** is formed. Then 3-nitro-1,2,4-triazole attacks to the intermediate **5** to give a nitrotriazolide intermediate **6**. Although the nucleophilic attack of the amine to **6** can be expected to lead to the formation of the thioamide **3**, the reaction of **6** with the thiocarboxylic acid affords acid anhydride intermediates **7a** and **7b**. There is also a possibility that the intermediate **5** reacts with the thiocarboxylic acid and then the anhydrides **7a** and **7b** are formed. The mixed anhydride **7b** is a possible acylating reagent of the amine.

Next, the effect of the reaction solvents was investigated using PyNTP (Table 1, entries 4–7). The reaction in $CHCl_3$ improved the selectivity (Table 1, entry 5). In contrast, the condensation reaction proceeded with low selectivity (Table 1, entries 6 and 7) in polar solvents such as acetonitrile and *N*,*N*-dimethylformamide (DMF). According to the P═S values of entries 6 and 7 (Table 1), it can be assumed that the nucleophilicity of the thiocarboxylic acid is higher in a polar solvent owing to the solvation of the counter cation, which results in a low chemoselective nucleophile attack to the phosphorus center. These results indicate that $CHCl_3$ is the most suitable solvent for the condensation reaction.

As 3-nitro-1,2,4-triazole is a good leaving group, the active intermediate **6** is susceptible to the nucleophilic attack of thiocarboxylic acid **1**. Therefore, to modulate the reactivity of the active intermediate **6**, a series of nucleophilic catalysts was investigated. Chlorotris(pyrrolidin-1-yl)phosphonium hexafluorophosphate (PyCloP) was selected as a condensing reagent for the investigation of the nucleophilic catalysts because its leaving group is a chloride ion, which is not an effective nucleophilic catalyst. Equimolar amounts of thiocarboxylic acid **1** (0.05 M) and amine **2** were allowed to react with 4 equivalents of PyCloP and 8 equivalents of a nucleophilic catalyst in $CHCl_3$ at rt for 18 h. When the reaction was conducted in the presence of a triazole derivative as a nucleophilic catalyst, 13 equivalents of base was used; otherwise, 5 equivalents was used. Then, the mixture was analyzed by RP-HPLC to determine the ratio between thioamide **3** and amide **4**. The results are shown in Scheme 2 and Table 2.

The reaction using PyCloP as a condensing reagent in the absence of an additive resulted in lower selectivity than the reaction with PyNTP and a higher P═S% value (Table 2, entries 1 vs. 2). On the other hand, in the presence of one of the triazoles gave lower P═S% values than in the absence of triazoles. (Table 2, entries 2 vs. 3–6). These results indicated that the triazoles were acted as nucleophilic catalysts. The acidity of the nucleophilic catalysts evaluated follows the order **8a** > **8b** > **8c** > **8d**, according to Hammett's rule [18]. When 8 equivalents of 3-nitro-1,2,4-triazole (**8a**) was added as a nucleophilic catalyst, the reaction selectivity increased (Table 2, entry 3). Furthermore, the addition of 3-cyano-1,2,4-triazole (**8b**), which is less acidic than **8a**, improved the selectivity (thioamide/amide = 77:23) (Table 2, entry 4), whereas nucleophilic catalysts with lower acidity, such as methyl-1,2,4-triazole-3-carboxylate (**8c**) and 3-chloro-1,2,4-triazole (**8d**), gave low selectivities (Table 2, entries 5 and 6). From these results, **8b** was selected as a suitable nucleophilic catalyst for the condensation reaction.

Table 1
Investigation of condensing reagents and solvents.

Entry	Condensing reagent	Solvent	P═S (%) [a]	Ratio (%)[b]	
				Thioamide	Amide
1	DCC	CH_2Cl_2	–	7	93
2	HBTU	CH_2Cl_2	–	0	100
3	PyBOP	CH_2Cl_2	2.2	20	80
4	PyNTP	CH_2Cl_2	3.0	65	35
5	PyNTP	$CHCl_3$	1.3	75	25
6	PyNTP	MeCN	9.5	58	42
7	PyNTP	DMF	12.6	51	49

a) Determined by ^{31}P NMR (see supplementary data).
b) Determined by reverse-phase high-performance liquid chromatography.

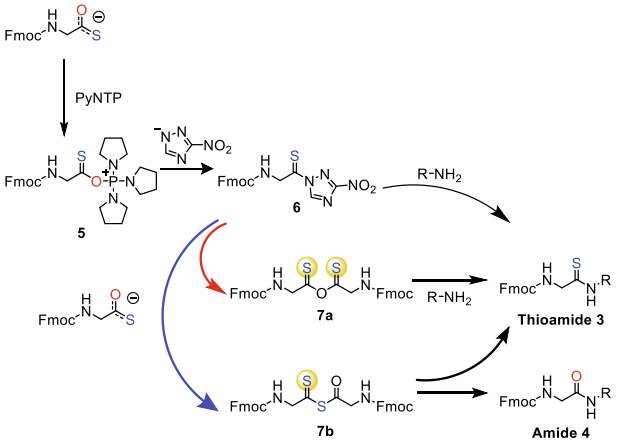
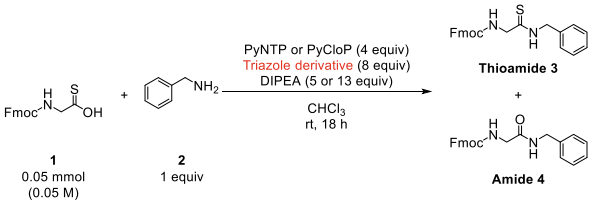
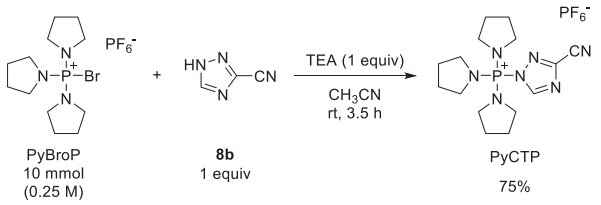


Fig. 2. Proposed mechanism for the condensation reaction via acid anhydride intermediates.

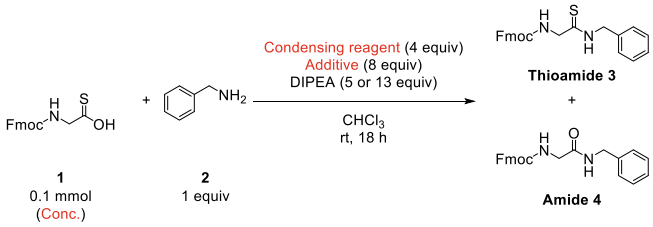


Scheme 2. Investigation of triazole derivatives.

Based on the abovementioned results, a new condensing reagent PyCTP containing the 3-cyano-1,2,4-triazole group on the phosphorus atom was synthesized from PyBroP and **8b**, as shown in Scheme 3. Then, a series of condensation reactions was



Scheme 3. Synthesis of PyCTP.



Scheme 4. Optimization of the reaction conditions.

conducted using phosphonium-type condensing reagents including PyCTP, and the product ratio of thioamide **3** to amide **4** was determined according to the peak areas of the RP-HPLC profiles and the isolated yields of **3** and **4** obtained by silica gel column chromatography purification. The results are shown in Scheme 4 and Table 3.

When PyNTP was used as a condensing reagent, thioamide **3** and amide **4** were isolated in 65% and 28% yields, respectively (Table 3, entry 1). The use of PyCloP and **8b** gave similar chemoselectivity, albeit lower isolated yields (Table 3, entries 1 vs. 2). It was found that the ratio of **3** to **4** became higher by using PyCTP

Table 2
Investigation of triazole derivatives.

Entry	Condensing reagent	Equiv of DIPEA	Triazole derivative (equiv)	P═S (%)[a]	Ratio (%)[b]	
					Thioamide	Amide
1	PyNTP	5	–	4.5	75	25
2	PyCloP	5	–	35.5	43	57
3	PyCloP	13	**8a** (8)	< 1	64	36
4	PyCloP	13	**8b** (8)	6.4	77	23
5	PyCloP	13	**8c** (8)	12.0	53	47
6	PyCloP	13	**8d** (8)	9.0	30	70

a) Determined by ^{31}P NMR. b) Determined by reverse-phase high-performance liquid chromatography.

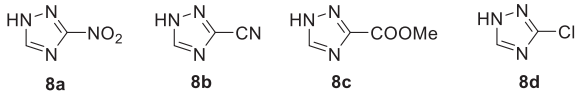
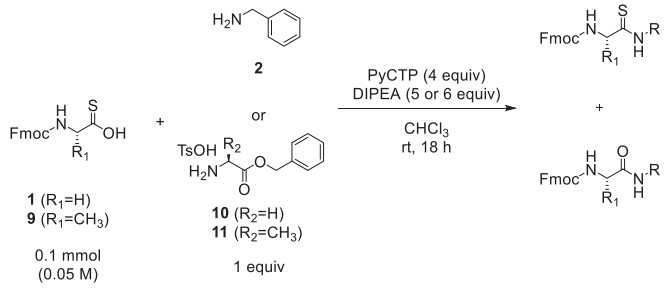


Table 3
Condensation reactions using various thiocarboxylic acids and amines.

Entry	Condensing reagent	Additive (equiv)	Equiv of DIPEA	Concentration of **1** (M)	Ratio (%)[a]		Isolated Yield (%)		
					Thioamide	Amide	Thioamide	Amide	Total
1	PyNTP	–	5	0.1	71	29	65	28	93
2	PyCloP	**8b** (8)	13	0.1	71	29	56	25	81
3	PyCTP	–	5	0.1	80	20	68	21	89
4	PyCTP	–	5	0.05	81	19	71	18	89

a) Determined by reverse-phase high-performance liquid chromatography.



Scheme 5. Condensation reactions using various thiocarboxylic acids and amines.

than by adding 3-cyano-1,2,4-triazole **8b** as a nucleophilic catalyst (Table 3, entries 2 vs. 3). In addition, PyCTP afforded a higher ratio and isolated yield of thioamide **3** than PyNTP (Table 3, entries 1 vs. 3). Finally, when the condensation reaction was conducted with a 0.05 M concentration of **1**, the best ratio and isolated yield of thioamide **3** were obtained.

With the optimized reaction conditions in hand, the condensation reactions were conducted using various thiocarboxylic acids and amines to investigate the effect of the structures of both substrates on the reaction outcome. Fmoc-thioglycine (**1**) and Fmoc-L-thioalanine (**9**) were selected as thiocarboxylic acids, and benzylamine (**2**), glycine benzyl ester *p*-toluenesulfonate (Gly-OBn, **10**), and L-alanine benzyl ester *p*-toluenesulfonate (Ala-OBn, **11**) were used as amines. Compound **9** was synthesized using the same

Table 4
Optimization of the reaction conditions.

Entry	Thiocarboxylic acid	Amine	Products	Ratio (%)[a]		Isolated Yield (%)		
				Thioamide	Amide	Thioamide	Amide	Total
1	**1**	**2**	**Thioamide 3** (X=S) **Amide 4** (X=O)	81	19	71	18	89
2	**9**	**2**	**Thioamide 12** (X=S) **Amide 13** (X=O)	81	19	69	20	89
3	**1**	**10**	**Thioamide 14** (X=S) **Amide 15** (X=O)	72	28	57	20	77
4	**9**	**10**	**Thioamide 16** (X=S) **Amide 17** (X=O)	83	17	76	8	84
5	**1**	**11**	**Thioamide 18** (X=S) **Amide 19** (X=O)	62	38	34	21	55
6	**9**	**11**	**Thioamide 20** (X=S) **Amide 21** (X=O)	78	22	66	14	80

a) Determined by reverse-phase high-performance liquid chromatography.

method as that for **1** [14]. The condensation reaction of equimolar amounts of thiocarboxylic acid and amine was performed in $CHCl_3$ for 18 h using 4 equivalents of PyCTP in the presence of 5 or 6 equivalents of DIPEA. The results are shown in Scheme 5 and Table 4 (entry 1 in Table 4 is equal to entry 4 in Table 3).

All the reactions investigated in Table 4 afforded thioamides preferentially. When the condensation reaction was conducted using amino acid derivatives, both the ratio and the isolated yield of the corresponding thioamides were higher with Fmoc-L-thioalanine **11** than with Fmoc-thioglycine **1** (Table 4, entries 3 vs. 4 and 5 vs. 6). This is most likely because of the fact that the formation of two acid anhydride intermediates is less favored in the case of Fmoc-L-thioalanine **11** because of the steric hindrance of the side chain; thus, the reaction of active intermediates and amines proceeded efficiently. For entry 6, it should be noted that the degree of racemization is not clear at this stage [19].

In conclusion, the formation of thioamide bonds using phosphonium-type condensing reagents was investigated, finding that a newly developed condensing reagent, PyCTP, was effective for the reaction. Although the formation of amides could not be completely avoided probably because of desulfurization via the formation of asymmetric anhydrides, thioamides were obtained successfully, with good chemoselectivities and isolated yields.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153179.

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