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New Intramolecular Five-Endo-Mode Cyclization of Allenyl Aryl Ketones

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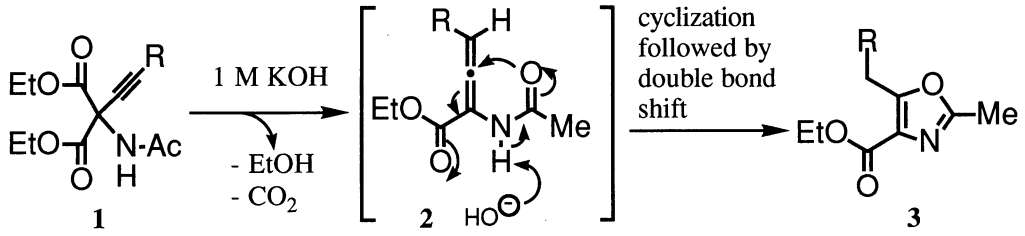
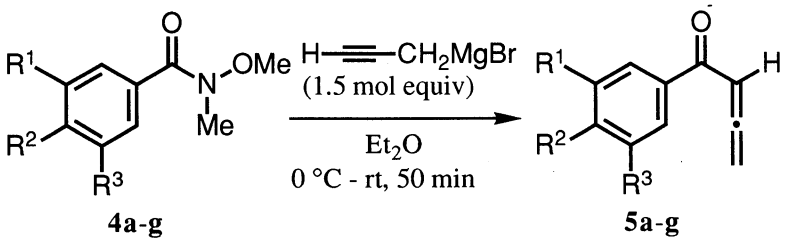
A convenient preparation of allenyl aryl ketones was achieved by the Weinreb-modified Grignard reaction of *N*-methoxy-*N*-methylamides with propargylmagnesium bromide. On treatment with BF_3•OEt_2, the allenyl aryl ketones were converted to methylenebenzocyclopetenones *via* a new 5-endo-mode cyclization.

In the course of development of new SH-enzyme inhibitors, we found that treatment of diethyl (acetylamino)ethynylmalonates (**1**) with 1 M (M = molar conc.) KOH afforded trisubstituted oxazoles **3** *via* a new mode of 5-endo cyclization of the resultant acetylaminoallenic esters **2** under the basic conditions.[1] We readily anticipated a possibility of a similar intramolecular 5-endo-mode cyclization[2] of allenyl aryl ketones under the Lewis acidic conditions for increasing electrophilicity of the conjugated allenic ketone moiety.



Now, we wish to report a convenient synthesis of conjugated allenyl aryl ketones utilizing the Weinreb-modified Grignard reaction[3] and their intramolecular 5-endo-mode cyclization. *N*-Methoxy-*N*-methylamides **4a-g**, prepared by a coventional method[3] with the corresponding carboxylic acids (or acid chlorides) and *N,O*-dimethylhydroxylamine hydrochloride, were treated with 1.5 mol equiv of propargylmagnesium bromide (1 M solution in Et_2O)[4] in anhydrous Et_2O at 0 °C and then room temperature with stirring to give the desired allenyl aryl ketones **5a-g** in high yields (70-88%) as shown in Table 1. Their allenic structure was confirmed by their characteristic ^1H NMR (200 MHz, $CDCl_3$) signals [δ 5.24-5.26 (d, 2H, J = 6.6 Hz) and 6.41-6.48 (t, 1H, J = 6.6 Hz)] due to allenic three protons. Although there have been some preparation methods for the conjugated allenyl ketones,[5] ours must be convenient.

Subsequently, intramolecular cyclization was attempted by employing an allenyl ketone **5a** and BF_3•OEt_2 as follows. To a solution of **5a** (741 mg, 3.6 mmol) in anhydrous CH_2Cl_2 (50 ml) was added BF_3•OEt_2 (447 μl, 3.6mmol) at 0 °C with stirring under N_2 atmosphere. After being stirred at 0 °C for 45 min, the reaction mixture was quenched with an aqueous $NaHCO_3$ solution (40 ml). The mixture was treated as usual to give a bicyclic product **6a** (601 mg, 81%) as colorless prisms (Et_2O-hexane = 1:1) after chromatographic purification.



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a: $R^1 = R^2 = OMe$, $R^3 = H$
b: $R^1 = R^2 = OCH_2O$, $R^3 = H$
c: $R^1 = R^3 = OMe$, $R^2 = H$
d: $R^1 = OMe$, $R^2 = R^3 = H$
e: $R^1 = R^2 = Me$, $R^3 = H$
f: $R^1 = Me$, $R^2 = R^3 = H$
g: $R^1 = R^2 = R^3 = H$

Table 1. Preparation of Allenyl Aryl Ketones **5a-g**

Allenyl Aryl Ketone **5**	Yield[a]/%	mp/ °C
5a	85	90-91
5b	88	70
5c	74	oil
5d	85	〃
5e	70	40
5f	85	32-33
5g	75	oil

a)All yields are those of isolated compounds.

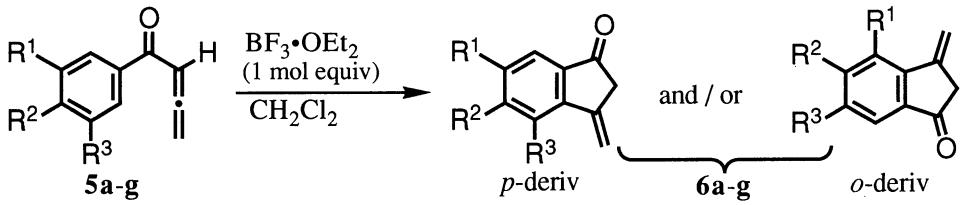
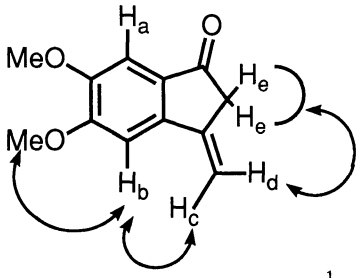


Table 2. Intramolecular Cyclization of Allenyl Aryl Ketones **5a-g**

Compd **5**	Reaction conditions		Product **6**	Yield[a]/%	mp / °C
	Temp/°C	Time/min			
5a	0	10	**6a**	81 (*p*)	142-143
5b	〃	30	**6b**	71 (*p*)	123-124
5c	-13 - -8	20	**6c**	50 (*p*)	89.5-90
5d	0	〃	**6d**	80 (*p*:*o* = 4:1)[b]	oil
5e	60	40	**6e**	25 (*p*:*o* = 8:1)[b]	〃
5f	〃	45	**6f**	40 (*p*:*o* = 2:1)[b]	〃
5g	〃	84	**6g**	17	〃

a) All yields are those of isolated compounds.
b) A ratio (*para : ortho*) was determined by the ^1H NMR (200 MHz, $CDCl_3$) analysis.

The reactions employing other compounds **5b-g** were similarly carried out to give the corresponding bicyclic products **6a-g** in various yields (Table 2). The chemical structure of compounds **6a-g** was determind on the basis of their ^1H NMR (200 MHz, CDCl3) spectrum data and NOE expriments (400 MHz, CDCl3) (*e.g.*, **6a** as shown in Fig. 1). Ozonolysis of **6a** followed by reduction of the resultant ozonide with dimethyl sulfide gave a 1,3-indandione derivative **7** [mp 226-227 °C (CH_2Cl_2-hexane); ^1H NMR (200 MHz, CDCl3) δ 3.19 (s, 2H), 4.03 (s, 2H), and 7.34 (s, 2H)] in 95% yield. In this cyclization reaction, existence of an electron-donating substituent on the aromatic moiety seems to be essential. Steric interaction between the aromatic substituent and the allenic moiety may controll the regioselectivity (*para : ortho* ratio) in the cyclization. Five-endo ring-closure reactions (Nu = $-O^{\ominus}$) at the sp^2 carbon atom of the allenic moiety were independently reported by Macomber,[6] Magnus,[7] and Marshall[4,8] groups. Cyclization at the sp carbon atom has been briefly described by Torii group[1] using SH nuclophile (Fig. 2). The intramolecular cyclization by our new method should proceed in



^{1}H Signal
δ 3.62 (H_e)
δ 5.23 (H_d)
δ 5.67 (H_c)
δ 7.14 (H_b)
δ 7.18 (H_a)

Fig. 1. NOE Experiment (400 MHz, $CDCl_3$) and ^{1}H NMR (200 MHz, $CDCl_3$) of compound **6a**.

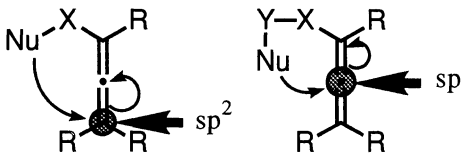
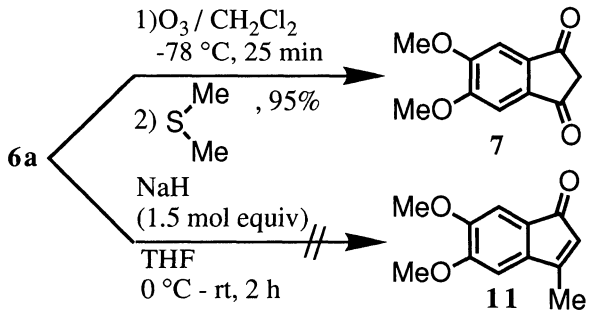
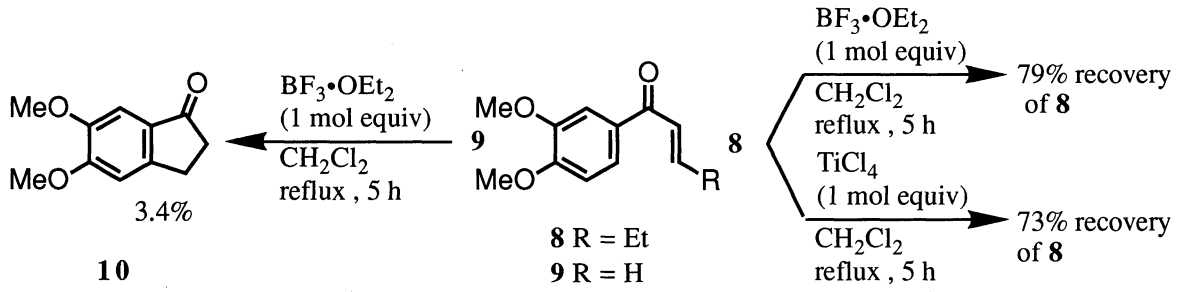


Fig. 2 . 5-Endo ring- closure mode at the sp^2- or sp- carbon atom of the allenic moiety.





the 5-endo-mode at the sp carbon atom of the allenic moiety because all reactions furnished exo-methylene products. Although there have been many papers on the Nazarov type reaction,[9] cyclization of alkenyl aryl ketones such as compounds **8** and **9** has never been reported.[10] In order to compare with our new 5-endo-mode cyclization, 5-endo-trigonal like ones were attempted by employing **8** and **9** in the presence of BF_3•OEt_2 or $TiCl_4$. However, these reactions resulted in 73% or 79% recovery of the starting compound and production of a small amount of **10** with miscellaneous compounds. Interestingly, the exo-methylene double bond of **6a-g** must be remarkably stable when compared with that of the corresponding conjugated enones like **11**. Isomerization of the exo-methylene double bond of **6a** toward **11** does not occur at all under the basic conditions. This unusual stability of **6a-g** is quite different from the case of simple methylenecyclopentanone reported by Allinger et al.[11]

Thus, we demonstrated a new 5-endo-mode cyclization of allenyl aryl ketones[12] which will be expanded to preparation of larger cyclic compounds. Compounds **6a-d** may be available for synthetic development of new antitumor agents similar to the duocarmycin analogs.[13]

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References

1) Y. Nagao, K. Kim, S. Sano, W.-S. Lee, Y. Komaki, and M. Kihara, the 113 th Annual Meeting of the Pharmaceutical Society of Japan, Osaka, March 1993, Abstr., p. 99; H. Tanaka, Y. Kameyama, A. Kosaka, T. Yamauchi, and S. Torii, *Tetrahedron Lett.*, **32**, 7445 (1991).
2) J. E. Baldwin, R. C. Thomas, L. I. Kruse, and L. Silberman, *J. Org. Chem.*, **42**, 3846 (1977) and references cited therein.
3) S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, **22**, 3815 (1981).
4) J. A. Marshall and X.-J. Wang, *J. Org. Chem.*, **56**, 960 (1991).
5) F. Jaffe, *J. Organometallic Chem.*, **23**, 53 (1970); C. C. Shen and C. Ainsworth, *Tetrahedron Lett.*, **1979**, 83; T. Flood and P. E. Peterson, *J. Org. Chem.*, **45**, 5006 (1980); J.-P. Pilott, B. Bennetau, J. Dunogues, and R. Calas, *Tetrahedron Lett.*, **22**, 340 (1981); S. G. Gauwberghs and P. J. De Clercq, *ibid.*, **29**, 6501 (1988); K. Diehl and G. Himbert, *Chem. Ber.*, **119**, 2874 (1986); G. Majetich, Y. Zhang, and G. Dreyer, *Tetrahedron Lett.*, **34**, 449 (1993).
6) R. S. Macomber and E. R. Kennedy, *J. Org. Chem.*, **41**, 3191 (1976).
7) D. Gange and P. Magnus, *J. Am. Chem. Soc.*, **100**, 7746 (1978).
8) J. A. Marshall and W. J. Dubay, *J. Org. Chem.*, **56**, 1685 (1991).
9) I. N. Nazarov, *Usp. Khim.*, **18**, 377 (1949); C. Santelli-Rouvier and M. Santelli, *Synthesis*, **1983**, 429; F. C. Cook, J. Schwindeman, and P. Magnus, *Tetrahedron Lett.*, **1979**, 1995; J. P. Marino and R. J. Linderman, *J. Org. Chem.*, **46**, 3696 (1981); S. E. Denmark, K. L. Habermas, G. A. Hite, and T. K. Jones, *Tetrahedron*, **42**, 2821 (1986).
10) Very recently, Majetich et al. reported the Friedel-Crafts annulations of various conjugated dienones. G. Majetich, Y. Zang, T. L. Feltman, and V. Belfoure, *Tetrahedron Lett.*, **34**, 441 (1993).
11) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Am. Chem. Soc.*, **90**, 5773 (1968).
12) Recent progress of the allenic compound chemistry, see : S. Nagashima and K. Kanematsu, *J. Synth. Org. Chem. Jpn.*, **51**, 608 (1993) and references cited therein.
13) D. L. Boger and K. Machiya, *J. Am. Chem. Soc.*, **114**, 10056 (1992).

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