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# A Fresh Look at the Staudinger Reaction on Azido Esters: Formation of 2*H*-1,2,3-Triazol-4-ols from $\alpha$-Azido Esters Using Trialkyl Phosphines

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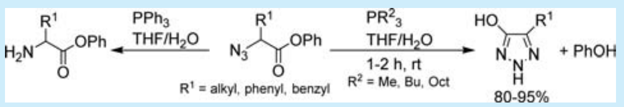
*Supporting Information*

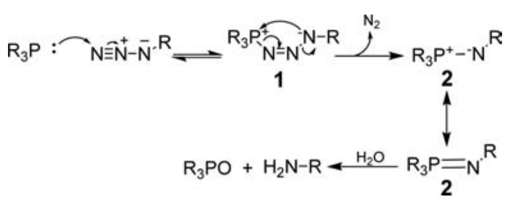
**ABSTRACT:** Phenyl esters of $\alpha$-azido acids react with trialkylphosphines in THF/$H_2O$ to give 5-substituted 2*H*-1,2,3-triazol-4-ols in good to excellent yields. In contrast, their reaction with $PPh_3$ in THF/$H_2O$ give the amino esters as the major product and no triazoles. Reaction between an $\alpha$-azido phenyl ester and $P(OEt)_3$ provided the corresponding phosphoramidate in excellent yield, but no triazole was formed.




Since its discovery almost 100 years ago,[1] the Staudinger reaction has proven to be one of the most versatile reactions in organic chemistry. Its importance in organic synthesis cannot be underestimated, as its many variants allows for the preparation of a wide variety of compounds.[2] It is also a key reaction in chemical biology due to its application in highly chemoselective ligations for the preparation of bioconjugates.[3]

In its original form, as reported by Staudinger and Meyer, the Staudinger reaction involves the reaction of a phosphine with an azide to form an iminophosphorane (**2** in Scheme 1).[1] The mechanism has been studied in detail, and it has been shown to proceed via initial formation of a phosphazide (**1** in Scheme 1) which, upon loss of $N_2$, produces the iminophosphorane.[2,4] The iminophosphorane can by hydrolyzed to give an amine and a phosphine oxide. Later, Staudinger reported that the nitrogen atom of the iminophosphorane is highly nucleophilic and can react with electrophiles, such as aldehydes and ketones, to give imines (aza-Wittig reaction).[5] Since this report, it has been shown that the iminophosphorane can react with a wide variety of electrophiles, including esters and amides, especially if the reaction is intramolecular, to give a wide variety of products.[2,3]

**Scheme 1. Mechanism of the Staudinger Reaction**

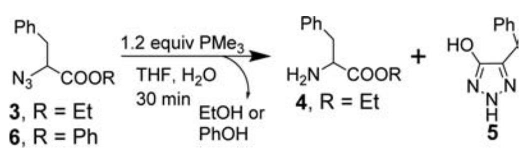



Although there are numerous examples in the literature demonstrating the reaction of an iminophosphorane with an electrophile, there are only a few reports describing the reaction of phosphazides with electrophiles even though, under appropriate conditions, and with the appropriate phosphines and azides, stable phosphazides can be isolated and characterized.[4,6]

Here we report a previously unnoticed variant of the Staudinger reaction on $\alpha$-azido esters in which phosphazides, generated from the reaction of trialkyl phosphines with phenyl esters of $\alpha$-azido acids in THF/$H_2O$, undergo an intramolecular cyclization to provide 2*H*-1,2,3-triazol-4-ols in good to excellent yields. Interestingly, when the reactions were conducted using $PPh_3$, triazoles were not obtained. Instead, the dominant products were the reduced amines resulting from the classic Staudinger pathway. Similarly, when the reaction was conducted using $P(OEt)_3$, a phosphoramidate was formed in high yield but no triazole was formed.

Our interest in the Staudinger reaction stems from our use of $\alpha$-azido acids as building blocks for solid phase peptide synthesis.[7−9] As part of these studies, we wished to determine the rate by which $PMe_3$ reduces the azido group in resin-bound peptides containing an *N*-terminal $\alpha$-azido residue to give the corresponding peptides with the desired amino terminus, compared to the analogous reaction in solution. We began these studies by studying the rate by which the simple model amino ester, compound **3** (Scheme 2), undergoes reaction with $PMe_3$ in solution. Hence, compound **3** was subjected to 1.2 equiv of $PMe_3$ and the reaction was followed by HPLC and $^1H$ NMR (Scheme 2). Surprisingly, the NMR spectrum revealed that, in addition to the expected $\alpha$-amino ester **4**, an almost equimolar amount of ethanol was formed within 30 min along with another unidentified compound. Subjecting compound **3**

**Scheme 2. Products Formed upon Treatment of Esters 3 and 6 with $PMe_3$/THF/$H_2O$**

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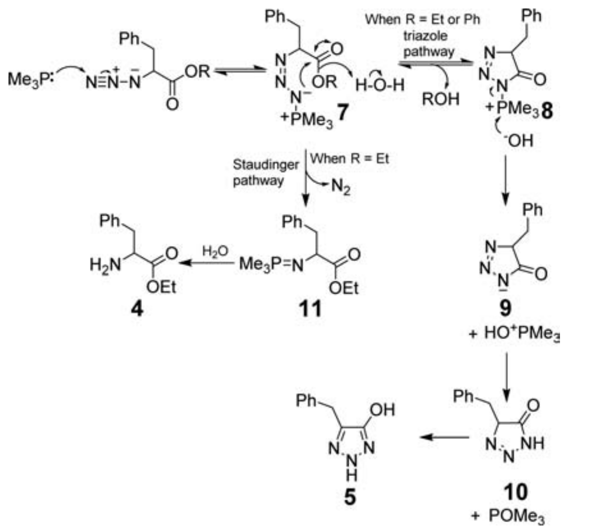
to just THF/$H_2O$ for 24 h did not result in any reaction of any kind indicating that the formation of ethanol was not due to hydrolysis of the ester bond. HPLC analysis of the reaction mixture after 30 min revealed two major peaks one of which was due to the expected product **4**. Isolation of the other product followed by $^1H$, $^{13}C$ NMR and HRMS analysis revealed it to be the 2*H*-1,2,3-triazol-4-ol **5**,[10] which was obtained in a 47% yield. This structural assignment was confirmed by X-ray crystallography (see the Supporting Information). Subjecting phenyl ester **6** to the same conditions gave triazole **5** as the sole product as determined by HPLC.

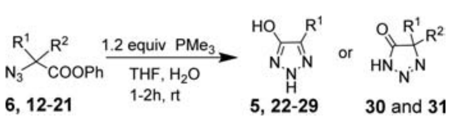
The formation of compound **5** is most likely due to cyclization of phosphazide **7**, to give intermediate **8** (triazole pathway, Scheme 3), before **7** can lose nitrogen and give the iminophosphorane **11** (Staudinger pathway). Hydrolysis of **8** gives compound **9** which upon protonation gives triazolone **10**. Tautomerization of **10** yields the aromatic triazole **5**. The fact that phenyl ester **6** gave only compound **5** indicates that loss of the leaving group is rate-determining.

**Scheme 3. Proposed Mechanism for Formation of Triazole 5**



A variety of other $\alpha$-azido phenyl esters were subject to $PMe_3$/THF/$H_2O$ (Table 1). In all cases, the esters reacted smoothly, usually within 1−2 h,[11] to give the corresponding triazoles in good to excellent isolated yields. HPLC analysis of the crude reaction mixtures revealed that the triazoles were essentially the sole product. Ester **19** gave triazole **29**, as determined by HPLC and MS; however, for unknown reasons, this compound was unstable and we were unable to isolate it. Triazalones **30** and **31** were obtained when using $\alpha,\alpha$-disubstituted azido esters **20** and **21**. These triazolones proved to be very thermosensitive and could not be subjected to temperatures greater than 50 °C with rapid loss of $N_2$ and polymerization.[12]

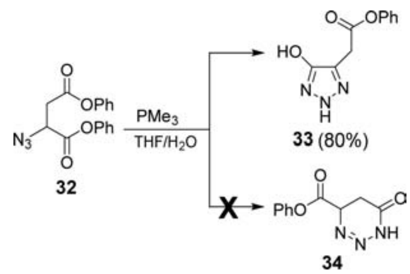
**Table 1. Formation of Triazole 5 and 22−31 from Azido Esters 6 and 12−21**



| substrate | $R^1$ | $R^2$ | product (% yield) |
|---|---|---|---|
| **6** | $CH_2Ph$ | H | **5** (89) |
| **12** | Ph | H | **22** (83) |
| **13** | $CH_2$-indole(Boc) | H | **23** (87) |
| **14** | $CH_2Ph$-*p*OtBu | H | **24** (95) |
| **15** | $CH_2CH_2COOtBu$ | H | **25** (89) |
| **16** | $(CH_2)_4NHBoc$ | H | **26** (84) |
| **17** | $CH_3$ | H | **27** (85) |
| **18** | $CH_2CH(CH_3)_2$ | H | **28** (88) |
| **19** | $CH_2OBn$ | H | **29** (0) |
| **20** | Ph | Ph | **30** (85) |
| **21** | $-(CH_2)_4-$ | | **31** (80) |

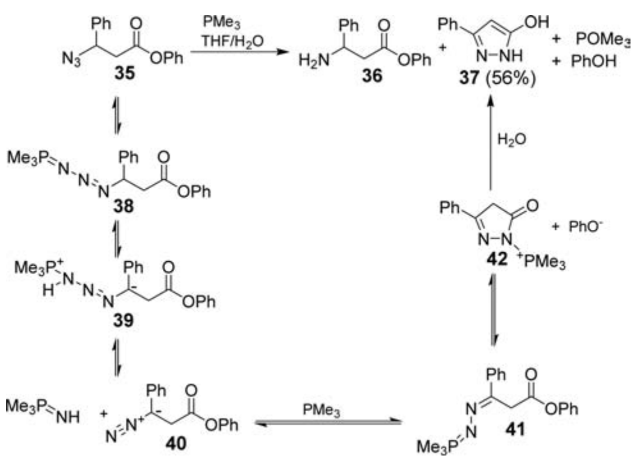
Subjecting ester **32** (Scheme 4), which could potentially form either a five-membered ring triazole (compound **33**) or the six-membered ring triazolone (compound **34**), to $PMe_3$/THF/$H_2O$ gave the five-membered ring triazole **33** exclusively, indicating that formation of five-membered triazole is favored over the formation of six-membered ring triazolone.

**Scheme 4. Formation of Triazole 33 from Ester 32**



When ester **35** was subjected to $PMe_3$ in THF/$H_2O$, in addition to amine **36**, 3-phenyl-1*H*-pyrazol-5-ol (**37**) was obtained in a 56% yield (Scheme 5). To account for the formation of **37** we propose that phosphazide **38** undergoes an intramolecular proton transfer to give betaine **39** which then undergoes elimination of trimethylphosphinimine to provide the diazo compound **40**. This reacts with $PMe_3$ to give phosphinazine **41** which cyclizes to produce compound **42** which loses $PMe_3$ to give compund **37**. The fact that the reaction required about 1.6 equiv of $PMe_3$ before all of **35** was consumed is consistent with this mechanism; however, further studies will be required before this mechanism can be validated.[13]

**Scheme 5. Proposed Mechanism for the Formation of 37 from 35**





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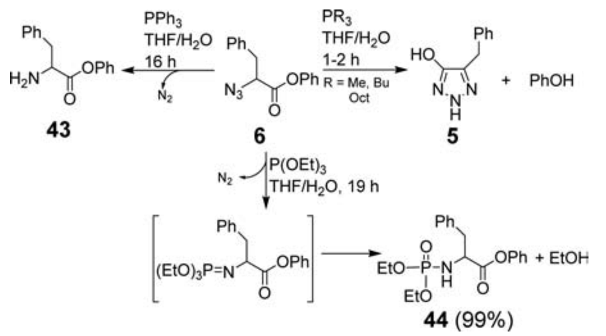
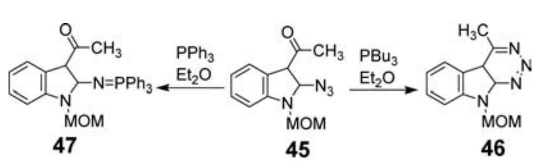
There are numerous reports in the literature describing the reduction of azido groups in $\alpha$-azido esters to give $\alpha$-amino esters using phosphines. The majority of these reports utilized $PPh_3$, though there are several instances where alkyl phosphines were used including $PMe_3$.[14−17] The formation of triazoles was not mentioned in any of these reports. Therefore, the reaction of ester **6** with other phosphines, as well with $P(OEt)_3$, was examined (Scheme 6). HPLC and MS analysis of the crude reaction mixtures from the reaction of $PBu_3$ and $POct_3$ with ester **6** in THF/$H_2O$ indicated that these phosphines also gave compound **5** as the major product with only trace amounts of amine **43**. However, triazole **5** was not formed when ester **6** was subjected to $PPh_3$ in THF/$H_2O$ for 16 h. Instead, amine **43** was the major product.[18] HPLC and MS analysis of the crude reaction mixtures from the reaction of the azido esters listed in Table 1 with $PPh_3$/THF/$H_2O$ for 16 h revealed that these esters also gave only products resulting from the Staudinger pathway. Moreoever, we did not detect compound **37** (by HPLC) when ester **35** was treated with $PPh_3$: only products resulting for the classical Staudinger pathway were detected. The reason for the difference in product distribution between $PPh_3$ and the other phosphines examined here is not entirely clear. However, it is possible that the more bulkyl phenyl groups in $PPh_3$ prevent the cyclization of the intermediate phosphazide, though electronic effects that may favor or disfavor the loss of nitrogen from the phosphazide probably also play a role. That electronic effects can also play a role in determining which pathway is favored is supported by the observation that $P(OEt)_3$ gave only phosphoramidate **44** in excellent yield. This compound was formed as a result of loss of nitrogen from the phosphazide (Staudinger pathway) to give the corresponding iminophosphorane followed by *N*-protonation and loss of EtOH (Scheme 6).[19]

**Scheme 6. Reaction of Compound 6 with Various Phosphines and $P(OEt)_3$**



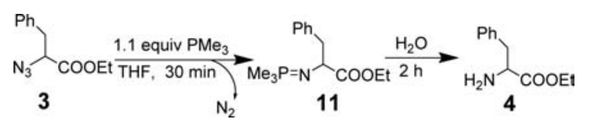
Although we are unaware of any reports describing the synthesis of triazoles using the route described here, it is worth noting that Molina and co-workers reported the synthesis of compound **46** in 78% yield by treating **45** with $PBu_3$ in ether (Scheme 7). Treating **45** with $PPh_3$ yielded iminophosphorane **47** in 90% yield.[6h]

**Scheme 7. Molina's Synthesis of Compounds 46 and 47**



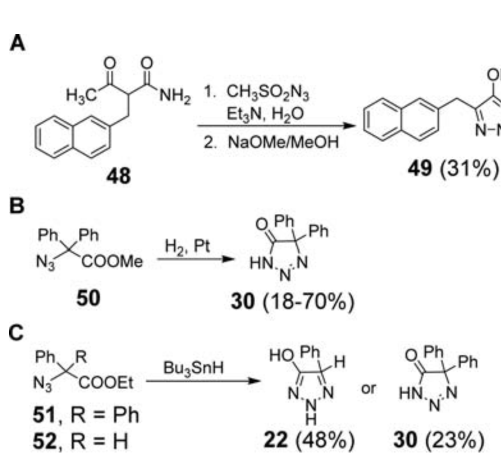
As mentioned earlier, there have been reports in the literature describing the reduction of azido groups in $\alpha$-azido alkyl esters using $PMe_3$[14−16] and $PBu_3$[17] in THF/$H_2O$ though none of these reports mentioned triazole formation as a competing reaction. In all of these cases, the amine product was not isolated but instead the crude or in situ generated amine was reacted with an electrophile, such as an activated ester to form an amide bond[14,16,17] or with BOC-ON.[15] It is worth noting that the yield of the amide or Boc-protected product was very poor to low (11−47%). It is possible that competing triazole formation may have contributed to these low yields. Loke et al. reported the reduction of an $\alpha$-azido benzyl ester to the corresponding amino ester in apparently quantitative yield (the amine was not purified) by reacting the azido ester with 1.1 equiv of $PMe_3$ in THF in the absence of water for 3 h followed by the addition of water.[20] Reaction of ester **3** with 1.1 equiv of $PMe_3$ in the absence of water gave iminophosphorane **11** in almost quantitative yield after 30 min, as determined by $^{31}P$ NMR of the crude reaction mixture ($\delta$ for **11** = 11.2 ppm), indicating the presence of water is required for cyclization to the triazole and loss of EtOH, possibly by acting as a general acid (Scheme 8). Addition of water and stirring for 2 h gave ester **4** as almost the sole product as determined by HPLC. Therefore, triazole formation can be avoided by performing the reaction in THF/$H_2O$ with $PPh_3$ or stepwise with $PMe_3$ and probably other alkylphosphines.[21]

**Scheme 8. Stepwise Approach to the Synthesis of Amine 4 from Azido Ester 3 Using $PMe_3$**



Very few reports have appeared in the literature describing the synthesis of triazoles of the type described here. Kees et al. reported the synthesis of triazole **49** in 31% yield by diazotization of $\beta$-ketoamide **48** with methane sulfonyl azide followed by cyclization of the resulting $\alpha$-diazoamide in NaOMe/MeOH (Scheme 9A).[22] Hohenlohe-Oehringen reported the synthesis of compound **30** in 70% yield via hydrogenolysis of $\alpha$-azido ester **50** (Scheme 9B).[23] However, Ikeda et al. later reported a yield of only 18%.[12] Finally, Benati et al. claimed to have prepared compounds **22** and **30** in 48%

**Scheme 9. Literature Routes to 2*H*-1,2,3-Triazol-4-ols**





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and 23% yield respectively by subjecting $\alpha$-azido esters **51** and **52** to $Bu_3SnH$ (Scheme 9C).[24] However, no characterization data of any kind for these compounds were provided. They suggested that the reaction proceeds via a free radical mechanism. The route to 2*H*-1,2,3-triazol-4-ols reported here represents a significant improvement on these literature procedures and now makes this class of compounds readily accessible.

In summary, we have reported a variant of the Staudinger reaction that appears to have escaped notice, in spite of the vast body of work that has been done on the Staudinger reaction over the past century. This Staudinger variant provides 2*H*-1,2,3-triazol-4-ols simply by reacting readily prepared $\alpha$-azido phenyl esters with triakyl phosphines. The reaction proceeds under very mild conditions and is complete usually within 1−2 h at rt. Thus, these types of triazoles, which were once challenging to produce in good yield, are now readily accessible. Further studies on the mechanism of this reaction and its implications on the synthesis of depsipeptides are in progress and will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02204.

Experimental procedures, characterization data and NMR spectra for esters **6**, **12−21**, **32**, and **35**, triazoles **5**, **22−29**, and **33**, triazolones **30** and **31**, pyrazole **37**, and phosphoramidate **44** (PDF)

X-ray crystallographic data for compound **5** (CIF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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(10) Tautomers other than the one shown are possible.

(11) Azido esters **20** and **21** required 10 h.

(12) Ikeda et al. reported that triazole **30** undergoes thermal polymerizations yielding poly($\alpha$,$\alpha$-diphenylglycine) at 50 °C higher. They also reported that it decomposes violently at temperatures above 75 °C; see: Ikeda, K.; Smets, G.; L'Abbe, G. *J. Polym. Sci., Polym. Chem. Ed.* **1973**, *11*, 1167−1176.

(13) To account for one of the products that was formed during their studies on the reaction of $PPh_3$ with $\alpha$-azidoacetonitriles, Molina and co-workers suggested a mechansim by which a phosphazide undergoes elimination of triphenylphosphinimine to provide a diazo compound which reacts with $PPh_3$ to give a phosphinazine. See ref 6e. See also ref 6i for examples of phosphine-mediated conversion of azides into diazo compounds.

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