A New Method for the Preparation of Nitrogen-containing Cyclic Compounds from *p*-Nitrobenzenesulfonamide and Alkyl Bis(diphenylphosphinite)s by Oxidation–Reduction Condensation Using 1-Azidoadamantane

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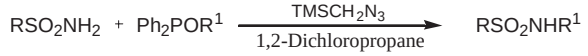
A new and efficient method was established for the preparation of nitrogen-containing cyclic compounds from *p*-nitrobenzenesulfonamide, bisphosphinites, and 1-azidoadamantane in good yields under neutral conditions.

It was recently reported from our laboratory that an oxidation-reduction condensation using a combination of alkyl diphenylphosphinites (Ph_2POR), prepared from alcohols and chlorodiphenylphosphine (Ph_2PCl), and quinones such as 2,6-dimethyl-1,4-benzoquinone and 2,6-di-*tert*-butyl-1,4-benzoquinone is successfully applied to the syntheses of esters,[1] ethers,[1b,2] alkyl nitriles,[3] alkyl aryl sulfides,[4] alkyl amides,[5] and isocyanides.[6] More recently, a new synthetic method of monoalkyl sulfonamides from alkyl diphenylphosphinites and unsubstituted sulfonamides in the presence of trimethylsilylmethyl azide was reported (Scheme 1).[7] In order to extend the scope of this condensation reaction, syntheses of nitrogen-containing cyclic compounds were studied.



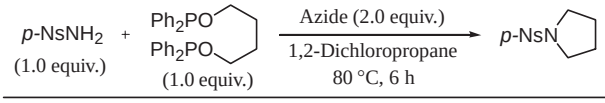
Scheme 1.

A nitrogen-containing cyclic compound is an important unit found in many of the physiologically active substances and medicines. Therefore, to develop its convenient method is always an important topic in synthetic organic chemistry and its related fields. Although many synthetic studies have been reported to date,[8] there have been known only a few methods that uses easily-available and easy-to-handle diols as starting materials.[9] Then, a new and efficient method for the preparation of nitrogen-containing cyclic compounds was studied by treating bisphosphinites, easily prepared from diols and Ph_2PCl with *p*-$NsNH_2$ and 1-azidoadamantane.

In the first place, cyclization reaction between 1.0 equiv. of 1,4-butanediyl bis(diphenylphosphinite)[10] and 1.0 equiv. of *p*-nitrobenzenesulfonamide (*p*-$NsNH_2$) was tried by using 2.0 equiv. of trimethylsilylmethyl azide, and the desired product was obtained in 46% yield (Table 1, Entry 1). Then, several other alkyl azides were examined to improve the yield (Entries 2–4) and it increased up to 64% when bulky 1-azidoadamantane was used (Entry 3). Next, optimization of the molar ratio of reagents was tried and the yield increased up to 73% even when 2.0 equiv. of the sulfonamide was used while the use of 1.5 equiv. of bisphosphinite further increased the yield up to 84% (Table 2).

Thus, the conditions of this procedure were optimized and the scope of this cyclization reaction was investigated next (Table 3). When the reaction of bisphosphinite derived from 2-methyl-1,4-butanediol was tired, the corresponding pyrrolidine derivative was obtained in good yield (Entry 2). Similarly, the reactions of bisphosphinites derived from 1,5-pentanediols afforded the corresponding piperidine derivatives in good yields (Entries 3 and 4). This method is also successfully applied to the syntheses of morpholine and thiomorpholine derivatives (Entries 5 and 6). Similarly, the reaction of the bisphosphinite prepared from 2-methyl-1,4-pentanediol was tried and the corresponding pyrrolidine derivative was obtained in good yield (Entry 7). The reaction of bisphosphinites prepared from 2,5-hexanediols having two secondary hydroxyl groups was next tried (Entries 8 and 9). The cyclization reaction of bisphosphinite prepared from 2,5-hexanediol with *p*-$NsNH_2$ afforded 1-(*p*-nitrobenzenesulfonyl)-2,5-dimethylpyrrolidine as a mixture of diastereomers (*trans*/*cis* = 1/1) in moderate yield (Entiry 8). On the other hand, 1-(*p*-nitrobenzenesulfonyl)-(2*S*,5*S*)-2,5-dimethylpyrrolidine was obtained with a 94% diastereomeric excess and a >99% enantiomer excess when the bisphosphinite prepared from (2*R*,5*R*)-dimethyl 2,5-hexanediol was used. This suggests that the reaction proceeded principally via S_N2 mechanism.

Table 1. Screening of alkyl azides



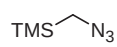
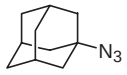
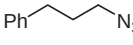
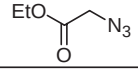
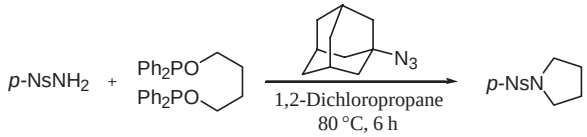
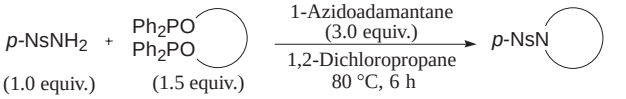
Entry	Azide	Yield/%	Entry	Azide	Yield/%
1		46	3		64
2		35	4		12

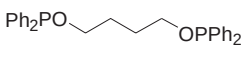
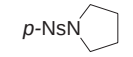
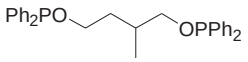
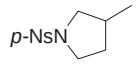
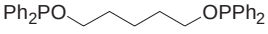
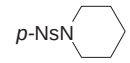
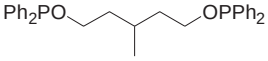
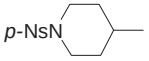
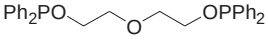
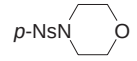
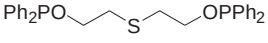
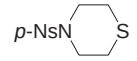
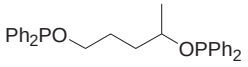
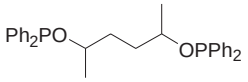
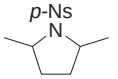
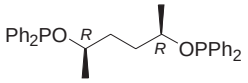
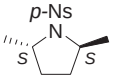
Table 2. Optimization of reaction conditions



Entry	*p*-$NsNH_2$ /equiv.	Bisphosphinite /equiv.	1-Azidoadamantane /equiv.	Yield /%
1	1.0	1.0	2.0	64
2	1.2	1.0	2.0	68
3	1.5	1.0	2.0	73
4	2.0	1.0	2.0	73
5	1.0	1.2	2.4	70
6	1.0	1.5	3.0	84

Table 3. Cyclizations of *p*-nitrobenzenesulfonamide and various bisphosphinites by using 1-azidoadamantane[a]

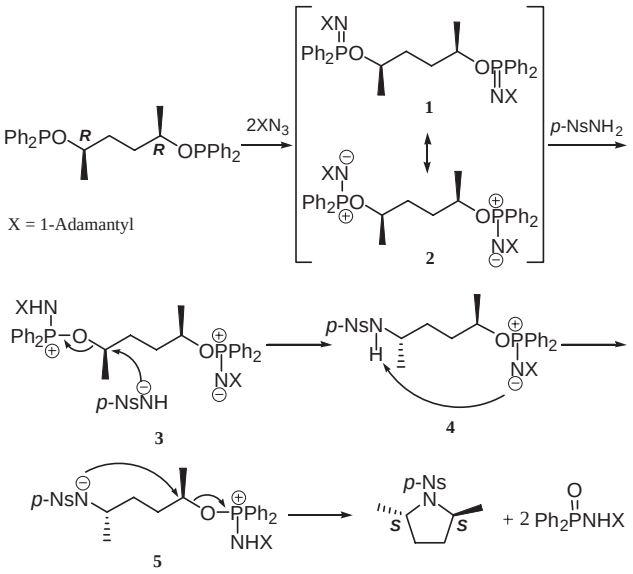


Entry	Bisphosphinite	Product	Yield/%
1			84[b]
2			72
3			75
4			82
5			77
6			84
7			70
8			51[c]
9[d]			54[e,f] (67)[g]

[a]Reactions were carried out on a 0.3 mmol scale. [b]When *o*-$NsNH_2$ was used, the corresponding pyrrolidine was obtained in 89% yield. [c]When *o*-$NsNH_2$ was used, the corresponding pyrrolidine was obtained in 47% yield. [d]DAICEL CHIRALPAK AD-H column was used for HPLC analysis. [e]The desired product was obtained with 94% de and >99% ee. $[\alpha]_D^{28} = +30.0$ ($CHCl_3$, *c*1.20). [f]$[\alpha]_D^{28} = -30.4$ ($CHCl_3$, *c*124) (preparation from (2*R*,5*R*)-2,5-dimethyl pyrrolidine, *p*-NsCl and Et_3N). [g]Bisphosphinite (2.0 equiv.) and 1-azidoadamantane (4.0 equiv.) were used.

A proposed mechanism is shown in Scheme 2: (2*R*,5*R*)-2,5-dimethylhexanediyl bis(diphenylphosphinite) reacted initially with 1-azidoadamantane to form the phosphinimidate, which was in turn transformed to the phosphonium salt **3** by the interaction with *p*-$NsNH_2$. A subsequence attack of the sulfonamide anion to the carbon atom adjacent to an oxygen atom of the alkoxy group afforded the compound **4** that has an *N*-alkyl sulfonamide and phosphinimidate groups in the same molecule. In a similar fashion, deprotonation of **4** and the following intramolecular nucleophilic attack took place to afford the corresponding pyrrolidine.

Typical experimental procedure is as follows: To a solution of sulfonamide (0.3 mmol) and bisphosphinite (0.45 mmol) in 1,2-dichloropropane (0.6 mL) was added 1-azidoadamantane (0.9 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for an additional 6.0 h at 80 °C. After completion of the reaction (detected by TLC), the crude product was purified by preparative TLC to afford the corresponding nitrogen-containing cyclic compound.



Scheme 2.

Thus, it is noted that various nitrogen-containing cyclic compounds are synthesized under neutral conditions by treating bisphosphinites, easily prepared from diols with *p*-$NsNH_2$ and commercially-available 1-azidoadamantane. Further study on this type of condensation reaction is now in progress.

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References and Notes

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10 Typical procedure is as follows; to stirred solution of 1,4-hexanediol (10 mmol) and DMAP (3 mmol) in dry THF (50 mL) were added Et_3N (22 mmol) followed by $ClPPh_2$ (21 mmol) under Ar atmosphere. After stirring at rt for 3 h, TLC showed complete consumption of the alcohol, and the resulted white slurry was concentrated by a rotary evaporator. After the dilution of residue with hexane/EtOAc, the mixture was filtered through a pad of alumina (activated, 300 mesh; purchased from Wako Pure Chemical Industries, Ltd) and Celite. The filtrate was concentrated under reduced pressure to give the desired bisphosphinite in 97%.

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