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Sequential [3+2] Cycloaddition/Air Oxidation Reactions: Triazoloyl Ion Assisted Oxidative Cleavage of Alkynes

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Upon treatment with sodium azide in DMF, bisalkynes undergo chemoselective [3+2] cycloaddition followed by oxidative cleavage of the other alkyne unit by atmospheric oxygen. The neighboring triazoloyl ion is found to assist the cleavage process ultimately to deliver an acid and an aldehyde.

Introduction

Oxidative cleavage of alkynes to carboxylic acids is one of the most important organic reactions. α-Diketones have been shown to be intermediates during the formation of the carboxylic acids. Various oxidants have been reported to effect this transformation, including $KMnO_4$,[1] RuO_4,[2] molybdenum and tungsten polyoxometalates,[3] methylrhenium trioxide,[4] an osmium(VI)–oxo complex in *t*BuOOH,[5] $InCl_3$/*t*BuOOH,[6] $NaBO_3$/AcOH,[7] Cr^{VI}/H_2SO_4,[8] and Pd(OAc)/$ZnCl_2$/O_2.[9] Recently, Hong et al.[10] and Enthaler[11] independently reported the $FeCl_3$-catalyzed cleavage of alkynes to carboxylic acids with *t*BuOOH and H_2O_2, respectively. In all of these methods, two molecules of a carboxylic acid were obtained from one molecule of an alkyne. Reports on the oxidative cleavage of alkynes to carboxylic acids and carboxaldehydes, however, are limited. Hatakeyama et al.[12] and Elrod et al.[13] reported that the OH radical initiated oxidation of alkynes with molecular oxygen could lead to the formation of carboxylic acids and carboxaldehydes, and this was investigated by FTIR and mass spectrometry, respectively. The role of neighboring groups in altering the course of the reaction and enhancing the reaction rate tremendously has been well recognized. Recently, the amide-directed oxidation of alkynes to α-diketones by using ceric ammonium nitrate as the oxidant was reported by Wang et al.,[14] and the formyl-assisted oxidation of alkynes to α-diketones by using I_2/H_2O was reported by Srinivasan et al.[15] To the best of our knowledge, no successful methodology is available for the isolation of carboxylic acids (RCOOH) and carboxaldehydes (R′CHO) from alkynes of the type RC≡CR′ by oxidative cleavage. This article describes the formation of carboxylic acid and carboxaldehyde derivatives by the one-pot reaction of bisalkynes with sodium azide and cheaper, abundant, and environmentally friendly molecular oxygen through sequential [3+2] cycloaddition and oxidation reactions.

Results and Discussion

The generation triazoles by the addition of azides to alkynes is a popular protocol,[16] and recently, Gulevskaya and co-workers reported the reaction of 2,3-dialkynylpyrazines with sodium azide to yield triazole derivatives through [3+2] cycloaddition followed by nucleophilic addition.[17] Inspired by this work, it was proposed to prepare novel triazole derivatives **2** from bisalkyne **1a**. Aiming for target molecule **2**, the reaction of **1a** with sodium azide (1.2 equiv.) in DMF at room temperature for 24 h was performed. However, this reaction afforded triazole **3** (Scheme 1) and not expected product **2**. When the reaction was carried out at 80 °C with cuprous iodide in DMSO as the catalyst to activate the alkyne to facilitate the cycloisomerization reaction, three different products (i.e., **4**, **5a**, and benzaldehyde) were isolated. Here again, expected product **2** was not detected (Scheme 1). The formation of bistriazole derivative **4** can be explained by the double cycloaddition of **1a** with sodium azide at the triple bonds. The formation of **5a** and benzaldehyde may be due to the oxidative cleavage of the alkyne moiety of monotriazole **6**, which should be the intermediate for this reaction – the ynone reacts faster than the alkyne in the cycloaddition with sodium azide. The driving force for the observed oxidation is uncertain.

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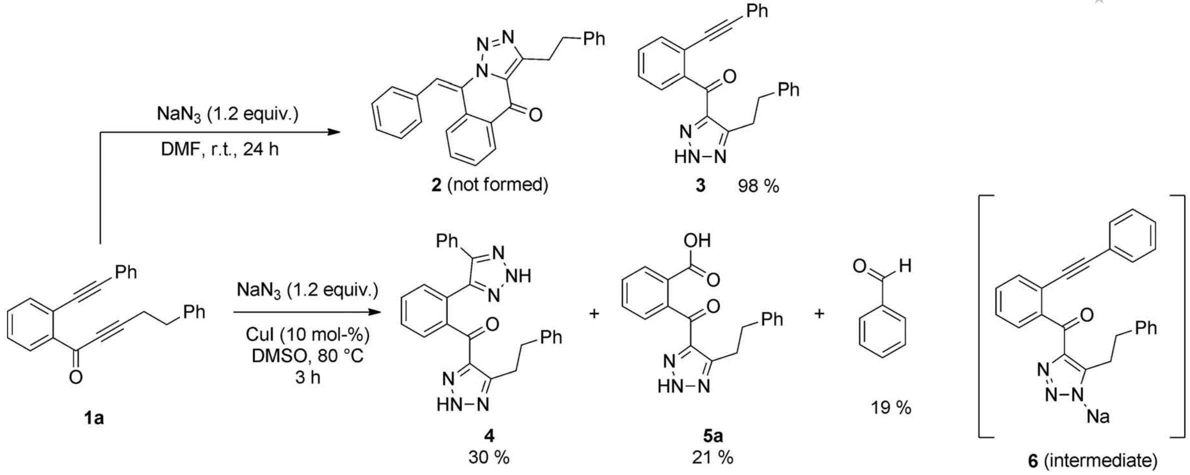


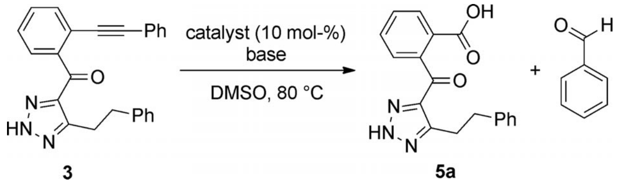
Scheme 1. Reaction between bisalkyne **1a** and sodium azide.

To investigate this oxidative cleavage in detail, the oxidation of monotriazole **3**, prepared from **1a** and sodium azide (1 equiv.) at room temperature, was subjected to different reaction conditions (Table 1). When heated in the presence of cuprous iodide as the catalyst under a nitrogen atmosphere in DMSO, monotriazole **3** did not yield any product and the starting material was recovered (Table 1, entries 1 to 3). Interestingly, when the reaction was carried out with sodium carbonate under a nitrogen atmosphere, a small amount of **5a** (5%; Table 1, entry 4) and benzaldehyde were isolated. As indicated in Scheme 1, the sodium salt of triazole **3** (i.e., **6**) may be involved in the oxidation, and the trace amount of oxygen in the reaction medium plays the role of the oxidant. Then, the reaction of monotriazole **3** with CuI/Na_2CO_3 in DMSO was carried out in an open flask at 80 °C for 1 h, and this resulted in good yield of the oxidative cleavage product (71%; Table 1, entry 5). This proves that atmospheric oxygen is involved in the oxidation. During the optimization process for the formation of **5a** from **3** under atmospheric oxygen, it was realized that the copper catalyst does not have any effect on the reaction (Table 1, entry 6). Bases such as Li_2CO_3, K_2CO_3, and Cs_2CO_3 did not improve the product yield (Table 1, entries 7 to 9). The reaction did not take place in the absence of sodium carbonate, even if the reaction was performed at a higher temperature for 24 h in an open flask (Table 1, entry 10).

Different solvents were tested for their suitability to this reaction, and it was noticed that DMF was superior to the other solvents (Table 2, entry 4). Solvents such as dioxane, THF, toluene, CH_3CN, acetone, water, ethanol, and CH_3CN/H_2O were completely ineffective for this class of oxidation (Table 2).

In an attempt to understand the mechanism of the reaction, the carbonyl group in **3** was reduced with sodium borohydride to obtain alcohol **7**. Alcohol **7**, when treated with sodium carbonate in DMF at 100 °C for 24 h, did not yield expected **8**, but instead it yielded acid **5a** and benzaldehyde, probably by oxidation of the hydroxy group followed by oxidation of the alkyne (Scheme 2). This clearly shows that the carbonyl group is essential for the oxidation of the alkyne.

Table 1. Reaction conditions for the oxidation of alkynes.



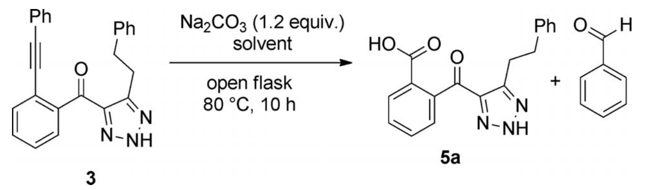
Entry	Catalyst	Base (equiv.)	Time [h]	Yield **5a** [%][a]
1	CuI	–	3	0[b]
2	CuI	–	24	0[b]
3	CuI	Et_3N (1.2)	24	0[b]
4	CuI	Na_2CO_3 (1.2)	5	5[b]
5	CuI	Na_2CO_3 (1.2)	1	71[c]
6	–	Na_2CO_3 (1.2)	1	70[c]
7	–	Li_2CO_3 (1.2)	1	15[c]
8	–	K_2CO_3 (1.2)	2	58[c]
9	–	Cs_2CO_3 (1.2)	1	32[c]
10	–	–	24	0[c]

[a] Isolated yield. [b] Reaction was carried out under a nitrogen atmosphere. [c] Reaction was carried out in an open flask.

When phenyl [2-(2-phenylethylnyl)phenyl]methanone (**9**) [18] was subjected to the same reaction condition, no reaction took place, and this indicates that the conversion of **3** into **5a** requires the triazole group (Scheme 3). Thus, it is clear that the sodium salt of the triazole ring and the carbonyl group have their roles in the oxidation process.

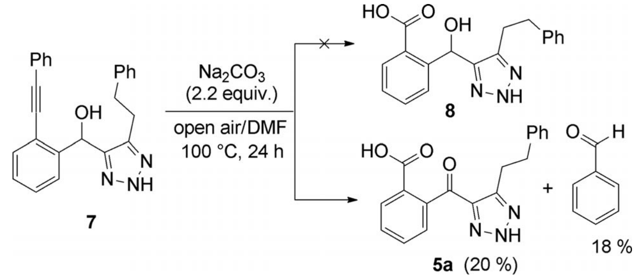
After stabilizing the oxidative cleavage reaction of **3**, the course of the reaction was attempted in a sequential manner staring from **1a** and involving [3+2] cycloaddition and oxidation. In an open flask, the initial cycloaddition of ynone **1a** with sodium azide (1 equiv.) was carried out at room temperature for 0.5 h, and the resulting reaction mixture was heated to 80 °C for 1 h. Product **5a** was easily isolated from the reaction mixture through acid–base workup in 68% yield (Scheme 4).

Table 2. Effect of solvent for the oxidation of alkyne **3**.

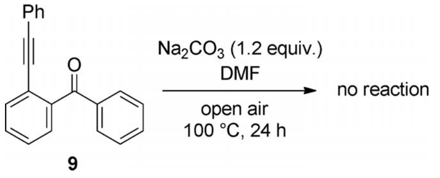


Entry	Solvent	Yield of **5a**[a]
1	toluene	n.r.
2	dioxane	n.r.
3	DMSO	71[b]
4	DMF	75[b]
5	EtOH	n.r.
6	H_2O	n.r.
7	acetone	n.r.[c]
8	CH_3CN	n.r.
9	THF	n.r.
10	CH_3CN/H_2O	n.r.

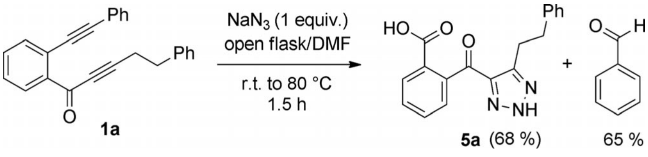
[a] Isolated product. n.r.: no reaction. [b] Reaction time was 1 h. [c] Reaction was carried out at 60 °C.



Scheme 2. Alkyne oxidation reaction of hydroxy derivative **7**.

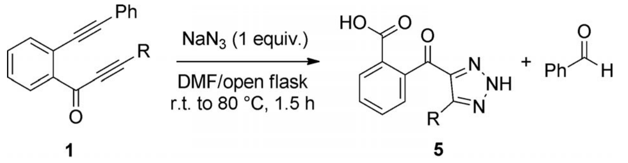


Scheme 3. Oxidation of [2(2-phenylethylnyl)phenyl]methanone (**9**).



Scheme 4. One-pot conversion of bisalkyne **1a** into **5a** and aldehyde.

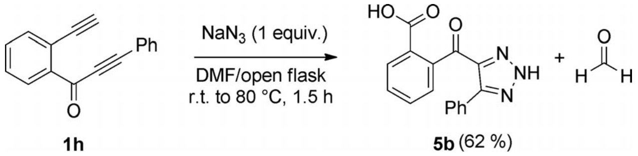
To expand the substrate scope of this protocol, a range of bisalkyne derivatives **1** were prepared from 2-ethynyl benzaldehyde (see the Supporting Information).[19] The optimized, open-flask, domino, sequential [3+2] cycloaddition/oxidation process was then effected on bisalkynes **1b**–**f** to generate a library of triazolecarboxylic acids **5b**–**f** (Scheme 5) in 66–72% yield. In the case of **1g**, in which the R substituent is a phenoxymethyl group, a complex reaction mixture was obtained.



1b: R = phenyl	**5b**: 69 %
1c: R = 2-fluorophenyl	**5c**: 66 %
1d: R = *n*-propyl	**5d**: 72 %
1e: R = *n*-pentyl	**5e**: 67 %
1f: R = 1-naphthyl	**5f**: 70 %
1g: R = phenoxymethyl	(complex mixture from **1g**)

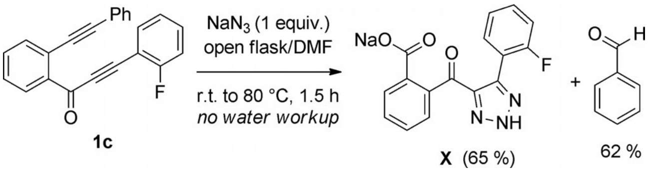
Scheme 5. Sequential [3+2] cycloaddition and oxidation of **1**.

Terminal alkyne **1h** also participated efficiently in the reaction sequence. Treatment of **1h** with sodium azide under the optimized reaction condition yielded carboxylic acid **5b** in 62% yield, and the other expected oxidation product was formaldehyde (Scheme 6).



Scheme 6. [3+2] Cycloaddition and air oxidation of **1h**.

In these reactions, sodium azide undergoes [3+2] cycloaddition followed by the cleavage of the alkyne with one molecule of oxygen and water stoichiometrically. The water molecule involved does not come from the water employed during workup, which was confirmed by the isolation of the sodium salt of **5c** (i.e., **X**) directly from the reaction mixture without any water workup, that is, the reaction mixture was cooled to 5 °C, and the solid obtained was filtered (Scheme 7), and the filtrate contained benzaldehyde. Moisture from the atmosphere or the solvent (DMF has a moisture content of <0.2%) may be the source of the water molecule. When the reaction of bisalkyne **1f** and sodium azide was carried out under the above-optimized conditions along with a small amount of added water, the yield of **5f** was not altered. Recently, Klapötke et al.[20] described the reaction of 4,5-dicyano-2*H*-1,2,3-triazole and sodium carbonate in acetonitrile to give the sodium salt of 4,5-dicyano-1,2,3-triazole in a monohydrate form without employing water during the reaction or isolation, and this shows that the sodium salt of 1,2,3-triazole is capable of absorbing water from the air.



Scheme 7. Preparation of **X**, the sodium salt of **5c**.

All the above results help us to propose a plausible mechanism for the conversion of **1** into **5** (Figure 1).

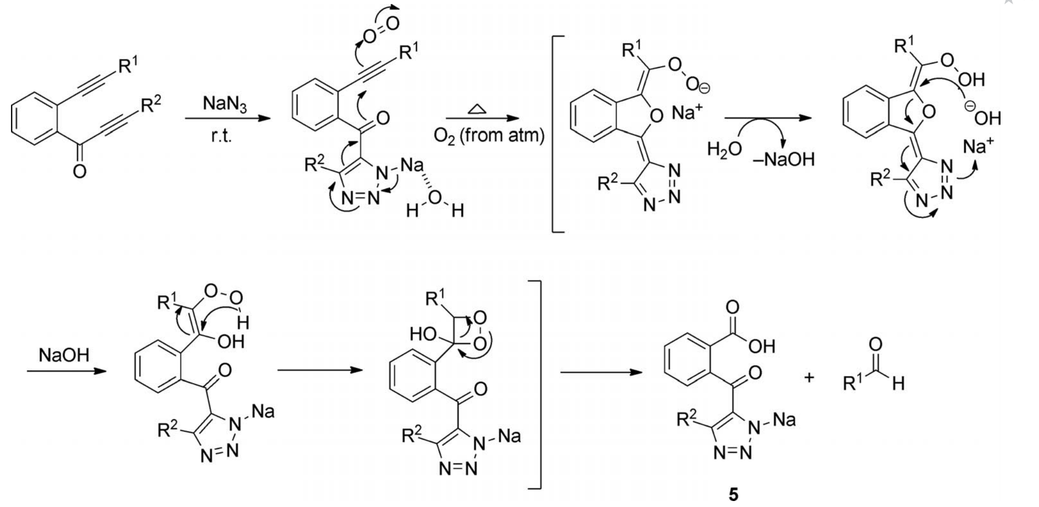


Figure 1. Proposed mechanism for the oxidation of alkynes mediated by the triazoloyl ion.

Conclusions

A simple, environmentally benign, metal-free method for the oxidative cleavage of alkynes to the corresponding carboxylic acids and aldehydes was developed. This reaction proceeds by neighboring group participation of the triazoloyl ion to the alkyne.

Experimental Section

General Procedure for the Synthesis of Triazolecarboxylic Acids 5 from 1: In an open flask, a mixture of bisalkyne **1** (150 mg, 1 equiv.) and sodium azide (1 equiv.) in DMF (15 mL) was stirred at room temperature for 0.5 h and then at 80 °C for 1 h. The reaction mixture was poured into cold water and extracted with ethyl acetate. The mass obtained after evaporation of ethyl acetate was purified by column chromatography (hexane/ethyl acetate) to obtain benzaldehyde. The aqueous layer was acidified with dilute hydrochloric acid (pH 2 to 3) and then extracted with methylene dichloride. The organic layer was washed with brine solution, dried with anhydrous sodium sulfate, and concentrated to afford **5** in pure form.

2-(5-Phenethyl-2*H*-1,2,3-triazole-4-carbonyl)benzoic Acid (5a): Pale yellow solid, m.p. 170–171 °C. IR (KBr): $\tilde{\nu}$ = 3435, 3172, 3060, 3022, 1681, 1666, 1598, 1567, 1489, 1453 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 2.98 (t, J = 8.2 Hz, 2 H, -CH$_2$), 3.24 (t, J = 8.2 Hz, 2 H, -CH$_2$), 7.20–7.32 (m, 5 H, Ar-H), 7.44–7.50 (m, 1 H, Ar-H), 7.55–7.71 (m, 2 H, Ar-H), 7.93 (t, J = 7.4 Hz, 1 H, Ar-H), 13.06 (br. s, 1 H, -COOH), 15.2 (br. s, 1 H, -NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 24.5, 33.7, 125.9, 126.1, 127.6, 128.3, 128.4, 129.3, 129.8, 130.5, 130.7, 132.0, 140.7, 141.7, 167.3, 190.8 ppm. $C_{18}H_{15}N_3O_3$ (321.33): calcd. C 67.28, H 4.71, N 13.08; found C 67.35, H 4.73, N 13.12. MS (ESI–): m/z = 322.1 $[C_{18}H_{15}N_3O_3 + H]^+$.

Supporting Information (see footnote on the first page of this article): Synthesis of the key starting materials **1**, **3**, and **7** and copies of the ^1H NMR and ^{13}C NMR spectra and other data for **1**, **3**, **5**, **7**, and X.

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