Copper-Mediated Conversion of Alkynes into Nitriles via Iodotriazoles

Ryosuke Kori, Keigo Murakami, Yoshitake Nishiyama, Tatsuya Toma, and Satoshi Yokoshima*

Graduate School of Pharmaceutical Sciences, Nagoya University; Furo-cho, Chikusa-ku, Nagoya 464–8601, Japan.
Received September 30, 2020; accepted December 2, 2020

We disclose our studies on a copper-mediated reaction of alkynes with trimethylsilyl azide to afford nitriles, and proposed a reaction mechanism, which involves an iodoalkyne and an iodotriazole as intermediates.

Key words  alkyn; azide; nitrile; copper; cycloaddition

Introduction

During our synthetic studies on tetrodotoxin, we discovered a novel reaction that involved the transformation of an alkyne into a nitrile.1) Heating alkyne 1 with copper(I) iodide (5 equivalent (equiv)) and trimethylsilyl azide (10 equiv) in N,N-dimethylformamide (DMF) and methanol at 100 °C afforded nitrile 2, albeit in 34% yield. Although some reactions that convert alkynes into nitriles have been reported to date,2–7) the conditions we discovered were novel. We have investigated the novel reaction, and herein we propose its reaction mechanism based on key intermediates, which were observed in the reaction.

Results and Discussion

We first conducted optimization studies of the reaction conditions by using 4-tert-butylphenylacetylene (3a) as a substrate. Under the original conditions shown in Chart 1, alkyne 3a was converted into nitrile 4a in 34% yield (Table 1, entry 1). Replacement of methanol with water afforded 4a in a similar yield of 33% (entry 2).8) Conducting the reaction under an argon atmosphere with degassing afforded only a trace amount of the nitrile, while conducting the reaction under oxygen atmosphere gave the nitrile in 29% yield (entries 3 and 4). Further optimization by changing the solvent, concentration, temperature, type of copper salts, azide source, amount of each reagent, or the ratio of the reagents, however, did not improve the yield, resulting in production of the corresponding nitrile in comparable or, in most cases, lower yields.9) For further investigations, we selected the conditions shown in entry 5 as standard conditions. Under these conditions, a solution of an alkyne (1 equiv), copper(I) iodide (CuI, 2.0 equiv), and trimethylsilyl azide (TMSN3, 5.0 equiv) in DMF–H2O (9 : 1, 0.02 M) was heated at 100 °C under air atmosphere.10)

To obtain a clue for improving the yield, we attempted to elucidate the reaction mechanism. A plausible intermediate of this reaction was triazole 5, which would be formed in the reaction mixture via cycloaddition of the alkyne with the azide (Chart 2). Triazole 5 was prepared in 86% yield by heating alkyne 3a with 1.5 equiv of trimethylsilyl azide in the presence of 5 mol% of copper(I) iodide in a mixture of DMF and methanol at 100 °C.11) Subjecting triazole 5 to the standard conditions, however, did not produce the nitrile: we observed only the decomposition of the triazole. Jiao and colleagues reported a silver-catalyzed transformation of alkynes into nitrile that proceeded through an alkenyl azide intermediate.12)

Table 1. Optimization of the Reaction Conditions

| Entry | Cosolvent | CuI (equiv) | TMSN3 (equiv) | Yield of 4a (%) |
|-------|-----------|------------|--------------|----------------|
| 1     | MeOH      | 5          | 10           | 34             |
| 2     | H2O       | 5          | 10           | 33             |
| 3a    | MeOH      | 5          | 10           | —              |
| 4a    | MeOH      | 5          | 10           | 29             |
| 5     | H2O       | 5          | 10           | 41 (28)        |

(a) Determined by 1H-NMR using 1,1,2,2-tetrachloroethane as an internal standard.
b) The reaction was carried out under argon atmosphere with degassing. c) Only a small amount of the product was detected. d) The reaction was carried out under oxygen atmosphere. e) Isolated yield in parentheses.

* To whom correspondence should be addressed. e-mail: yokosima@ps.nagoya-u.ac.jp

© 2021 The Pharmaceutical Society of Japan
We attempted reacting alkenyl azide 6 under our standard conditions, however, this condition did not yield the desired nitrile.\(^{12}\) With intermediates 5 and 6 ruled out, other potential intermediate were evaluated. During the optimization studies, an interesting product, iodotriazole 7, was obtained, when the reaction was conducted at 60 °C. To our delight, subjecting iodotriazole 7 to the standard conditions afforded the requisite nitrile in 37% yield \(^{13}\) (Chart 3). Iodotriazoles can be formed by a reaction of iodoalkynes with azides in the presence of copper salts.\(^{14,15}\) Iodoalkyne 8, prepared by treatment of alkyne 3a with N-iodosuccinimide (NIS) and silver nitrate,\(^{16}\) was subjected to the standard conditions to give nitrile 4a in 28% yield. These results, together with the fact that nitrile cannot be produced from triazole 5, suggested that the reaction proceeds via the iodoalkyne and the iodotriazole as intermediates.

A proposed reaction mechanism is shown in Chart 4. Cu\(^+\) is oxidized with oxygen to generate Cu\(^{2+}\), which reacts with iodide anions to form CuI and I\(_2\).\(^{17-19}\) Iodination of alkyne A produces iodoalkyne B, which undergoes cycloaddition with hydrazoic acid derived from hydrolysis of TMSN\(_3\) to afford iodotriazole C.\(^{10}\) It is noteworthy that Zhu and colleagues reported preferential production of an iodotriazole in a Cu-catalyzed reaction of an alkyne with an azide in the presence of an iodinating agent via the formation of an iodoalkyne.\(^{19}\) Although the mechanism of transformation of the iodotriazole into the nitrile is unclear, based on literature reports of Cu(I)-mediated azidation of aryl iodides\(^{20-22}\) and thermal decomposition of N-aryl-azidotriazole 9 into 10,\(^{23,24}\) we propose a mechanism involving conversion of iodotriazole C into azidotriazole D, followed by sequential elimination of two molecules of nitrogen and one molecule of hydrogen cyanide to produce nitrile G.

Although product yields have remained low, the standard conditions and the original conditions (Table 1, entry 1) were applied to several alkynes (Chart 5). Phenylacetylene derivatives with a bromide or an internal alkyne could be converted into the corresponding nitriles 4b or 4c. Aliphatic nitrile 4d bearing an ester moiety and 4e were also prepared. An alkyne substrate bearing an alkoxy group at the propargylic position was converted into the corresponding nitrile 4f.

**Conclusion**

In conclusion, we have investigated a novel copper-mediated reaction of alkynes with trimethylsilyl azide to produce nitriles. We proposed a reaction mechanism that includes an iodoalkyne and an iodotriazole as key intermediates.

**Acknowledgments** We would like to thank Dr. Kin-ichi Oyama (Chemical Instrumentation Faculty, Research Center for Materials Sciences, Nagoya University) for elemental analysis. This work was financially supported by JSPS KAKENHI (Grant Numbers JP17H01523) and by the Platform Project for Supporting Drug Discovery and Life Science Research (Basis for Supporting Innovative Drug Discovery and Life Science Research; BINDS) from the Japan Agency for Medical Research and Development (AMED) under Grant Number JP19am0101099.

**Conflict of Interest** The authors declare no conflict of interest.

**Supplementary Materials** The online version of this ar-
References and Notes

1) Murakami K., Toma T., Fukuyama T., Yokoshima S., Angew. Chem. Int. Ed., 59, 6253–6257 (2020).
2) Shen T., Wang T., Qin C., Jiao N., Angew. Chem. Int. Ed., 52, 6677–6680 (2013).
3) Okamoto N., Ishikura M., Yanada R., Org. Lett., 15, 2571–2573 (2013).
4) Dutta U., Lupton D. W., Maiti D., Org. Lett., 18, 860–863 (2016).
5) Lin Y., Song Q., Eur. J. Org. Chem., 2016, 3056–3059 (2016).
6) Osawa A., Mera A., Namba K., Tanino K., Synlett, 24, 207–210 (2013).
7) Huang X., Jiao N., Org. Biomol. Chem., 12, 4324–4328 (2014).
8) Methanol or water was required as a cosolvent to generate hydrazoic acid in situ via a reaction with trimethylsilyl azide. See also ref 11.
9) For details, see Supplementary Materials.
10) A polar compound was detected in the aqueous layer after the partition, and it was isolated via acidification of the aqueous layer with hydrochloric acid followed by extraction with ethyl acetate. Although the precise structure could not be determined, the polar compound seems to have a highly electron-withdrawing group at the para position of the tert-butyl group on the benzene ring. 

$$^{1}$$H-NMR (CDCl$_3$) $\delta$8.54 (brs, 2H), 7.54 (brs, 2H), 1.34 (s, 9H);
$$^{13}$$C-NMR (CDCl$_3$) $\delta$159.4, 131.7, 131.2, 125.8, 35.3, 30.8.

11) Jin T., Kamijo S., Yamamoto Y., Eur. J. Org. Chem., 2004, 3789–3791 (2004).
12) Even in the presence of a terminal alkyne (1-decyne, 1 equiv), triazole 5 or alkenyl azide 6 could not be converted into nitrile 4a under the standard conditions.
13) Huang Q., Zheng M., Yang S., Kuang C., Yu C., Yang Q., Eur. J. Med. Chem., 46, 5680–5687 (2011).
14) Hein J. E., Tripp J. C., Krasnova L. B., Sharpless K. B., Fokin V. V., Angew. Chem. Int. Ed., 48, 8018–8021 (2009).
15) García-Alvarez J., Diez J., Gimeno J., Green Chem., 12, 2127–2130 (2010).
16) Juríček M., Stout K., Kouwer P. H. J., Rowan A. E., Org. Lett., 13, 3494–3497 (2011).
17) Kaufman G. B., Pinnell R. P., Inorg. Synth., 6, 3–6 (1960).
18) Brotherton W. S., Clark R. J., Zhu L., J. Org. Chem., 77, 6443–6455 (2012).
19) Barsoum D. N., Okashah N., Zhang X., Zhu L., J. Org. Chem., 80, 9542–9551 (2015).
20) Suzuki H., Miyoshi K., Shinoda M., Bull. Chem. Soc. Jpn., 53, 1765–1766 (1980).
21) Zhu W., Ma D., Chem. Commun., 2004, 888–889 (2004).
22) Andersen J., Madsen U., Björkling T., Liang X., Synlett, 2005, 2209–2213 (2005).
23) L’abbé G., Beenaerts L., Tetrahedron, 45, 749–756 (1989).
24) Smith P. S., Krbechek L. O., Resemann W., J. Am. Chem. Soc., 86, 2025–2033 (1964).