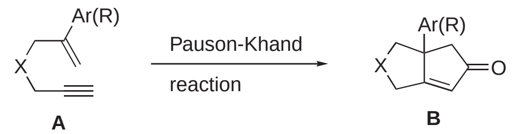
Intramolecular Pauson-Khand Reaction of Various 2-Aryl-1,6-Enynes: Synthesis of Bicyclic Compounds Bearing Quaternary Carbon Center

Miyuki Ishizaki,* Hiroshi Satoh, and Osamu Hoshino*
Faculty of Pharmaceutical Sciences, Tokyo University of Science, Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo 162-0826

(Received June 28, 2002; CL-020541)

Intramolecular Pauson-Khand reaction of various 2-aryl-1-hepten-6-ynes and its aza-derivative (acyclic *exo*-methylene compounds) efficiently produced 1-aryl-bicyclo[3.3.0] octenones and azaoctenone bearing quaternary carbon center in good yields. The reaction of 1,7-enynes was also investigated.

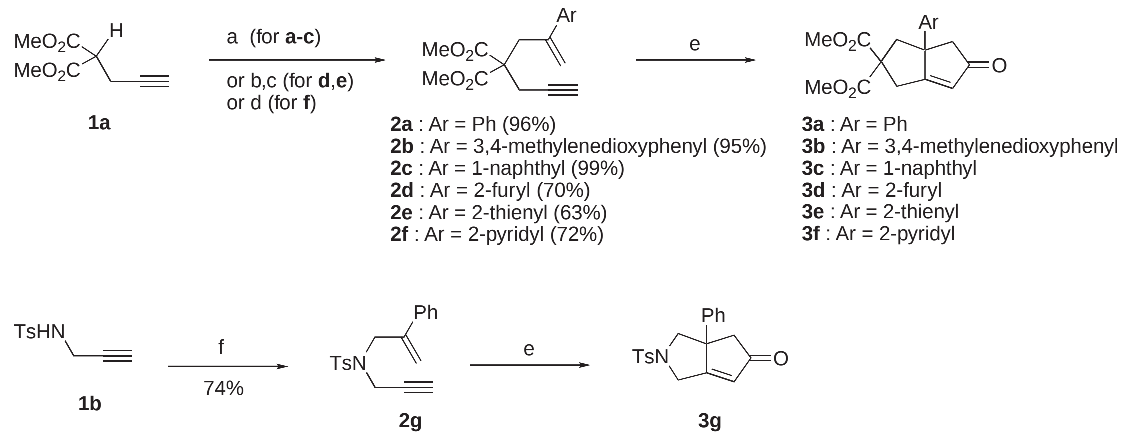
Pauson-Khand reaction has been widely recognized as one of powerful methods to construct cyclopentenone derivatives.[1] Since the first report of the reaction in cyclic system, most studies were focused on the reaction of enynes bearing *endo*-olefins.[1] Recent studies[2] in our laboratory showed convenient construction of polycyclic compounds bearing quaternary carbon center(s) by the reaction of *exo*-cyclic olefins. However, as for the reaction of acyclic *exo*-olefins, there is no report on the derivatives with *aromatic* substituents except for reports on the only two derivatives with *aliphatic* substituents [**A**: R=Me, X=$C(CO_2Me)_2$[3a–g] or R=CH_2OBn, X=$C(CO_2Et)_2$[3h,i] in Scheme 1]. Here, we wish to report intramolecular Pauson-Khand reaction of *acyclic exo*-olefins **A** having *aromatic* substituents to give the corresponding bicyclo[3.3.0]octenones and 7-azaoctenone **B** bearing quaternary carbon center (Scheme 1).



Scheme 1. Ar=Aromatic group; R=Aliphatic group; X=C $(CO_2Me)_2$ or NTs.

Various Pauson-Khand precursors **2a–g**[4] bearing *exo*-methylene group were synthesized from dimethyl propargylmalonate (**1a**) or *N*-propargyltosylamide (**1b**) as shown in Scheme 2. Thus, reaction of **1a,b** with 2-aryl-3-iodopropenes,[4] which were easily obtained from corresponding alcohols,[5] gave enynes **2a–c,g**. Enynes **2d,e** were prepared by reaction of **1a** with aryl bromomethyl ketones[6] followed by Wittig olefination. Pyridyl substituted enyne **2f** was obtained by Mitsunobu reaction of **1a** with 2-pyridyl-2-propenol[7] in the presence of TMAD.[8]

With enynes in hand, intramolecular Pauson-Khand reaction of *exo*-enynes **2a–g** was performed by following methods after treatment with $Co_2(CO)_8$; reaction with 9–12 equivalents of NMO (*N*-methylmorpholine *N*-oxide)[9a] in CH_2Cl_2 at r.t. (Method A); refluxing in toluene (Method B); heated at 83 °C with BuSMe in 1,2-dichloroethane (Method C).[9b] The results are shown in Table 1. The reaction of α-styryl type enynes **2a,b** gave corresponding bicyclic cyclopentenones **3a,b**[4] in good yields (entries 1–6) by Methods A–C. Similar reaction of naphthyl compound **2c** afforded cyclized product **3c** in moderate yields by Methods B and C (entries 8,9). However, Method A resulted in a low yield. It can be explained by considering that bulky naphthyl group in **2c** would interfere proximity of alkyne-cobalt moiety and olefinic part owing to low reaction temperature (entry 7). Reaction of other enynes **2d–f** bearing heterocycles such as furan, thiophene and pyridine also smoothly proceeded to furnish bicyclic compounds **3d–f** in moderate to good yields (entries 10–18). For the reaction of malonates **2a–f**, it was found that thermal conditions (Methods B and C) were superior to oxidative condition (Method A). On the other hand, the reaction of tosylamide **2g** gave cyclized product **3g**, the yield of which was similar regardless of the methods employed (entries 19–21).



Scheme 2. Reagents and conditions: a) NaH, $ArC(=CH_2)CH_2I$, DMF, r.t.; b) NaH, $ArC(=O)CH_2Br$, DMF, r.t.; c) PPh_3MeBr, *t*-BuOK, THF, r.t.; d) $2\text{-}PyC(=CH_2)CH_2OH$, TMAD, Bu_3P, benzene, r.t.; e) Pauson-Khand reaction (see Table 1); f) $PhC(=CH_2)CH_2I$, K_2CO_3, DMF, 0 °C to r.t.

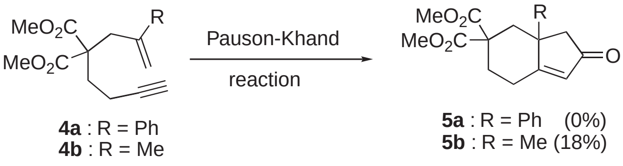
Copyright © 2002 The Chemical Society of Japan

Table 1. Pauson-Khand reaction of *exo*-enynes (**2a–g**)

Entry	Substrate	Method[a]	Time/h	Product	Yield/%
1	**2a**	A	2	**3a**	56
2	**2a**	B	8	**3a**	70
3	**2a**	C	10	**3a**	73
4	**2b**	A	2	**3b**	40
5	**2b**	B	8	**3b**	62
6	**2b**	C	10	**3b**	66
7	**2c**	A	2	**3c**	4
8	**2c**	B	8	**3c**	57
9	**2c**	C	8	**3c**	48
10	**2d**	A	2.5	**3d**	66
11	**2d**	B	5	**3d**	70
12	**2d**	C	12	**3d**	79
13	**2e**	A	2	**3e**	49
14	**2e**	B	5	**3e**	62
15	**2e**	C	10	**3e**	66
16	**2f**	A	2	**3f**	45
17	**2f**	B	2	**3f**	46
18	**2f**	C	3	**3f**	51
19	**2g**	A	2	**3g**	61
20	**2g**	B	8	**3g**	60
21	**2g**	C	10	**3g**	64

a) Method A; reaction with 9–12 equivalents of NMO at r.t. in CH_2Cl_2. Method B; refluxing in toluene. Method C; heated at 83 °C with BuSMe in 1,2-dichloroethane.

Next, we examined the reaction of homologue **4a**[4] of **2a**, because there were no reports on the reaction of *acyclic* 1,7-enynes bearing *exo*-methylene group.[10] Unfortunately, the reaction of **4a** by Methods A–C failed to give desired cyclopentenone **5a**. To examine effect of aromatic group, similar reaction of methyl derivative **4b** was performed to furnish **5b** in 18% yield only by Method B. Since many successful reports on the Pauson-Khand reaction of 1,7-enynes bearing *endo*-olefin have appeared,[1] further studies concerning with *acyclic* 1,7-enynes having *exo*-methylene group are in progress.



Scheme 3.

In summary, we have investigated intramolecular Pauson-Khand reaction of various *acyclic exo*-1,6- and 1,7-enynes **2a–g** and **4a,b**. The present method provides convenient approach to bicyclic cyclopentenones **3a–g** having aromatic substituents at quaternary carbon center.

References and Notes

1 For reviews, a) K. M. Brummond and J. L. Kent, *Tetrahedron*, **56**, 3263 (2000). b) A. J. Fletcher and S. D. R. Christie, *J. Chem. Soc.*, *Perkin Trans. 1*, **2000**, 1657. c) Y. K. Chung, *Coord. Chem. Rev.*, **188**, 297 (1999).

2 a) M. Ishizaki, K. Iwahara, K. Kyoumura, and O. Hoshino, *Synlett*, **1999**, 587. b) M. Ishizaki, K. Iwahara, Y. Niimi, H. Satoh, and O. Hoshino, *Tetrahedron*, **57**, 2729 (2001). c) M. Ishizaki, Y. Niimi, and O. Hoshino, *Chem. Lett.*, **2001**, 546. d) M. Ishizaki, Y. Kasama, M. Zyo, Y. Niimi, and O. Hoshino, *Heterocycles*, **55**, 1439 (2001).

3 a) M. E. Krafft, L. V. R. Bonaga, and C. Hirosawa, *J. Org. Chem.*, **66**, 3004 (2001). b) K. Hiroi, T. Watanabe, R. Kawagishi, and I. Abe, *Tetrahedron: Asymmetry*, **11**, 797 (2000). c) M. E. Krafft, C. Hirosawa, and L. V. R. Bonaga, *Tetrahedron Lett.*, **40**, 9177 (1999). d) M. E. Krafft, L. V. R. Bonaga, and C. Hirosawa, *Tetrahedron Lett.*, **40**, 9171 (1999). e) T. Sugihara and M. Yamaguchi, *Synlett*, **1998**, 1384. f) D. B. Belanger, D. J. R. O'Mahony, and T. Livinghouse, *Tetrahedron Lett.*, **39**, 7637 (1998). g) D. B. Belanger and T. Livinghouse, *Tetrahedron Lett.*, **39**, 7641 (1998). h) N. Jeong, Y. K. Chung, B. Y. Lee, S. H. Lee, and S.-E. Yoo, *Synlett*, **1991**, 204. i) N. Jeong, S. H. Hwang, Y. Lee, and Y. K. Chung, *J. Am. Chem. Soc.*, **116**, 3159 (1994).

4 All new compounds gave satisfactory ^1H NMR, IR, and mass spectral data.

5 W. Cabri, I. Candiani, and A. Bedeschi, *J. Org. Chem.*, **57**, 3558 (1992).

6 S. Kajigaeshi, T. Kakinami, T. Okamoto, and S. Fujisaki, *Bull. Chem. Soc. Jpn.*, **60**, 1159 (1987).

7 R. M. Moriarty, M. P. Duncan, and O. Prakash, *J. Chem. Soc.*, *Perkin Trans. 1*, **1987**, 1781.

8 T. Tsunoda, J. Otsuka, Y. Yamamiya, and S. Ito, *Chem. Lett.*, **1994**, 539.

9 a) S. Shambayati, W. E. Crowe, and S. L. Schreiber, *Tetrahedron Lett.*, **31**, 5289 (1990). b) T. Sugihara, M. Yamada, M. Yamaguchi, and M. Nishizawa, *Synlett*, **1999**, 771.

10 Motherwell et al. and the authors reported intramolecular Pauson-Khand reaction of *exo*-cyclic 1,7-enynes, containing cyclopropane[11] and cyclohexane.[2b]

11 H. Corlay, E. Fouquet, E. Magnier, and W. B. Motherwell, *J. Chem. Soc.*, *Chem. Commun.*, **1999**, 183.