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Alternate pathway for the click reaction of 2-(2-azidophenyl)-4,5-diaryloxazoles

Pravin C. Patil, Frederick A. Luzzio

^aDepartment of Chemistry, University of Louisville, 2320 South Brook Street, Louisville, Kentucky 40292 USA

Abstract

The CuSO₄/ascorbate-mediated ‘click’ reaction of 2-(2-azidophenyl)-4,5-diaryloxazoles and arylacetylenes proceeded through an alternate pathway whereby reduction of the azide predominated over formation of the 1,2,3-triazole-forming cycloaddition. The unimolecular product, 2-(2-aminophenyl)-4,5-diphenyloxazole, was isolated which appears to be a formal reduction of the arylazide to the corresponding arylamine. A series of oxazoles which possessed various substituents (F, Cl, Br, OCH₃) on the 4,5-diaryl rings and having the 2-azido group on the 2-oxazolyphenyl position were submitted to the same ‘click’ conditions and gave the corresponding arylamine products (73–99%). The reaction appears to be specific toward the *ortho*-azido substitution of the polycyclic system, as the corresponding azidomethyl-substituted phenyl oxazoles do not give the ‘reduction’ products but gave the expected click products with the acetylenic co-reactants.

Graphical Abstract

Keywords

amines; azides; click chemistry; nitrenes; reduction

1. Introduction

The Huisgen dipolar azide/alkyne cycloaddition otherwise known as the ‘click’ reaction allows for the connection of two molecular fragments through the concomitant formation of

Supporting Information:

General synthetic procedures for compounds **2,12–19, 30–36** and the ¹H, ¹³C, FTIR and HRMS data for compounds **1–9, 12–19, 22, 30–36** can be found in the online version at <http://dxdoi.org/>

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a 1,2,3-triazole linker.¹ The reaction has found many applications in synthetic and biological chemistry and materials science and only requires azide and acetylene co-reactants. The click reaction may be run under mild conditions so that the connection of peptides, carbohydrates, nucleosides, sensitive heterocycles and polycyclics may be facilitated. Many click reactions utilize the fairly standard Cu⁺⁺/ascorbate reaction system which requires compatibility with any functionality located on one or both the reacting partners. Our ongoing research in the area of click chemistry involves the construction of small-molecule peptido-mimetics which inhibit the adherence of *Porphyromonas gingivalis* to *Streptococcus gordonii* as a preventive for multispecies oral biofilm formation. Several hundred inhibitory candidates have been prepared and the general structure of a typical peptidomimetic biofilm inhibitor along with its retro-synthesis toward the click partners is shown in Scheme 1.² Our basic structural motif of the azidophenylloxazoles employed the azide group at the 3- and 4-position and gave the corresponding triazoles in good to excellent yields. However, the click reaction (CuSO₄/sodium ascorbate) of azide **1** with phenylacetylene did not give the expected 1,2,3-triazole but rather the corresponding amine **2** in 89% isolated yield (Scheme 1). Under the reaction conditions, the bimolecular reaction was completely sidestepped and resulted in what appeared to be a formal reduction of the azide to the corresponding amine. After conducting numerous click reactions with triaryl azidoxazole reactants of similar structural composition, albeit with the azide group in different positions (See Retrosynthesis, Scheme 1), this type of azide 'reduction' or otherwise side reaction was unprecedented in our work. Although the transformations of aryl or alkyl azides to the corresponding amines generally entail catalytic reduction with hydrogen, metal hydride treatment or the Staudinger reaction,³ the reaction detailed herein could qualify as a useful alternative in specific cases where selectivity is warranted. The formation of the amine **2** was confirmed by conversion to the corresponding acetamide derivative **3** (acetic anhydride/pyridine). Furthermore, a control reaction of **1** with the exact copper-ascorbate reaction system but without the acetylene co-reactant again gave exclusively the amine **2** (89%).

Results and Discussion

To establish the scope of the reaction, we then examined a set of triarylloxazole substrates **4–11** in which the 4,5-aryl groups were substituted with halogens or methoxy groups and had the azido group situated in the ortho-position on the 2-aryl group similar to initial substrate **1** (Table 1). The eight substrates were submitted to the copper-ascorbate system and gave the corresponding amino-substituted triarylloxazoles **12–19** in isolated yields of 73–99% (Table 1). Liu reported a similar anomalous reaction whereby azido compound **20** gave the corresponding amine **21** rather than the desired click cycloaddition (Scheme 3).⁴ The occurrence of an intermediate nitrene (both singlet and triplet forms) was proposed as well as its subsequent reduction under the click conditions. Liu's extensive studies disclosing the nitrene intermediates included both trapping and ESR experiments. Interestingly, similar to our substrates **1** and **4–11**, the Liu benzoxadiazole substrate **20** does have the azide group positioned on the ring ortho to the fused heterocycle bearing nitrogen. So to probe any proximity effects that the ortho-positioned heterocycle may have on the azide, we synthesized the benzylic azide **22** from 2-(azidomethyl)benzoic acid (See Supporting Information and submitted it to the click conditions (Table 2). When reacted with a series of

arylalkynes **23–29** under click conditions, benzylic azide **22** gave exclusively the bimolecular click products **30–36** and no ‘reduction’ to the corresponding benzylic amine: (Table 2). Consistent with the copper/ascorbate mechanism and NMR spectra of the products, the click reactions gave the 1,2,3- triazoles of 1,4-substitution.⁵ In essence, placing the methylene ‘spacer’ between the azide and the aryl ring in substrate **22** promoted its reaction as a normal click component. From previous work, complement reactions whereby the 2-(3-azidophenyl)-4,5-diaryloxazoles and the 2-(4-azidophenyl)-4,5-diaryloxazoles were evaluated as click reactants, the products were exclusively those of the bimolecular ‘click’ pathway as the azide group was positioned *meta* and *para* to the oxazole ring.^{2a} The control reaction using no acetylene ruled out any copper-acetylide species, invoked in the actual click mechanism, as the reducing agent, electron-transfer agent or coordinating species to the azide.⁵ In mechanistic terms, the enhanced reactivity of the azide group toward reduction under click conditions may be due to its proximity to the 2-(or otherwise *ortho*) oxazolyl group.⁶ Addition of ascorbate to the reaction mixture containing aqueous Cu (II) and the azide substrate results in immediate vigorous loss of nitrogen accompanied by darkening of the homogenous mixture. Upon reduction of copper (II) by ascorbate, coordination of the resultant copper (I) to both the proximal azide nitrogen and the oxazolyl nitrogen is followed by loss of nitrogen.⁷ The resultant nitrene then reacts with hydrogen atoms, as proposed in Liu’s mechanism, to give the product amine. Again, one may consider the structure of Liu’s substrate **20** whereby the benzoxadiazole has an *ortho* nitrogen for complexation and reduction of the azide. Trapping experiments were also conducted whereby 1-hexene or cyclohexene were added to the reaction mixtures, again in the absence of any acetylene co-reactant, but under the aqueous THF conditions. However, no aziridine products were formed under the reaction conditions with the amine being the predominant product.

In summary, under the conditions of the click reaction, and in the absence of the acetylenic co-reactant, reduction of an azide to an amine through a possible nitrene intermediate was observed. Several azido-phenyloxazoles of varying substitution were submitted to the Cu(II) ascorbate system in order to probe the structural demands of the reaction. Apparently, the 4,5-diaryloxazole *ortho* to the azide component is the common modality for reduction of the azides to the corresponding amines, while in contrast, the azidomethyl compound **22** gave the expected click products in high yield.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights:

1. Structurally specific arylazides may be reduced to amines.
2. The reduction is independent of any acetylenic reacting components.
3. The reaction may be an alternative to standard types of azide reductions.
4. The pathway of the Cu-mediated reduction may involve nitrene intermediates.

Scheme 1.

Retrosynthesis of click biofilm inhibitors using the 2-(4-azidophenyl) and 2-(3-azidophenyl)-4,5-diaryloxazoles and arylacetylenic click partners.

^aReagents/Conditions: CuSO₄·5H₂O/sodium ascorbate/THF/H₂O

Scheme 2.

Reaction of 2-(2-azidophenyl)-4,5-diphenyloxazole **1** under click conditions to give 2-(2-aminophenyl)-4,5-diphenyloxazole **2**.

^aReagents/Conditions: CuSO₄·5H₂O/sodium ascorbate/THF/H₂O

^aReagents/conditions: "Cu"/DMF/t-BuOH/H₂O

Scheme 3.

Unexpected reduction of nitrobenzoxadiazole **20** to amine **21**.

^aReagents/conditions: "Cu"/DMF/t-BuOH/H₂O

Table 1.

Reduction of selected 2-(2-azidophenyl)-4,5-disubstituted Oxazoles **4–11** to the corresponding amines under ‘click’ conditions to the corresponding 2-(aminophenyl)-4,5-disubstituted oxazoles **12–19**.

Substrate	Product (Yield%)
4 , R ¹ =R ² =4-FC ₆ H ₄	12 (90%)
5 , R ¹ =R ² =4-Cl C ₆ H ₄	13 (98%)
6 , R ¹ =R ² =4-Br C ₆ H ₄	14 (84%)
7 , R ¹ =R ² =3-Br C ₆ H ₄	15 (89%)
8 , R ¹ =R ² =4-OCH ₃ C ₆ H ₄	16 (86%)
9 , R ¹ =Ph, R ² =CH ₃	17 (73%)
10 , R ¹ =Ph, R ² =C ₃ H ₇ - <i>n</i>	18 (90%)
11 , R ¹ =Ph, R ² =C ₇ H ₁₅ - <i>n</i>	19 (99%)

^a Reagents/conditions: CuSO₄·5H₂O/sodium ascorbate/THF/H₂O/30–60 min.

Table 2.

Reaction of 2-(2-azidomethyl)phenyl-4,5-diphenyloxazole **22** with selected arylacetylenes **23–29** to give click products **30–36**.

Arylacetylene [R]	Product (Yield%)
23	30 (62)
24	31 (36)
25	32 (69)
26	33 (96)
27	34 (88)
28	35 (82)
29	36 (87)

Reagents conditions: (a) CuSO₄·5H₂O (0.1 equiv); (b) Na ascorbate (0.5 equiv); (c) THF-H₂O, rt, 2–16h.