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Decarboxylative cycloaromatization of enediyne model compounds — mechanism of the radical and ionic pathway

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Abstract

Stable α-alkynylacetic acid derivatives related to *cis*-enediyne were synthesized and the rate of decarboxylative cycloaromatization of 3,5-difluoro derivative **7c** was found to be much faster than that of the corresponding phenyl derivative **7a**. The cycloaromatization reaction mechanisms of **7c** under various conditions were investigated.

Keywords: diynes; enynes; radicals; ionization; mechanisms.

Simple acyclic (*Z*)-1,2,4-heptatrien-6-ynes, which undergo cycloaromatization to produce reactive dehydrotoluene biradicals (Myers–Saito-type cyclization),[1] have been investigated as chemical models for a class of potent antitumor antibiotics, neocarzinostatin,[2] and related natural enediyne drugs.[3] The preparation of enyne–allene models possessing characteristic triggering devices which initiate the generation of dehydrotoluene biradicals is a challenge which is currently being met by many research groups.[4] Recently, we reported a development of the enediyne models **1** which produce the reactive enyne–allenes **2** and ultimately result in a cycloaromatization via a reaction cascade triggered by hydrolysis of the malonyl ester group (Scheme 1).[5] From the reaction products we could not detect the compounds **5** which would be formed directly from biradicals **3**, and the products were the acetals **6**. From the results of deuterium-labeling studies, we concluded that the reaction involves an ionization process of toluene biradicals **3** producing zwitterionic species **4**. For the elucidation of this cascade reaction mechanism and development of biologically active substances, the preparation of thermally stable carboxylic acid derivatives, which cycloaromatize under mild conditions, is essential. For this purpose, we designed novel α-alkynylacetic acid derivatives. Reported in this communication is a study on the preparation and the reactivities of α-alkynylphenylacetic acid **7a**. In order to accelerate the decarboxylation step, analogous compounds **7b**,**c** having electron-withdrawing 3-fluoro- and 3,5-difluorophenyl groups were prepared as well.

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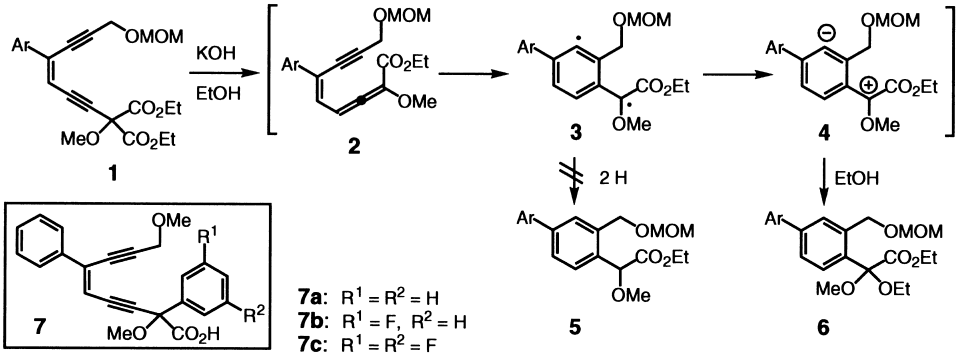
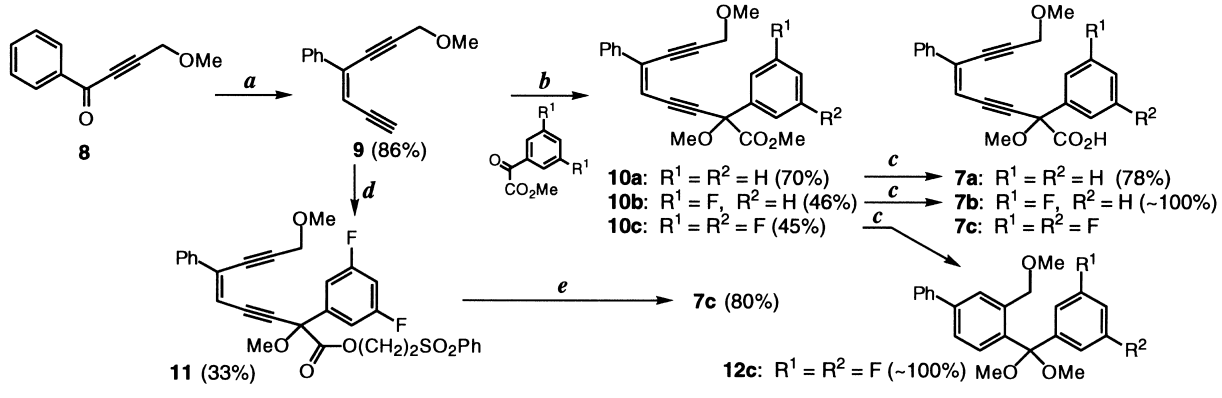


Scheme 1.

The carboxylic acids **7a–c** were synthesized as shown in Scheme 2. Propargyl bromide was allowed to react with the alkynylketone **8**[6] in the presence of zinc to provide the *tert*-alcohol, which was then treated with MsCl and Et_3N to furnish predominantly the enediyne **9** having the *cis* geometry.[7] The lithium salt of the enediyne **9** was treated with methyl benzoylformate followed by methylation of the resultant alcohol to give the desired α-alkynylphenylacetate **10a**. Mono- and difluoro derivatives **10b** and **10c** were prepared in a similar manner, respectively. While the hydrolysis of **10a** and **10b** with KOH (2 equiv.) in MeOH at room temperature afforded the thermally stable carboxylic acids **7a** and **7b**, respectively, the hydrolysis of **10c** under similar conditions gave the acetal **12c** in a good yield. Therefore, the carboxylic acid **7c** was prepared by an alternative method via the phenylsulphonylethyl ester **11** (Scheme 2).[8]



Scheme 2. *a*: (i) Propargyl bromide, Zn, THF, 0°C, 5 min; (ii) MsCl, Et_3N, CH_2Cl_2, 0°C, 10 min. *b*: (i) *n*-BuLi, THF, −78°C, 15 min; (ii) CH_3I, Ag_2O, $CaSO_4$, rt, 12 h. *c*: KOH (2 equiv.), MeOH, rt. *d*: (i) *n*-BuLi, THF, −78°C, then 2-phenylthioethyl 3,5-difluorobenzoylformate, −78°C, 15 min; (ii) Ag_2O, $CaSO_4$, MeI, rt, 9 h; (iii) *m*CPBA, CH_2Cl_2, rt, 10 min. *e*: DBU, MeOH, 37°C, 0.5 min, then Amberlyst-15, 0°C, 10 min

For preliminary investigations on decarboxylative cycloaromatization of **7a–c**, the reactions of **7a–c** with KOH (2 equiv.) in MeOH at 37°C affording the acetals **12** were carried out, and the results are summarized in Table 1. As we expected, the reaction rate of **7c** was much faster than that of **7a**,**b**, and therefore **7c** was found to be suitable for further mechanisitic study.

A series of decarboxylative cycloaromatization reactions under various conditions were carried out and the results are summarized in Table 2. The products **12–17** (Scheme 3) were isolated and characterized by means of spectroscopic analysis. The intermediate corresponding to enyne–allene could not be detected on TLC or by ^1H NMR during each reaction. Compound **7c** was essentially stable in the absence of a base in MeOH or benzene, while it cycloaromatized in the presence of Et_3N (entries 1–7). The reaction

Table 1
Decarboxylative cycloaromatization of **7** to give **12** (2 equiv. KOH, MeOH, 37°C)

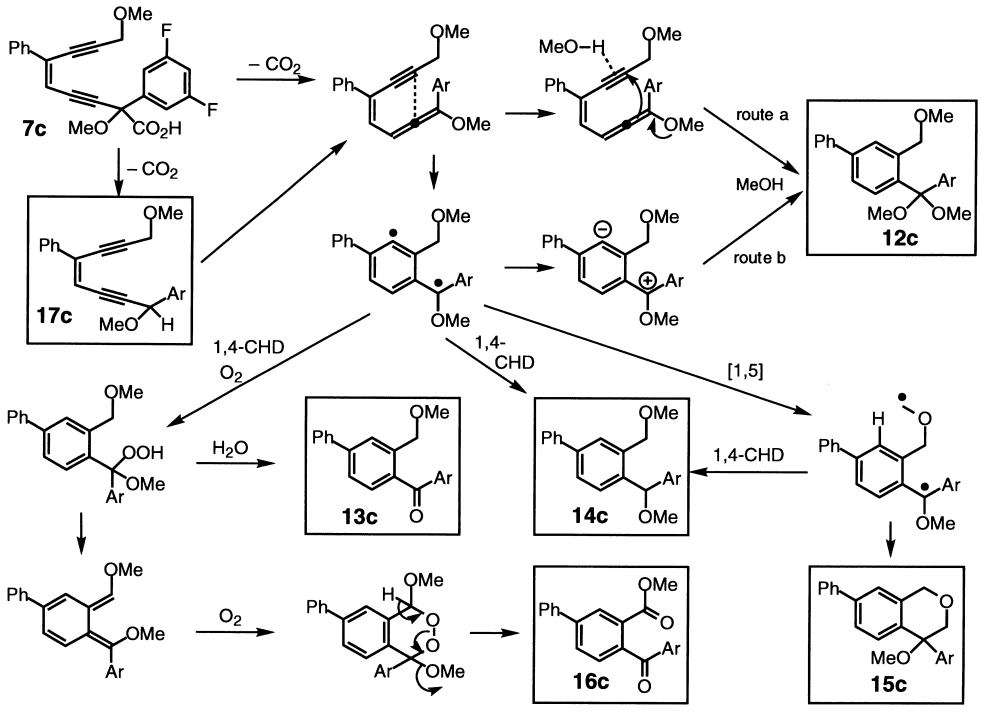
Substrate	R^1	R^2	Yield of **12** / %	Reaction time / h
7a	H	H	87	1080
7b	F	H	98	72
7c	F	F	70	0.5

Table 2
Decarboxylative cycloaromatization of **7c** to give **12c**[a]

					Product / yield (%)					
Entry	Solvent	Base[b]	Additive[c]	Reaction time / min	**12c**	**13c**	**14c**	**15c**	**16c**	**17c**
1	MeOH	Et_3N	-	390	76	0	0	0	0	7
2	MeOH	Et_3N	O_2	390	83	0	0	0	0	8
3	MeOH	Et_3N	CHD/O_2	390	77	0	0	0	0	8
4	Benzene	Et_3N	-	70	0	6	0	50	0	13
5	Benzene	Et_3N	O_2	70	0	10	0	16	0	14
6	Benzene	Et_3N	CHD	70	0	24	23	10	0	10
7	Benzene	Et_3N	CHD/O_2	70	0	35	0	2	11	15
8	DMF	-	-	1<	0	7	0	31	0	13
9	DMF/MeOH (9:1 v/v)	-	-	1<	58	7	0	0	7	11

[a]Each reaction was carried out at 37°C. Yield was determined by HPLC after removal of polar products by using silica gel chromatography.
[b]For entries 1~7, 1.1 equiv of Et_3N was added, respectively.
[c]The reactions for entries 1, 4, 8, and 9 were carried out under Ar atmosphere, and under O_2 atmosphere for entries 2, 3, 5, and 7. For entries 3, 6, and 7, 50 equiv of 1,4-cyclohexadiene (CHD) was added, respectively.

rates in MeOH were relatively slow and the reactions in the absence or presence of a radical scavenger (O_2 or 1,4-cyclohexadiene) produced the acetal **12c** and the enediyne **17c** in similar yields, respectively. The reaction of enediyne **17c** under similar conditions gave **12c** in 69% yield. These results suggest that the cycloaromatization proceeded via an ionic cyclization pathway (Scheme 3, route a) but not via the biradical intermediate (route b). On the other hand, the reaction in benzene (entry 4) afforded the isochromane **15c** predominantly, which is assumed to be formed from the biradical via a 1,5-hydrogen shift followed by recombination (Scheme 3). Formation of another product **13c** might be ascribed to ionization of the biradical to generate the zwitterionic intermediate followed by a reaction with water adventitiously contained in the solvent. When the same reaction was carried out in an oxygen atmosphere (entry 5), the yield of **13c** was slightly increased, indicating the possibility that the participation of oxygen can not be ruled out for the formation of **13c**. The results of similar reactions in the presence of cyclohexadiene (entries 6 and 7) substantiates the radical mechanism of these reactions. The product **14c** must be formed by the hydrogen abstraction of the biradical intermediate before or after a 1,5-hydrogen shift, and **16c** is assumed to be formed by the incorporation of molecular oxygen. As compared with the above reactions, the reaction in a polar solvent such as DMF (entry 8) was found to be relatively fast without the addition of a base, and the major product was **15c**. In contrast with this reaction, a similar reaction in the presence of MeOH afforded the acetal **12c** predominantly, which suggests that the ionic pathway is accelerated by the proton source rather than the polar conditions. Thus, we propose the mechanisms for these cycloaromatization reactions as represented in Scheme 3. Studies on the analogues of this class of compounds, involving enzyme-induced biradical generation, are in progress.



Scheme 3.

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