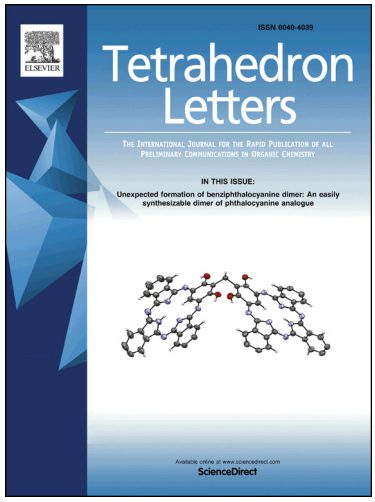

Pummerer Rearrangement using Bis(*p*-nitrophenyl) Phosphorazidate as an Azidation Reagent: A Novel Synthesis of Azidomethyl Sulfides

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Pummerer Rearrangement using Bis(*p*-nitrophenyl) Phosphorazidate as an Azidation Reagent: A Novel Synthesis of Azidomethyl Sulfides

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ABSTRACT

A novel method for the synthesis of azidomethyl sulfides by Pummerer rearrangement using bis(*p*-nitrophenyl) phosphorazidate (*p*-NO_2DPPA) as an azidation reagent was developed. Various methyl sulfoxides were converted into the corresponding azidomethyl sulfides. Importantly, this reaction enables the preparation of azidomethyl sulfides without the use of toxic or explosive azide sources.

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The Pummerer rearrangement, whereby sulfoxides react with electrophiles to give α-substituted sulfides, has been widely studied since it was first reported in 1909.[1] Different substituted groups can be introduced at the α-position of the sulfide by employing different nucleophiles.[2] However, although a broad range of Pummerer rearrangement reactions are known, only two reactions have been reported in which the azide ion is employed as the nucleophile.[3]

The azide group is an extremely useful functional group as it can be converted into a wide range of substituents. In particular, Huisgen cycloaddition, which affords triazoles from azides and alkynes, has been extensively used in click chemistry to prepare functional substances.[4] Recently, triazoles derived from α-azido sulfides have been attracting increasing attention owing to their application as bioactive compounds such as histone deacetylase inhibitors,[5] ricin toxin A inhibitors,[6] and quorum sensing modulators (QSM).[7]

The general strategy for the synthesis of α-azido sulfides is the use of substitution reactions between α-halo sulfides and azidating agents.[8] However, these reactions can be problematic owing to the use of toxic or explosive azide sources. Consequently, safer and more user-friendly methods for the synthesis of α-azido sulfides would be of enormous benefit to organic chemistry.

The azidation reagent bis(*p*-nitrophenyl)phosphorazidate (*p*-NO_2DPPA)[9] is less explosive than other currently employed azidation regents owing to its stabilization by the conjugated phosphorus atom. Thus, we reasoned that the use of *p*-NO_2DPPA as the azide ion source in the Pummerer rearrangement would be an attractive strategy. We also hypothesized that *p*-NO_2DPPA would also act as an electrophile for the activation of the sulfoxide moiety.

Herein, we report the use of *p*-NO_2DPPA as both the electrophile and azide source in the Pummerer rearrangement for the synthesis of α-azido sulfides. This method enables the preparation of α-azido sulfides without the use of toxic or explosive azide sources *via* a facile synthetic procedure.

First, we investigated whether azidation *via* Pummerer-type reactions with *p*-NO_2DPPA is feasible using methyl phenyl sulfoxide as a model substrate. The reaction conditions were explored by varying different reaction parameters, including reagent equivalents, reaction time, and the base and solvent employed (Table 1).

In the absence of base or at room temperature, the reaction does not proceed in toluene, even in the presence of two equivalents of *p*-NO_2DPPA (Table 1, entries 1–2). Conversely, the desired α-azido sulfide is obtained in 41% yield in the presence of two equivalents of 1,4-diazabicyclo[2.2.2]octane (DABCO) at reflux (Table 1, entry 3). However, under these

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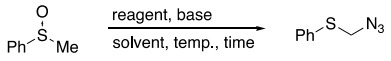
conditions, the extended reaction time leads to decomposition of the product, decreasing the yield (Table 1, entries 4–6). The yield is improved by increasing the quantities of *p*-NO_2DPPA and DABCO employed, whereas the use of an excess of DABCO over *p*-NO_2DPPA lowers the yield (Table 1, entries 7–9). The reaction proceeds smoothly using 2.5 equivalents of *p*-NO_2DPPA and DABCO to give the product in 79% yield in 2 h (Table 1, entry 10). Each corresponding sulfide was obtained in all cases. Moreover, a considerable amount of the starting material (methyl phenyl sulfoxide) remained, except for the optimum condition (Table 1, entry 10).

Table 1. Optimization of the reaction conditions.



entry	reagent (eq.)	base (eq.)	solvent	temp (°C)	time (h)	yield (%)
1	*p*-NO_2DPPA (2.0)	-	toluene	110	16	trace
2	*p*-NO_2DPPA (2.0)	DABCO (2.0)	toluene	rt	16	nd
3	*p*-NO_2DPPA (2.0)	DABCO (2.0)	toluene	110	0.5	41
4	*p*-NO_2DPPA (2.0)	DABCO (2.0)	toluene	110	1	64
5	*p*-NO_2DPPA (2.0)	DABCO (2.0)	toluene	110	2	61
6	*p*-NO_2DPPA (2.0)	DABCO (2.0)	toluene	110	16	36
7	*p*-NO_2DPPA (2.0)	DABCO (2.5)	toluene	110	1	40
8	*p*-NO_2DPPA (2.5)	DABCO (2.0)	toluene	110	1	62
9	*p*-NO_2DPPA (2.5)	DABCO (2.5)	toluene	110	1	64
10	*p*-NO_2DPPA (2.5)	DABCO (2.5)	toluene	110	2	79
11	*p*-NO_2DPPA (2.5)	DMAP (2.5)	toluene	110	2	66
12	*p*-NO_2DPPA (2.5)	quinuclidine (2.5)	toluene	110	2	57
13	*p*-NO_2DPPA (2.5)	pyridine (2.5)	toluene	110	2	30
14	*p*-NO_2DPPA (2.5)	pyridine (5.0)	toluene	110	2	58
15	*p*-NO_2DPPA (2.5)	2,6-lutidine (5.0)	toluene	110	2	28
16	*p*-NO_2DPPA (2.5)	Et_3N (5.0)	toluene	110	2	trace
17	*p*-NO_2DPPA (2.5)	DIPEA (5.0)	toluene	110	2	trace
18	*p*-NO_2DPPA (2.5)	DBU (5.0)	toluene	110	2	trace
19	*p*-NO_2DPPA (2.5)	DABCO (2.5)	DMF	110	2	18
20	*p*-NO_2DPPA (2.5)	DABCO (2.5)	1,4-dioxane	101	2	70
21	*p*-NO_2DPPA (2.5)	DABCO (2.5)	THF	66	2	8
22	*p*-NO_2DPPA (2.5)	DABCO (2.5)	MeCN	82	2	37
23	*p*-NO_2DPPA (2.5)	-	pyridine	115	2	16
24	*p*-NO_2DPPA (2.5)	DABCO (2.5)	CPME	106	2	65
25	*p*-NO_2DPPA (2.5)	DABCO (2.5)	xylene	138	2	16
26	DPPA (2.5)	DABCO (2.5)	toluene	110	2	47
27	DPPA (3.0)	DABCO (3.0)	toluene	110	2	54
28	DPPA (3.5)	DABCO (3.5)	toluene	110	2	66
29	DPPA (4.0)	DABCO (4.0)	toluene	110	2	61
30	DPPA (5.0)	DABCO (5.0)	toluene	110	2	53

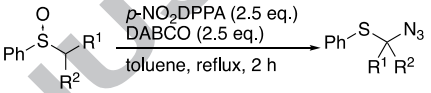
Although the desired product is obtained in satisfactory yield under the above conditions, we attempted to further optimize the reaction conditions by investigating different bases. However, no improvement over the use of DABCO is observed (Table 1, entries 11–18).

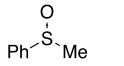
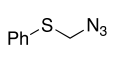
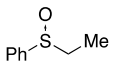
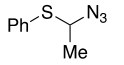
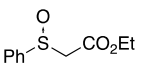
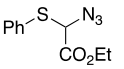
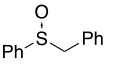
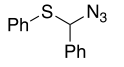
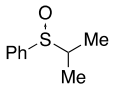
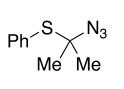
The effect of different solvents was also examined, and it was found that the use solvents other than toluene lowers the yield (Table 1, entries 19–25). The use of DPPA[10] affords the desired product in moderate yield, but a large excess of reagents is required owing to the low reactivity of DPPA compared to that of *p*-NO_2DPPA (Table 1, entries 26–30). When the reaction was performed under same conditions, the use of DPPA decreased the yield compared with *p*-NO_2DPPA (Table 1, entries 10 *vs.* 26).

Encouraged by these results, the substrate scope was investigated using various sulfoxides, as shown in Table 2. However, sulfoxides with substituent groups other than the methyl group do not afford the corresponding α-azido sulfides in high yields. This may be due to the reactions being suppressed by steric hindrance at the reaction center. In addition, sulfoxides adjacent to the active methylene groups give the disulfide as a byproduct. These results indicate that this reaction is significantly affected by steric hindrance.

Therefore, we limited the substrate scope to methyl sulfoxides and expanded the reaction to the broad range of methyl sulfoxides shown in Table 3. Both aromatic and aliphatic sulfoxides afford the desired products, i.e., the azidation selectively occurs on the methyl group alone (Table 3, entries 11 and 13–18). Aromatic sulfoxide containing an electron-donating group afford improved yield, while aromatic sulfoxides containing an electron-withdrawing group afford decreased yields (Table 3, entries 3–7). Using aromatic sulfoxides with electron-withdrawing groups, the corresponding sulfides are obtained in significant amounts (Table 3, entries 4, 5 and 7).[3a] Furthermore, heteroaromatic sulfoxides give lower yields than their aromatic counterparts (Table 3, entries 9–10). However, sulfoxides adjacent to benzyl or ester groups do not afford the desired products (Table 3, entries 6, 11, 12, and 17), and sulfoxides in proximity to tertiary carbon atoms are also not converted owing to the instability of the substrates (Table 3, entries 19–20).

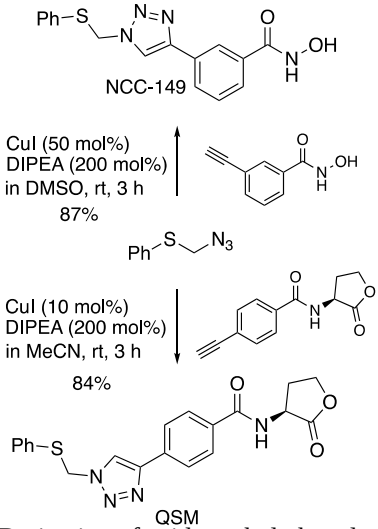
Table 2. Scope of the Pummerer-type azidation.



entry	substrate	product	yield (%)
1			79
2			17
3			13 (55)[a]
4			trace (50)[a]
5			nd

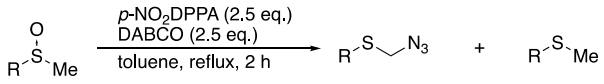
a) Diphenyl disulfide was obtained as a byproduct.

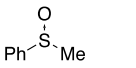
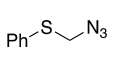
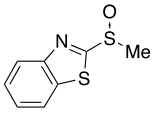
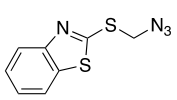
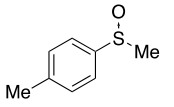
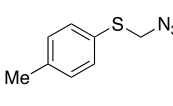
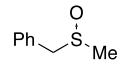
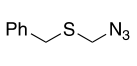
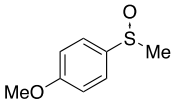
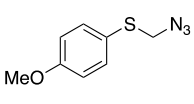
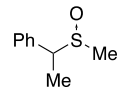
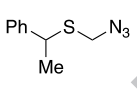
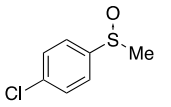
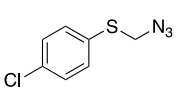
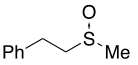
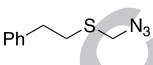
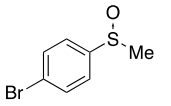
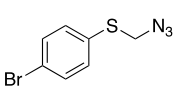
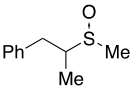
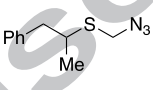
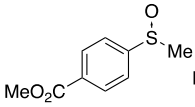
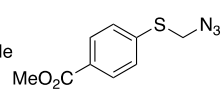
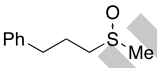
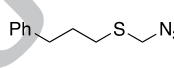
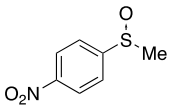
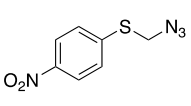
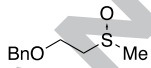
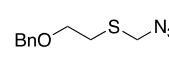
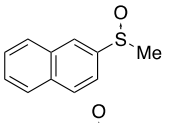
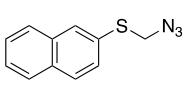
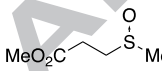
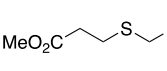
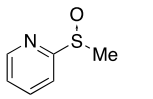
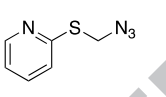
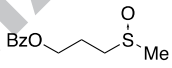
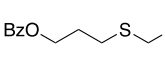
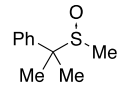
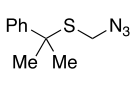
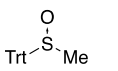
Next, we demonstrated the application of azidomethyl sulfides to the synthesis of bioactive compounds. As shown in Scheme 1, the synthesized azidomethyl phenyl sulfide was reacted with alkynes in the presence of CuI as a catalyst to give a histone deacetylase inhibitor (NCC–149)[5] and a QSM[7] in high yields. Therefore, our strategy for the synthesis of azidomethyl sulfides provides safer synthetic routes to various functional substances.



Scheme 1. Derivation of azidomethyl phenyl sulfide to bioactive compounds.

Table 3. Synthesis of various azidomethylsulfides.



entry	substrate	product	yield (%)	sulfide (%)	entry	substrate	product	yield (%)	sulfide (%)
1			79	14	10			complex mixture	
2[a]			77	14	11			7	trace
3			88	5	12			complex mixture	
4			65	33	13			75	17
5			44	39	14			68	17
6			1	78	15			68	16
7			62	25	16			35	36
8			71	21	17			1	10
9			14	32	18			66	25
					19			complex mixture	
					20			complex mixture	

a) Reaction time was 1 h.

A plausible reaction mechanism for this reaction is shown in Scheme 2. As discussed above, we believe that the reaction proceeds *via* a Pummerer-type rearrangement.[3b] The oxygen atom of the sulfoxide attacks *p*-NO_2DPPA to generate a sulfonium intermediate and releases the azide ion. Subsequently, the sulfonium intermediate undergoes elimination to produce the thionium ion, which is subject to nucleophilic addition of the azide ion to give the desired α-azido sulfide.

In conclusion, we have developed a novel method for the synthesis of azidomethyl sulfides *via* the Pummerer rearrangement using *p*-NO_2DPPA as the azidation reagent. Various methyl sulfoxides were easily converted into the corresponding azidomethyl sulfides. The azidation selectively occurs on the methyl group when hydrogen atom abstraction is possible from two places. This observation suggests that the elimination of the phosphonate group in the sulfonium intermediate proceeds *via* an E1CB process. The advantages of this method are the use of less toxic and explosive azide sources and the simplicity of the synthetic procedure.

Scheme 2. Plausible reaction mechanism.

General procedure

p-NO_2DPPA (91.3 mg, 0.25 mmol) and DABCO (28.0 mg, 0.25 mmol) were added to a solution of the sulfoxide (0.10 mmol) in toluene (0.35 mL). After stirring for 2 h at reflux, the mixture was diluted with AcOEt/*n*-hexane (1:5) (30 mL). Then, the mixture was washed with saturated aqueous $NaHCO_3$ (25 mL) and brine (25 mL), and dried over Na_2SO_4. Concentration of the solvent *in vacuo* followed by purification of the residue on a silica gel column (AcOEt:*n*-Hexane 1:5–0:1) gave the desired α-azido sulfide.

Acknowledgments

This work was supported by JSPS Grant-in-Aid for Scientific Research (C), 26450145, and Professor Y. Uozumi's JST-ACCEL program (JPMJAC1401).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://xxxxx.

References and notes

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Highlights

- Various azidomethyl sulfides were prepared *via* Pummerer rearrangement using *p*-NO_2DPPA.
- Methyl sulfoxides were easily converted into the corresponding azidomethyl sulfides.
- Azidosulfides could be prepared without the use of toxic or explosive azide sources.
- Bioactive compounds were prepared using the synthesized azidomethyl sulfide.

Graphical Abstract

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Pummerer Rearrangement using Bis(*p*-nitrophenyl) Phosphorazidate as an Azidation Reagent: A Novel Synthesis of Azidomethyl Sulfides

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Kotaro Ishihara, Takayuki Shioiri, and Masato Matsugi *