Pergamon

Tetrahedron Letters, Vol. 36, No. 6, pp. 943-946, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(94)02379-4

Internal Activation of Acrylate-Type Dienophiles in Diels-Alder Reactions

Toshiyuki Kan and Yasufumi Ohfune*

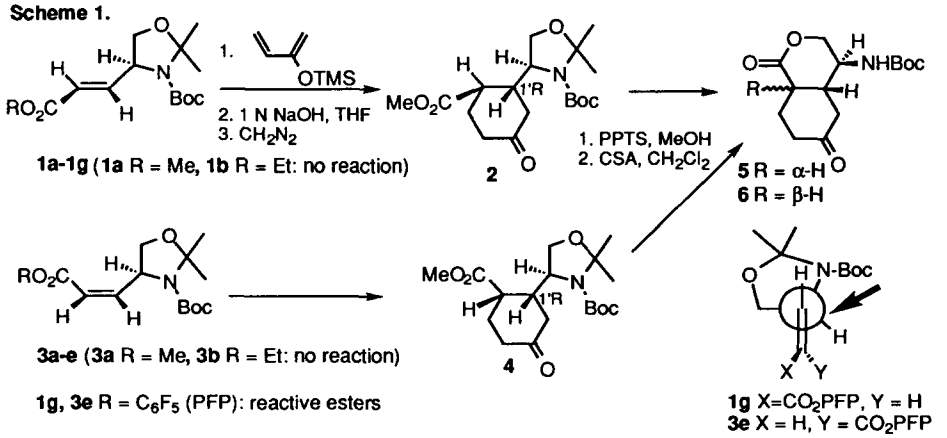
Suntory Institute for Bioorganic Research, Shimamoto-cho, Osaka 618, Japan

Abstract Diels-Alder reactions of less reactive acrylate-type dienophiles with dienes were achieved by replacing its ester counterpart to a pentafluorophenyl group, which remarkably enhanced the reactivity of the dienophiles to give the corresponding cycloadducts in excellent yields with a high stereoselectivity.

The methyl or ethyl (2*E*) and (2*Z*)-acrylate derivatives, **1a,b** and **3a,b**, have been employed as useful chiral synthons for the syntheses of various unusual amino acids.[1] It was considered that [n+2]-type cycloaddition to these acrylate derivatives would provide potential synthetic values for the construction of carbocycles possessing a chiral amino acid residue.[2] However, the Diels-Alder reactions of **1a,b** and **3a,b** with dienes such as 2-trimethylsilyoxybutadiene were not successful and resulted in the recovery (160 °C) or decomposition (180 °C) of the starting materials. Their poor reactivities to the diene were considered to be due to steric and/or stereoelectronic reasons with regard to the dienophiles. To this problem, this paper describes an efficient solution that an electronegative ester counterpart introduced into the acrylate-type dienophiles remarkably accelerated the rate of the Diels-Alder reactions giving rise to the desired cycloadducts **2** and **4**.

Our initial attempts to enhance the reactivity of the dienophile were the use of a Lewis acid catalyst.[3] However, the reaction of **1a** with 2-trimethylsilyloxybutadiene in the presence of a catalytic amount of

Scheme 1.



$Eu(fod)_3$ at 100 °C resulted in a complete recovery of **1a**. At more than 130 °C, the diene was decomposed.

Examined next were the Diels-Alder reactions employing the acrylate **1g** possessing an electronegative pentafluorophenyl (PFP) group[4] which was expected to activate the electron deficient C-C double bond of the dienophile. The [4+2]-cycloaddition of the PFP ester **1g** with 2-trimethylsilyloxybutadiene proceeded smoothly at 130 °C to give the desired cycloadduct. The yield was 84% after conversion to the corresponding methyl ester **2**.[5] It is noted that the product was composed of a single diastereomer whose stereochemistry was ascertained as depicted in Scheme 1 by the ^1H NMR studies of the corresponding lactone **5**.[6] Among the other electronegative ester counterparts such as 2,2,2-trifluoroethyl and p-nitrophenyl groups, the PFP group was the most effective one in view of its yields and stereoselectivity (Table 1). In the case of the (2*Z*)-acrylate derivatives **3a-e**, the PFP ester **3e** also gave the desired cycloadduct **4** in good yield.[6]

Table 1. Diels-Alder reactions of **1** and **3** with 2-trimethylsilyloxy-1,3-butadiene[a].

Dienophile		Yield (%)[b]	Product (1'R : 1' S)	Temperature (°C)
1a,b	R = Me, Et	no reaction	——	160
1a,b	R = Me, Et	decomp	——	180
1c	R = CH_2CF_3	47[c]	**2** (75 : 25)	130
1d	R = $CH(CF_3)_2$	71[c]	**2** (100 : 0)	130
1e	R = C_6H_5	no reaction	——	130
1f	R = p-NO_2-C_6H_4	52[c]	**2** (100 : 0)	130
1g	R = C_6F_5 (PFP)	84	**2** (100 : 0)	130
3a,b	R = Me, Et	no reaction	——	130
3c	R = CH_2CF_3	no reaction	——	130
3d	R = $CH(CF_3)_2$	12[c]	**4** (100 : 0)	130
3e	R = C_6F_5 (PFP)	54[c]	**4** (100 : 0)	130

[a]All reactions were performed in toluene for 3 days using a sealed tube. [b]The yields were isolated yields as the corresponding methyl esters (ref 5). [c]Starting material was recovered as the methyl ester **1a** or **3a** (from the reaction of **1c**, 34% of **1a** was recovered; **1d**, 20%; **1f**, 36%; **3d**, 71%; **3e**, 22%).

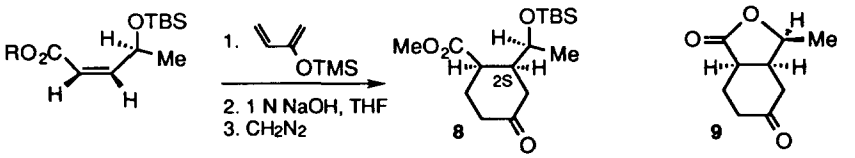
As an additional example, the methyl acrylate derivative **7a**[7] did not react with 2-trimethylsilyloxybutadiene even at 130 °C for 5 days and the starting material was completely recovered. However, the reaction of its PFP ester **7b** underwent stereoselective cycloaddtion to give in 94 % yield the cycloadduct **8**[6] (2*S*-**8** : 2*R* isomer = 93 : 7). Thus, the PFP group was found to activate the dienophiles which did not react with 2-trimethylsilyloxybutadiene. The exclusive formation of the 1'*R* cycloadducts **2** and **4** and the 2*S* adduct **8** can be explained by the attack of the diene from the less hindered side of the dienophiles (Scheme 1).[8]

Inspection of the ^{13}C NMR spectral data of the PFP derivative **1g** revealed that its C2 carbon signal appeared at higher field (118.8 ppm) and the C3 carbon shifted to lower field (151.0 ppm) than those of the unreactive phenyl derivative **1e** (C2, 125.9 and C3, 148.0 ppm), respectively. These data suggest that the electronegative ester counterpart strongly activates its electron deficient C-C double bond.

The reaction profiles of the methyl esters **1a** and **3a** and the PFP derivatives **1g** and **3e** with other dienes were summarized in Table 2. In the case of the PFP derivatives, remarkable rate enhancement was observed

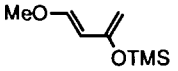
and the correponding cycloadducts were obtained in good yields, while the methyl esters did not react except with cyclopentadiene.

Scheme 2.

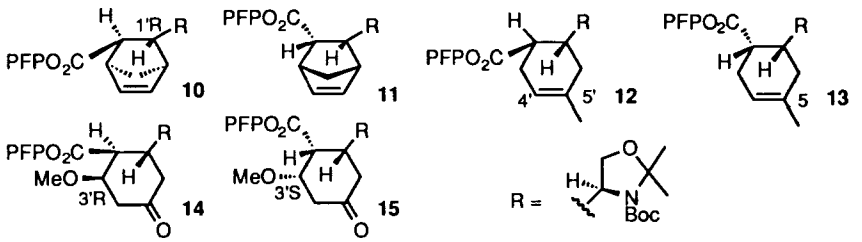


7a R = Me (130 °C, 5 days; no reaction)
7b R = PFP (130 °C, 5 days; 94% yield; 2S-**8** : 2R-**8** = 93 : 7)

Table 2. Reaction profiles of the acrylates **1a**, **1g**, **3a**, **3e** with several dienes.[a]

Dienes	**1a** (2*E* Me ester)	**1g** (2*E* PFP ester)	**3a** (2*Z* Me ester)	**3e** (2*Z* PFP ester)
	130 °C, 3days Me ester of **10**, 46% yield 3 : 3 : 1 : 1[b]	r.t., 3days **10**, 77% yield 5 : 3 : 1 : 1[b]	130 °C, 3days no reaction	50 °C, 3days **11**, 71% yield 40 : 4 : 3 : 1[b]
	130 °C, 5days no reaction	130 °C, 3days **12**, 79% yield 3 : 2[c,d]	130 °C, 5days no reaction	130 °C, 5days **13**, 68% yield 3 : 2[c,d]
	130 °C, 5days no reaction	80 °C, 5days **14**, 84% yield 2.5 : 1[d,e]	130 °C, 5days no reaction	80 °C, 5days **15**, 67% yield 3 : 1[d,f]

[a]All reactions were carried out in toluene using a sealed tube.The products were isolated as a mixture of the PFP esters. The yields were isolated yields as a mixture of cycloadducts.The products ratio was determined by ^{1}H NMR. [b]The products were a mixture of the 1'R/1'S and endo/exo isomers (1'R-endo : 1'R-exo : 1'S-endo : 1'S-exo). [c]The products were a mixture of **12** and its 4'-Me regioisomer. [d]None of the 1'S isomers were detected. [e]The products were a mixture of **14** and its 3'S isomer. [f]The products were a mixture of **15** and its 3'R isomer.



Thus, the PFP group was proven to be an excellent ester counterpart of acrylate-type dienophiles for the Diels-Alder reactions. In particular, this method would be useful when dienes and/or dienophiles are labile under high temperature or to Lewis acid catalysts. Studies regarding the conversion of the resulting cycloadducts into the conformationally restricted glutamate analogs[9] as well as an extension of the present findings for further applications are in progress.

Acknowlegement: We thank New Energy and Industrial Technology Development Organization (NEDO), Ministry of International Trade and Industry, Japan, for financial support.

References and Notes

1. Ohfune, Y. *Acc. Chem. Res.* **1992**, *25*, 360.
2. For a [3+2] cycloaddition, see: Raghavan, S.; Ishida, M.; Shinozaki, H.; Nakanishi, K.; Ohfune, Y. *Tetrahedron Lett.* **34**, 5765 (1993).
3. Oppolzer, W. *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 315-399, and references cited therein.
4. Prepared from **1a** in two steps; (1) 1 *N* NaOH, THF, 0 °C, 4 h, then room temperature, 10 h; (2) pentafluorophenol, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide-HCl, CH_2Cl_2, 0 °C, 1 h; 93% overall yield. The PFP esters, **3e** (88%) and **7b** (95%), were prepared from **3a** and **7a** in a manner similar to the preparation of **1g**.
5. Due to a difficulty to isolated the PFP cycloadducts from the reaction mixture containing polymeric dienes, the cycloadducts from **1g**, **3e**, and **7b** were obtained as the corresponding methyl esters **2**, **4**, and **8** by successive treatments with (1) 1 *N* NaOH and (2) CH_2N_2. No racemization during all synthetic processes was ascertaind by converting the prepared or recovered PFP esters **1g**, **3e**, and **7b** to their corresponding methyl esters whose $[\alpha]_D$ values were in accord with the authentic samples.
6. The structures of these compounds were fully characterized by the ^1H NMR data and COSY and NOESY experiments of the corresponding lactones **5**, **6**, and **9**. Their spectroscopic data and physical constants were as follows. **5**: mp 170.5-171.0 °C; $[\alpha]_D$ -23.1° (*c* 0.63, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9 H), 1.78 (dddd, 1 H, *J* = 4.5, 12.5, 14.0, 14.0 Hz), 1.92 (dddd, 1 H, *J* = 4.0, 8.1, 14.1, 14.1 Hz), 2.34 (dd, 1 H, *J* = 14.1, 14.1 Hz), 2.38 (ddd, 1 H, *J* = 6.5, 14.0, 14.0 Hz), 2.53 (ddd, 1 H, *J* = 2.1, 2.4, 6.5 Hz), 2.55-2.65 (m, 2 H), 2.76 (ddd, 1 H, *J* = 2.3, 4.0, 14. 1 Hz), 3.94 (m, 1 H), 4.12 (dd, 1 H, *J* = 5.7, 11.7 Hz), 4.48 (dd, 1 H, *J* = 4.8, 11.7 Hz), 4.74 (br d, 1 H, *J* = 8.9 Hz). **6**: mp 157.5-158.0 °C; $[\alpha]_D$ +19.2° (*c* 0.53, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9 H), 1.92 (dddd, 1 H, *J* = 5.0, 5.0, 11.5, 15.0 Hz), 2.24 (dd, 1 H, *J* = 15.0, 15.0 Hz), 2.32 (dddd, 1 H, *J* = 1.5, 4.5, 4.5, 15.0 Hz), 2.51-2.67 (m, 3 H), 3.17 (m, 1 H), 3.59 (dddd, 1 H, *J* = 5.7, 7.2, 11.5, 12.5 Hz), 4.29 (br dd, 1 H, *J* = 11.5, 11.5 Hz), 4.46 (dd, 1 H, *J* = 5.7, 11.5 Hz), 4.83 (d, 1 H, *J* = 7.2 Hz). **9**: oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (d, 3 H, *J* = 6.4 Hz), 2.12 (m, 1 H), 2.26 (dd, 1 H, *J* = 11.5, 14.0 Hz), 2.35 (dd, 1 H, *J* = 6.5, 14.0 Hz), 2.25-2.50 (m, 3 H), 2.87 (dddd, 1 H, *J* = 4.6, 6.5, 6.5, 11.5 Hz), 2.99 (ddd, 1 H, *J* = 3.5, 6.5, 6.5 Hz), 4.65 (dq, 1 H, *J* = 4.6, 6.4 Hz).
7. Kan, T.; Hosokawa, S.; Nara, S.; Oikawa, M.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 5532.
8. It could not be determined whether the reaction proceeded through the steric model (in Sceme 1) or a Felkin-Anh model, because both models gave the same 1'*R* adduct as the preferential isomer.
9. (a) Shimamoto, K.; Ishida, M.; Shinozaki, H.; Ohfune, Y. *J. Org. Chem.* **56**, 4167 (1991). (b) Ohfune, Y.; Shinozaki, H. *Drug Design for Neuroscience*; Kozikowski, A. P., Ed.; Raven Press: New York, 1993; p 261.

(*Received in Japan* 14 *October* 1994; *accepted* 30 *November* 1994)