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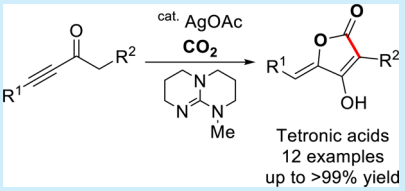
Access to Tetronic Acids via Silver-Catalyzed CO_2 Incorporation into Conjugated Ynones

Yuta Sadamitsu, Keiichi Komatsuki, Kodai Saito, and Tohru Yamada*

Department of Chemistry, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

Supporting Information

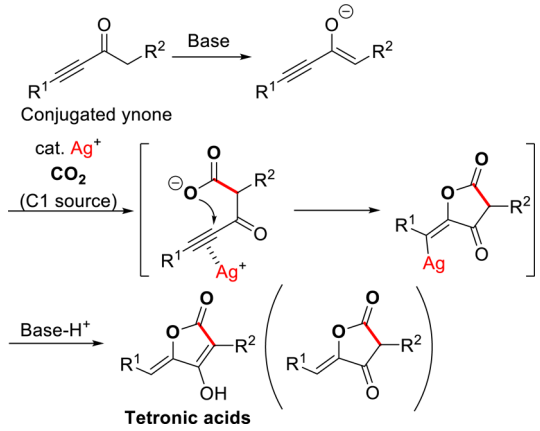
ABSTRACT: Facile and versatile access to highly functionalized tetronic acids has been successfully achieved through the reaction of conjugated ynones with carbon dioxide. In the presence of a base, the enolates generated from the ynones capture CO_2 via a carbon−carbon bond-forming reaction, accompanied by a 5-*exo*-*dig* cyclization reaction of the resulting carboxylate to the alkyne, activated by a silver catalyst. The present method should be applicable to the synthesis of a wide variety of tetronic acids.



Tetronic acids, or 4-hydroxy-5*H*-furan-2-ones, are found in a range of natural products[1] and are considered as important scaffolds for the construction of bioactive and pharmaceutical compounds.[2] Although several methods for the synthesis of their derivatives have been reported, multiple steps are generally required, e.g., introduction of a substituent at the 3-position of the 2-furanone, protection and deprotection sequences, halogenation or diazotization, and a transition-metal-catalyzed coupling reaction.[3] Also, for substitution at the 5-position, organolithium reagents are generally employed to obtain the corresponding carbanion. Therefore, many limitations involving availability of electrophiles and tolerance of the functional groups are of concern.[4] Recently, a silver-catalyzed synthesis of tetronic acids from (*E*)-2-en-4-ynoic acid was reported,[5] though the preparation of the starting materials was complex.

Carbon dioxide is an attractive carbon source, having no toxicity in itself and availability at a low cost, as well as easy handling.[6] Since CO_2 adducts are considered thermodynamically unstable, after nucleophilic addition to CO_2, decarboxylation often occurs competitively to form the starting compound. Therefore, in order to incorporate CO_2 into organic molecules, countermeasures are frequently needed to suppress the decarboxylation process.[7] The successive intramolecular cyclization of an activated alkyne by transition metal catalysts[8] is one of the most commonly used and reliable methods, widely applied to the syntheses of various multisubstituted heterocycles.[9] A silver-catalyzed CO_2 incorporation reaction, based on the above-mentioned strategy, had been reported by this group. It was revealed that propargyl alcohols[10] and alkynyl anilines[11] were applicable as heteroatom nucleophiles for these reactions with activated alkynes by silver catalysts. Recently, methods for CO_2 incorporation with carbon−carbon bond formation were developed using carbon nucleophiles, such as alkynyl ketones[12] and alkynyl allylsilanes.[13] In this paper, we report that a readily prepared conjugated ynone has been employed as a carbon nucleophile to synthesize tetronic acid derivatives using CO_2 in the presence of a silver catalyst (Scheme 1).

Scheme 1. Synthesis of Tetronic Acids Based on CO_2 Fixation into Ynones



Various organic bases were examined first, since enolate generation from the ynone would be crucial to capture the CO_2. Under 2.0 MPa pressure of CO_2, the ynone **1a** was treated with organic bases in the presence of a catalytic amount of silver acetate in DCM (Table 1). When triethylamine or *N*-methylimidazole (MeIm) was employed, no reaction occurred, and the ynone **1a** was quantitatively recovered (entries 1 and 2). Using DMAP, the reaction proceeded slightly to afford the corresponding cyclic compounds in 19% yield (entry 3). Stronger bases were expected to generate the corresponding enolate to effectively capture the CO_2. The use of 1,1,3,3-tetramethylguanidine (TMG) resulted in a 37% yield (entry 4), whereas 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), DBU, and 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) were found effective against the 5-*exo*-*dig* cyclization to afford tetronic acid **2a** in 74%, 86%, and 90% yields, respectively (entries 5−7). On the other hand, when this reaction was carried out under a lower pressure of CO_2, the yield of the

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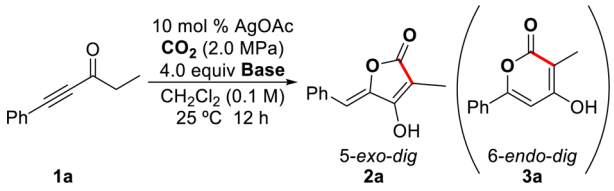
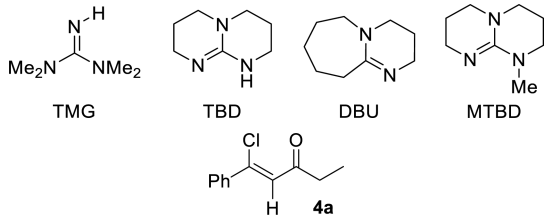
Table 1. Examination of Reaction Conditions



entry[a]	base	recovery/%[b,c]	yield 2 + 3 (2:3)[b]/%[d]
1	Et_3N	92	nd
2	*N*-MeIm	94	trace
3	DMAP	44	19 (79:21)
4	TMG	41	37 (>95:5)
5	TBD	1	77 (>95:5)
6	DBU	trace	86 (>95:5)
7	MTBD	trace	90 (>95:5)
8[e]	MTBD	trace	trace
9[f]	MTBD	trace	92 (>95:5)

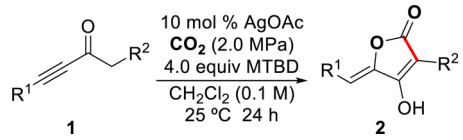
[a]The reaction was carried out with 0.10 mmol of substrate. [b]Detected by ^{1}H NMR. [c]After quenching by 4 M solution of HCl in 1,4-dioxane, **1a** was converted to **4a**. The yield was estimated from the yield of **4a**. [d]Isolated yield. [e]N_2 (balloon) was used instead of CO_2. [f]The reaction time was 24 h.

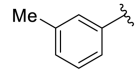
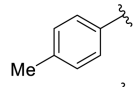
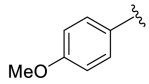
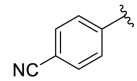
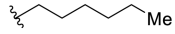


desired product decreased, but no starting material was recovered. Even when this reaction was performed under a nitrogen atmosphere, no starting material was recovered (entry 8), but quantitative formation of a byproduct was observed. Based on the ^{1}H NMR, ^{13}C NMR, and MS analyses, the byproduct was identified to be the corresponding 1,4-adduct of MTBD on the starting ynone (see Supporting Information). Therefore, in this reaction, it was assumed that a higher CO_2 pressure was required to selectively promote the CO_2 incorporation; thus, the reaction was carried out for 24 h under 2.0 MPa of CO_2 to afford the corresponding product **2a** in 92% yield (entry 9).

The optimized conditions were applied to various ynones (Table 2). Substituents on the alkyne termini (R^1) were first examined (entries 1−6). The substrates bearing phenyl (**1a**), *o*-tolyl (**1b**), *m*-tolyl (**1c**), and *p*-tolyl (**1d**) groups were converted to the corresponding tetronic acids (**2a**−**d**) in 92%, 88%, 74%, and 87% yield, respectively (entries 1−4). When the substrate bearing a *p*-methoxyphenyl group (**1e**) reacted, the desired product **2e** was obtained quantitatively (entry 5). When the substrate bearing a *p*-benzonitrile group (**1f**) was employed, the corresponding product **2f** was obtained in 62% yield (entry 6). These results suggested that an electron-withdrawing group on the aryl group of the alkyne termini caused a decrease in the nucleophilicity of the enolate, resulting in the lower yield. Various of substituents on the α-position of the carbonyl (R^2) were next examined (entries 7−11). When substrates with no substituent (**1g**) or bearing an *n*-hexyl group (**1h**) were employed, the 5-*exo*-*dig* cyclization proceeded to afford the corresponding tetronic acids **2g** and **2h** in 95% and 97% yield, respectively (entries 7 and 8). On the other hand, when the

Table 2. Substrate Scope for Various Tetronic Acids



entry[a]	R^1	R^2	1	2	yield 2/%[b]
1	Ph	Me	**1a**	**2a**	92
2[d]		Me	**1b**	**2b**	88
3[d]		Me	**1c**	**2c**	74
4[d]		Me	**1d**	**2d**	87
5		Me	**1e**	**2e**	>99
6[c]		Me	**1f**	**2f**	62
7[d]	Ph	H	**1g**	**2g**	95
8[g]	Ph		**1h**	**2h**	97
9[e,h]	Ph		**1i**	**2i**	88[i]
10[e,f,g]	Ph		**1j**	**2j**	77[j]
11[c,e,h]	Ph	Ph	**1k**	**2k**	75

[a]The reaction was carried out using 0.10 mmol of substrate. [b]Isolated yield. [c]DBU was used instead of MTBD. [d]3.0 equiv of MTBD. [e]CH_3CN was used as solvent at 40 °C. [f]48 h. [g]20 mol% AgOAc. [h]20 mol% AgOTf. [i]The product was an 89:11 mixture of **2i** and **3i**. [j]The product was an 85:15 mixture of **2k** and **3k**.

reactions of substrates bearing isopropyl (**1i**) and cyclohexyl (**1j**) groups were examined, 6-*endo*-*dig* cyclization occurred versus the 5-*exo*-*dig* cyclization to afford the tetronic acids **2** and the hydroxypyrones **3** in 88% (**2i**:**3i** = 89:11) and 77% (**2j**:**3j** = 85:15) yield, respectively (entries 9 and 10). These results suggested that a sterically demanding R^2 substituent tends to promote the 6-*endo*-*dig* cyclization (entries 7−10), though the precise reason is still unclear. The effect of the substituent on the aromatic groups R^2 was examined. The substrate bearing a phenyl group (**1k**) was converted to the corresponding tetronic acid **2k** in 75% yield with a high regioselectivity (entry 11).

Next, using this protocol, we conducted the synthesis of aspulvinone E[14] having various bioactivities (Scheme 2).[15] The internal alkyne **1l**, which is a precursor for the CO_2 incorporation reaction, was prepared from the reaction of ethyl (4-methoxyphenyl)acetate with the lithium acetylide, generated from (4-methoxyphenyl)acetylene with *n*-BuLi. The silver-catalyzed intramolecular cyclization involving the CO_2

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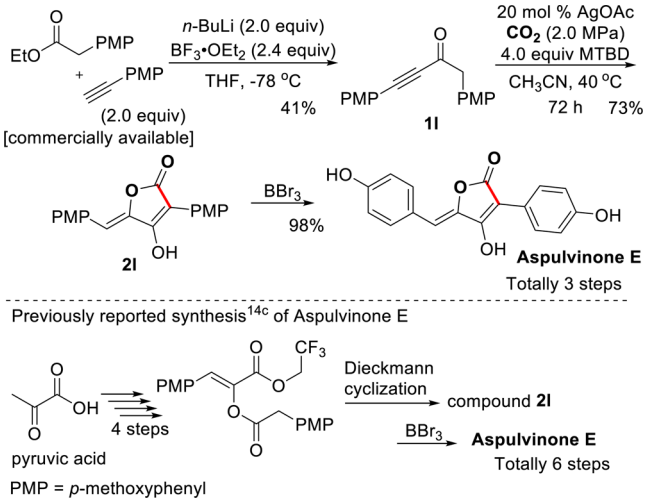
Scheme 2. Synthetic Application



fixation of **1l** proceeded to afford the corresponding product **2l** in 73% yield. Demethylation of **2l** was performed based on the conditions of a previous report,[14c] resulting in aspulvinone E in 98% isolated yield. Overall, the synthesis of aspulvinone E was achieved in three steps from commercially available materials. In one previous report,[14c] the synthesis of aspulvinone E from pyruvic acid was achieved using a Dieckmann cyclization as a key step. However, multiple steps were required to synthesize the cyclization precursor (trifluoroethyl 2-cinnamate), and six steps were required to synthesize aspulvinone E. Therefore, our protocol can be regarded as noteworthy in terms of step-economy.

In conclusion, we have developed a highly efficient synthesis of tetronic acid derivatives through ynone enolate trapping carbon dioxide and silver-catalyzed 5-*exo*-*dig* selective cyclization. This sequence allows a facile and versatile access to functionalized tetronic acid derivatives. Further application of this reaction to the synthesis of various tetronic acids is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01309.

Experimental procedures, analytical data for all new compounds, and NMR spectra for the products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yamada@chem.keio.ac.jp.

ORCID

Tohru Yamada: 0000-0002-4177-5019

Notes

The authors declare no competing financial interest.

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This paper is dedicated to Professor Emeritus Teruaki Mukaiyama of The University of Tokyo in celebration of his 90th birthday.

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