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STEREOSELECTIVE SYNTHESIS OF 3a,4,5,7a-TETRAHYDRO-5,7a-ETHANOPHTHALIDE DERIVATIVES USING SUCCESSIVE INTRA- AND INTERMOLECULAR DIELS-ALDER REACTIONS

Michihiko NOGUCHI,* Shinji KAKIMOTO, and Shoji KAJIGAESHI
Department of Industrial Chemistry, Faculty of Engineering,
Yamaguchi University, Tokiwadai, Ube 755

Some 2-pyrone-6-carboxylic acid esters bearing appropriate dienophiles at ester moieties underwent the intramolecular Diels-Alder reaction followed by the extrusion of carbon dioxide to give 3a,4-dihydrophthalide derivatives. The dihydrophthalides added to the second dienophiles intermolecularly to give 3a,4,5,7a-tetrahydro-5,7a-ethanophthalide derivatives. The stereoselectivity of the 5,7a-ethanophthalides was liable for the two successive reactions.

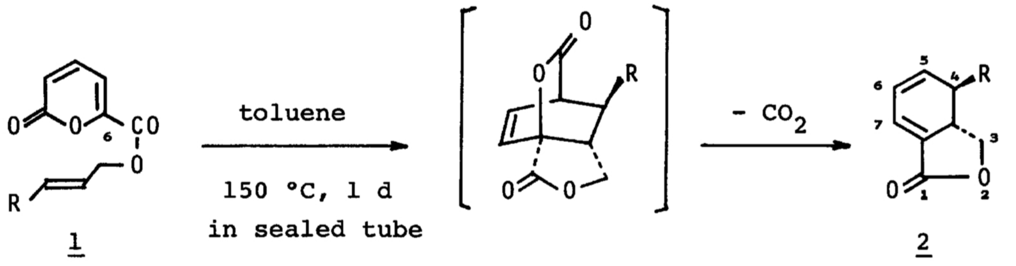
Recent studies on the intramolecular cycloaddition reactions have significantly advanced the synthetic methodologies for the polycyclic compounds.1) Among them, the successive inter- and intramolecular reactions such as Domino2) and Tandem3) Diels-Alder reaction are attracted as the potentiality to construct the stereochemically interesting polycycles.

Now, in the course of our study on the intramolecular cycloaddition reactions our attention has been focused on the reaction of 2-pyrones, which behave as 4 pi addenda in the reaction with 2 or 6 pi components. Moreover, the subsequent pericyclic decarboxylation from the initially formed [4+2] or [4+6] cycloadducts regenerates a diene moiety, which appears to constitute an attractive tool for the synthesis of polycycles.4)

In this communication we wish to report the utilities and limitation of the successive cycloaddition reactions involving the "diene-regenerable" Diels-Alder reaction of 2-pyrone for the stereoselective synthesis of tricyclic systems.

Herein, 2-pyrones bearing appropriate dienophiles at 6-position underwent the intramolecular Diels-Alder reaction accompanied with the extrusion of carbon dioxide to afford the condensed 1,3-cyclohexadiene derivatives, which added to the second dienophiles to give the tricyclic products.

Three 2-pyrone-6-carboxylix acid esters 1a-1c5) were examined to cyclize to the 3a,4-dihydrophthalide derivatives 2a-2c as shown in the scheme. The structural elucidation of 2 was accomplished on the basis of the spectral data (Tables 1 and 2). Especially, in the ^{1}H NMR spectrum of 2a the pronounced large coupling constants (J= 18.5 and 9.8 Hz) between 3a-H and the methylene protons at 4-position were assigned to trans and cis configurations, respectively.7) Also, from the coupling constants between the vicinal protons, 3a-H and 4-H, (J= 12.5 and 18.5 Hz) in dihydrophthalides 2b and 2c, the configurations between the two protons were concluded to be trans in both cases. Predictively, the intramolecular



1

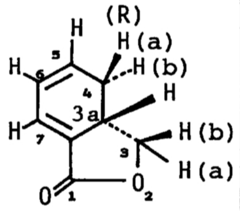
2

(Y. 66-72%)

Table 1. 3a,4-Dihydrophthalides 2

		Mp	IR	M^+	^{13}C NMR ($CDCl_3$) δ(ppm)							
	R	°C	ν_{CO}/cm^{-1}	m/e	3-C	3a-C	4-C	5-, 6-, and 7-C			7a-C	1-C
a	H	62-63	1750	136	73.1	32.6	26.9	125.0	129.1	131.8	125.6	169.8
b	CO_2Me	51-52	1770	194	74.5	33.5	41.9	123.5	125.7	132.0	125.9	161.5
c	Ph	66-67	1750	212	72.5	40.8	47.0	125.5	129.8	137.2	126.0	169.5

Table 2. ^1H NMR Spectral Data of Dihydrophthalides 2



2a

Compd[a)]	δ(ppm) 3-H(a)	3-H(b)	3a-H	4-H(a)	4-H(b)	5-H	6-H	7-H
2a	4.72 t	3.91 t	3.11 tdddd	2.57 ddd	2.08 dddd	6.19 dddd	6.26 ddd	6.95 dd
R= H	J (Hz) 3(a),3(b)= 3(a),3a= 3(b), 3a= 9.1, 3a,4(a)= 9.8, 3a,4(b)= 18.5, 3a,5= 1.8, 3a,7= 3.2, 4(a),4(b)= 16.8 4(a),5=5.7, 4(b),5= 2.6, 4(b),6= 2.8, 5,6= 9.6, 6,7= 4.5							
2b R=CO_2Me	4.75 t	4.00 t	3.78 m	——	3.58 ddd	6.02 ddd	6.25 ddd	7.10 d
2c R= Ph	4.45 t	4.00 t	3.25 tddd	——	3.60 ddd	6.15 dddd	6.37 ddd	7.03 dd

a) Measured in $CDCl_3$.

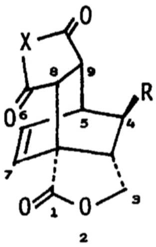
Diels-Alder reaction proceeded with the retention of the stereochemistry on the dienophile moiety.

Now, the subsequent intermolecular Diels-Alder reaction of 2 with some 2 pi dienophiles was done immediately because 2 were not so stable.[8)]

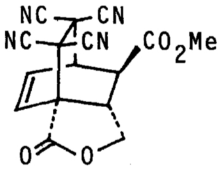
When an equimolar mixture of 2a and N-phenylmaleimide (NPMI) was heated under reflux in xylene for 20 h, the 3a,4,5,7a-tetrahydro-5,7aethanophthalide derivative 3a was obtained in 58% yield as a sole adduct. Similarly, the reaction of 2a and 2b with NPMI, maleic anhydride, and/or tetracyanoethylene gave the corresponding adducts 3, 4, and 5(Table 3).

The common structural framework for the cycloadducts 3-5 was suggested because the signal patterns of protons at 5, 6, and 7-position were almost identical in those ^{1}H NMR spectra. Further structural confirmation was accomplished by the elaborate analysis of the adjacent four (or three) protons at 3a, 4, and 5-position in 3 and 4 using double resonance techniques and Dreiding models as well as IR and ^{13}C NMR spectral data.[9] Finally, since the difference in chemical shift of two methine protons, 8-H and 9-H, was relatively small ($\Delta\delta$= 0.1-0.2 ppm), the exo configuration for these protons was plausible in consideration of the deshielding effect[10] by lactone carbonyl moiety. These results were shown in Table 4.

Table 3. Cycloadducts from Dihydrophthalides 2 and Olefinic Dienophiles

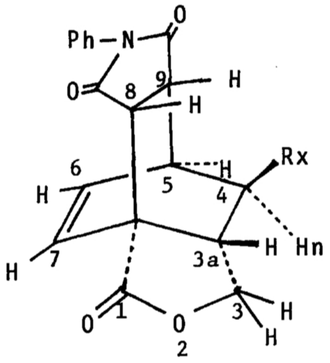


Compd	X	R	Yield %	Mp °C
3a	N-Ph	H	58	210-213
3b	N-Ph	CO_2Me	80	232-235
4a	O	H	62	222-224
4b	O	CO_2Me	62	234-236



5 (Y. 65%)
Mp 185-188 °C

Table 4. ^{1}H NMR Spectral Data of Cycloadducts 3



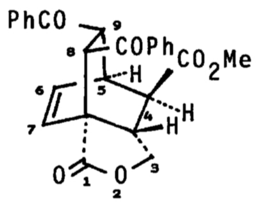
Compd[a)]	δ (ppm) 3a-H	4-Hn	4-Hx	5-H	9-H	8-H
3a	2.32 m	1.47 ddd	1.65 ddd	3.4 b)	3.4 b)	3.52 d
R= H	J (Hz) 3a,4n= 9.2, 3a,4x= 14.2, 4n,4x= 15.0, 4n,5= 1.5, 4x,5= 5.8					
3b	3.21 ddd	3.32 dd	——	3.4 b)	3.5 b)	3.70 d
R=CO_2Me	J (Hz) 3s,4= 9.2 (trans) 4,5= 2.8 (4-H; endo)					

a) Measured in Polysol®. b) Overlapped one another.

These structural assignment revealed that the second Diels-Alder reaction occurred in a specific manner, i.e., the attack of dienophile to 2 took place from the side of the substituent (R). Probably, the transition state leading to trans fused lactone (not obtained) should be less favorable than that leading to cis fused one (3, 4, or 5) owing to the ring distortion. Also, in the reaction with cis olefinic dienophile the orientation of addition was an endo approarch.

Herein, it should be emphasized that the stereochemistry at 3a-position in dihydrophthalides 2 resulted from the initial intramolecular Diels-Alder reaction of 2-pyrones 1 caused that of the second intermolecular one. Thus, the stereoselectivity of the final product depends upon the two successive reactions.

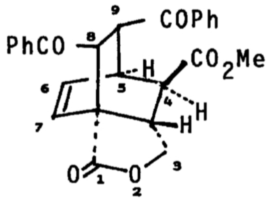
On the other hand, in the reaction of 2b with trans-1,2-dibenzoylethylene two



6

(Mp 113-116 °C)

δ(ppm)
CH_3; 3.68
3a-H; 3.3
8-H; 4.83
9-H; 3.60
J (Hz)
3a,4= 9.6 (trans)
4,5= 2.9 (4-H;endo)



7

(Mp 192-194 °C)

δ(ppm)
CH_3; 3.17
3a-H; 3.6
8-H; 4.56
9-H; 4.16
J (Hz)
3a,4= 9.8 (trans)
4,5= 2.9 (4-H;endo)

diastereoisomers, 6 and 7, were obtained as 1:1 mixture in a total yield of 66%.

However, under similar conditions the dihydrophthalide 2b did not react with the dienophiles bearing only one electron-withdrawing group such as ethyl acrylate and phenylvinylsulfoxide.

As mentioned above, the cycloaddition reaction of the condensed 1,3-cyclohexadiene derivatives, which were accessible by the intramolecular "diene-regenerable" Diels-Alder reaction of 2-pyrones, would develop the stereoselective preparation of polycycles as a new synthetic tool.

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5) Esters 1 were prepared from 2-pyrone-6-carboxylic acid and the corresponding allyl halides in the presence of DBU according to the reported method.6) All new compounds in this paper gave satisfactory elemental analyses.
6) N. Ono, T. Yamada, T. Saito, K. Tanaka, and A. Kaji, Bull. Chem. Soc. Jpn., 51, 2401 (1978).
7) To our knowledge other examples on such large coupling constant between vicinal protons have not been found. However, the assignment shown for 2 was established by a careful analysis (including decoupling) of their 200-MHz ^{1}H NMR spectra.
8) On allowing to stand at room temperature for three weeks even in crystalline form the dimerization of 2 and aromatization to phthalides were observed.
9) 3b; IR(KBr): ν_{CO} 1770, 1740, 1705 cm^{-1}; ^{13}C NMR(DMSO-d_6): δ(ppm) 35.7, 43.7, 44.5, 47.0, 49.8, 53.8, 69.9, 127.9, 130.1, 131.1, 133.3, 172.4, 176.3, 177.2, 177.8.
10) In ^{1}H NMR spectra of 6 and 7, the methine proton at 8-position appeared in lower field than that at 9-position in each case. Moreover, the endo proton at 8-position in 6 was observed in lower field than the exo one in 7.

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