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An investigation of the reactions between azido alcohols and phosphoramidites

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Abstract

The reactions of several β -, γ -, and δ -azido alcohols with dibenzyl and dimethyl *N,N*-diisopropylphosphoramidites were examined. Detailed analysis of the intermediates and products formed from the reactions under different conditions provided useful information to gain insights into their mechanisms involving intramolecular Staudinger reaction, as well as the structure-reactivity relationships of both substrates. The reactions of γ - and δ -azido alcohols with dibenzyl *N,N*-diisopropylphosphoramidite could produce 6- and 7-membered cyclic phosphoramidates, thereby providing a new synthetic method for these biologically important molecules.

Graphical Abstract

Keywords

Staudinger reaction; azido alcohol; phosphoramidite; cyclic phosphoramidate; cyclization

The Staudinger reaction is valuable for creating phosphorous-nitrogen bonds via the reaction between phosphites and organic azides (Scheme 1).¹ This reaction forms first a phosphazide ylide intermediate, which can convert into a phosphazine intermediate by losing a molecule of nitrogen. Next, the resultant phosphazine is transformed into phosphoramidate as the end-product either spontaneously or under mild acidic conditions.

Previously, we observed the undesirable formation of a cyclic phosphoramidate (**1**) in the synthesis of a CD52 GPI anchor when an azido alcohol (**2**) was reacting with a

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Supporting Information

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phosphoramidite.² We hypothesized that the reaction first formed an azido phosphite intermediate **3**, which underwent an intramolecular Staudinger reaction to result in **1** (Scheme 2). According to this mechanism, it was expected that other azido alcohols might behave similarly, thereby forming a novel synthesis of cyclic phosphoramidates.

To the best of our knowledge, the Staudinger reaction has not been used to synthesize cyclic phosphoramidates, which are useful compounds in the design and development of pesticides, cancer chemotherapeutics and enzyme inhibitors.^{3–7} Current synthetic routes to these molecules include the reactions of phosphoryl trichloride with amino alcohols or other methods using relatively harsh reaction conditions.^{3–7} One exception to this is the recent development by the Johnston group of a new method for the synthesis of *C*- and *P*-chiral cyclic phosphoramidates employing Brønsted acid-catalyzed intramolecular phosphoramidic acid addition to alkene.⁸

To investigate the above hypothesis, we prepared several azido alcohols and probed their reactions with phosphoramidites. The reaction of dibenzyl *N,N*-diisopropylphosphoramidite **4** with a δ -azido alcohol **5** in the presence of tetrazole was very fast (finished in about 10 min at room temperature) to produce a less polar product, which remained unchanged in the mixture for hours. However, our attempt to isolate this product by silica gel column chromatography failed. We suspected that it might be the azido phosphite intermediate that was oxidized in air on the column. To examine this assumption, we treated the reaction mixture with *m*-chloroperbenzoic acid (*m*-CPBA) before workup, in an effort to transform the azido phosphite into the corresponding phosphate. Indeed, under revised conditions, azido phosphate **6** was isolated as the major product in a 75% yield (Table 1, entry 1) after silica gel column chromatography. Similarly, the reaction of **4** with γ -azido alcohol **7** or β -azido alcohols **9** and **11** afforded azido phosphates **8**, **10** and **12**, respectively, in good to excellent isolated yields (Table 1, entries 2–4). These results have proved unambiguously that while the reactions between **4** and alcohols are easy and fast to afford azido phosphites that are stable in the reaction mixture at room temperature, under these conditions inter- and intramolecular Staudinger reactions were very slow. Buoyed by our previous discovery of cyclic phosphoramidate formation,² we began to explore different conditions to promote the intramolecular Staudinger reaction of the azido phosphite intermediates formed from the above reactions. We found that in the presence of tetrazole, the reactions of **4** with **5** and **7** at 80 °C gave cyclic phosphoramidates **13** and **14**, respectively, in good to moderate yields (Table 2, entries 1 and 2). The reaction products were conveniently isolated by column chromatography and fully characterized with HR-MS and NMR. To our surprise, however, the reaction between **4** and *cis*- β -azido alcohol **9** under the same conditions resulted in a complex mixture but did not produce a significant amount of the corresponding cyclic phosphoramidate, even though the azido and the hydroxyl groups in **9** were at *cis* positions, which are favorable for intramolecular reactions. Not surprisingly, the reaction between **4** and unfavorable *trans*-azido alcohol **11** did not afford the cyclic phosphoramidate either. The results suggested that the ring size of the reaction intermediate or product might play a critical role in intramolecular Staudinger reactions of azido phosphites.

In view of the potential influence of electronic and steric effects of the phosphite group on its Staudinger reactions,⁹ we studied subsequently the reactions of the same set of azido

alcohols with phosphoramidite **15** bearing methyl instead of benzyl esters. We anticipated that this would facilitate the intramolecular Staudinger reaction of the resultant azido phosphite intermediates. Indeed, even at room temperature the reaction of **15** with **5** produced a modest yield (40%) of the desired cyclic phosphoramidate **16** (Table 3, entry 1). More interestingly, a substantial quantity (10%) of cyclic phosphorazide **17** was also obtained. Clearly, **17** was stable to column chromatography. The reactions of **15** with azido alcohols **7** and **9** were quite complex and the isolated major products were phosphorazides **18** and **19** (Table 3, entries 2, 3), respectively. For azido alcohol **11**, the reaction with **15** was clean but the product was isolable only after oxidation with *m*-CPBA to afford azido phosphate **20** in an excellent yield (91%), suggesting the formation of a stable azido phosphite intermediate. These results revealed that the azido phosphite intermediates formed from the reactions of dimethyl phosphoramidite **15** with azido alcohols could undergo intramolecular Staudinger reactions even at room temperature, except where the cyclization was hindered by unfavorable *trans* configurations in substrate **11**. Evidently, these reaction conditions were much milder than those required for the intramolecular Staudinger reaction to occur with dibenzyl phosphoramidite **4**.

The results shown in Table 2 and Table 3 clearly demonstrated that the reaction yield and stability of the cyclic phosphoramidate products followed an order of: 7-membered ring > 6-membered ring > 5-membered ring. In agreement with this trend, the results in Table 3 also suggested that the reaction yield of phosphorazide intermediates was in a reversed order, namely, **19** > **18** > **17**. For the reaction of **15** with **7** or **9**, no cyclic phosphoramidate product was observed, whilst the latter reaction gave the highest isolated yield of phosphorazide **19**. Both the cyclic phosphoramidate and the cyclic phosphorazide products should have been formed via intramolecular Staudinger reaction (see Scheme 2). However, the observation of mainly cyclic phosphorazide for the reactions of **15** with **7** and **9**, as well as a mixture of cyclic phosphoramidate and phosphorazide for the reaction of **15** with **5**, also indicated that intramolecular Staudinger reactions of the azido phosphite intermediates were not the limiting factor for the transformation into phosphoramidate products. Yet, another interesting finding was that at room temperature **17** could not be converted into **16** on treatment with tetrazole and diisopropanylamine, indicating that **16** obtained from the reaction of **15** with **5** might be formed through a more reactive intermediate rather than through cyclic phosphorazide **17**. Furthermore, heating β -azido phosphites at 80 °C gave complex results that were different from the reactions of β -azido alcohols with phosphites or phosphines.^{10,11}

To explain the above results and observations, we propose that the phosphazide ylide intermediate generated by intramolecular Staudinger reaction of azido phosphite endured two competitive pathways as shown in Scheme 3. One of these pathways involved ring contraction via automatic elimination of a nitrogen molecule to produce phosphazine **21** that could undergo protonation and nucleophilic de-*O*-alkylation to afford cyclic phosphoramidate **1** (Scheme 3A). Another pathway involved direct protonation and nucleophilic dealkylation of the phosphazide ylide intermediate to give cyclic phosphorazide **22**. It seemed that once phosphazide **22** was formed it could not be converted into phosphoramidate under the probed conditions. However, as some of the reactions were very

complex and gave low yields of identified products, we could not completely eliminate the possibility of intermolecular Staudinger reaction of azido phosphites to form oligo-/polymers, which are difficult to purify and characterize.

Moreover, the results indicated that the ring contraction reaction was highly dependent on the reaction condition and the substrate structure. It was favorable at higher temperature and with larger cyclic phosphazide ylides (8-membered ring, producing 6-membered ring product). At 80 °C, cyclic phosphoramidates were obtained as the major products and no phosphazide was isolated in a significant yield from any of the reactions, probably because, even if phosphazides were generated, they would decompose at a high temperature. In addition to the 7- and 6-membered ring products **13** and **14** that were readily formed from the reactions of **4** with **5** and **7** (Table 2), the by-product observed in our synthesis of a CD52 GPI anchor was an 8-membered ring cyclic phosphoramidate, which could be formed at room or lower temperature.² Therefore, it seemed that the 8-membered cyclic phosphoramidate product was even more readily generated from intramolecular Staudinger reaction than the 7-membered cyclic phosphoramidate, such as **13**. Continuing this trend, 5-membered cyclic phosphoramidate products were not observed from the reaction of **9** with either **4** or **15**.

To further verify the conclusion that it would be difficult to form 5-membered cyclic phosphoramidates through intramolecular Staudinger reaction, we prepared two more β -azido alcohols, **23** and **24**, and probed their reactions with **4** and **15** under above-described conditions (Scheme 4). The results were in agreement with our prediction. As shown, the reactions of **23** and **24** with dibenzyl phosphoramidite **4** at room temperature produced the corresponding azido phosphites as major products, which were converted into azido phosphates **25** and **28**, respectively, after *m*-CPBA oxidation; however, at 80 °C, these reactions were complex and no major products could be isolated and identified. For the reactions of **23** and **24** with dimethyl phosphoramidite **15** at room temperature, a significant amount of phosphazides **26** and **29** were isolated. The results were similar to that of the reactions between related 1,2-azido alcohol **9** and phosphoramidites **4** and **15**. In addition, aziridine phosphoramidate **27** was also observed in the reaction of **23** with **15**, and similar products were reported previously.^{12–14}

In summary, the reactions between phosphoramidites and azido alcohols were examined in detail. It was disclosed that the results of these reactions were dependent on the substrate structure and reaction conditions. The capture of azido phosphite intermediates or isolation of cyclic phosphorazide products from the reactions carried out at room temperature enabled us to gain more insights into the mechanisms of these reactions and the structure-reactivity relationships of both substrates. Significantly, it was observed that the reactions of γ - and δ -azido alcohols and their larger homologs with dibenzyl *N,N*-diisopropylphosphoramidite could produce corresponding cyclic phosphoramidates in good yields. These yields may be improved further via optimization of reaction conditions, paving the foundation for a new and facile method to access these important molecules under neutral and mild conditions. This method could be especially useful for synthesizing large cyclic phosphoramidates, such as macrocyclic phosphoramidates.¹⁵

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References and Notes

- (1). Gololobov YG; Zhmurova IN; Kasukhin LF Tetrahedron 1981, 37, 437.
- (2). Xue J; Guo Z J. Am. Chem. Soc 2003, 125, 16334. [PubMed: 14692775]
- (3). Kumar A; Coe PL; Jones AS; Walker RT; Balzarini J; De Clercq E J. Med. Chem 1990, 33, 2368. [PubMed: 2391680]
- (4). Bentrude WG; Khan MR; Saadein MR; Sopchik AE Nucleos. Nucleot 1989, 8, 1359.
- (5). Takaku H; Ito T; Yoshida S; Aoki T; De Clercq E Nucleos. Nucleot 1987, 6, 793.
- (6). Jones AS; McGuigan C; Walker RT J. Chem. Soc., Perkin Trans. 1 1985, 199.
- (7). Jones AS; McGuigan C; Walker RT; Balzarini J; De Clercq E J. Chem. Soc., Perkin Trans. 1 1984, 1471.
- (8). Xue J; Wu J; Guo Z Org. Lett 2004, 6, 1365. [PubMed: 15101743]
- (9). Toda Y; Pink M; Johnston JN J. Am. Chem. Soc 2014, 136, 14734. [PubMed: 25336273]
- (10). Weitzberg M; Aizenshtat Z; Jerushalmy P; Blum J J. Org. Chem 1980, 45, 4252.
- (11). Ittah Y; Shahak I; Tsaroom S; Blum J J. Org. Chem 1978, 43, 4271.
- (12). Danishefsky SJ; Larson E; Springer JP J. Am. Chem. Soc 1985, 107, 1274.
- (13). Larson ER; Danishefsky SJ J. Am. Chem. Soc 1985, 105, 6715.
- (14). Basarab GS; Jordan DB; Gehret TC; Schwartz RS Bioorg. Med. Chem 2002, 19, 4143.
- (15). Or YS; Ma J; Wang G PCT, 2013, WO 2013/173759 A2.
- (16). General experimental procedure for the reactions listed in Table 2: To the solution of an azido alcohol 5 or 7 (0.774 mmol in 8 mL of anhydrous toluene) were added 1.2 equivalents of dibenzyl N,N-diisopropyl phosphoramidite 4 (0.32 mL, 0.929 mmol) and then 1.2 equivalents of tetrazole (1.98 mL 0.47 M solution in acetonitrile, 0.929 mmol). After the solution was heated at 80 °C with stirring for 2 h, it was diluted with dichloromethane, washed with 20 mL of 10% sodium bicarbonate solution and two 20 mL- portions of brine water, dried with Na₂SO₄, and concentrated under vacuum. Silica gel column chromatography of the residue gave the desired product 13 or 14. 3-Benzyloxy-3-oxo-1,4,5-trihydrobenzo[7]-2,4,3-oxazaphosphine (13): a white solid, 60% yield; ¹H NMR (CDCl₃, 300 MHz): δ 7.48–7.12 (m, 9 H), 5.22–5.05 (m, 4 H), 4.27 (ddd, J = 17.2, 10.4 and 8.0 Hz, 1 H), 3.92 (ddd, J = 28.3, 17.2 and 5.6 Hz, 1 H), 3.48–3.36 (m, 1 H). HR-FABMS: calcd for C₁₅H₁₇NO₃P (M + H)⁺ 290.0946, found 290.0931. 2-Benzyloxy-2-oxo-5,5-dimethyl-1,3,2-oxazaphosphinane (14): a white solid, 45% yield; ¹H NMR (CDCl₃, 300 MHz): δ 7.45–7.33 (m, 5 H), 5.04 (d, J = 10.0 Hz, 2 H), 3.98 (dd, J = 2.8 and 14.0 Hz, 1 H), 3.84 (dd, J = 2.2 and 11.2 Hz, ½ H), 3.73 (dd, J = 2.5 and 11.4 Hz, ½ H), 3.26–3.10 (m, 1 H), 3.00 (dd, J = 4.6 and 15.2 Hz, 1 H), 2.84 (ddd, J = 3.0, 7.0 and 12.7 Hz, ½ H), 2.70 (ddd, J = 2.78, 7.5 and 12.5 Hz, ½ H), 1.22 (s, 3 H), 0.79 (s, 3 H). HR-FABMS: calcd for C₁₂H₁₉NO₃P (M + H)⁺ 256.1103, found 256.1105.
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Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Table 1.

Reaction of azido alcohols with (BnO)₂PNiPr₂ **4** at rt

Entry	Azido alcohol	Product	Yield (%)
1	5	6	75
2	7	8	70
3	9 (racemic)	10 (racemic)	70
4	11 (racemic)	12 (racemic)	92

Table 2.Reaction of azido alcohols with (BnO)₂PNiPr₂ **4** at 80 °C

Entry	Azido alcohol	Product	Yield (%)
1	5	13	60
2	7	14	45
3	9	decomposed	-
4	11	decomposed	-

Table 3.Reaction of azido alcohols with (MeO)₂PN*i*Pr₂ **15** at rt

Entry	Azido alcohol	Product	Yield (%)
1	5	16	40
		17	10
2	7	18	21
3	9	(racemic) 19	41
4*	11	(racemic) 20	91

* Reaction conditions: 1.2 equiv tetrazole, CH₂Cl₂, rt, 10 h; then *m*-CPBA (1.2 equiv), rt, 0.5 h.