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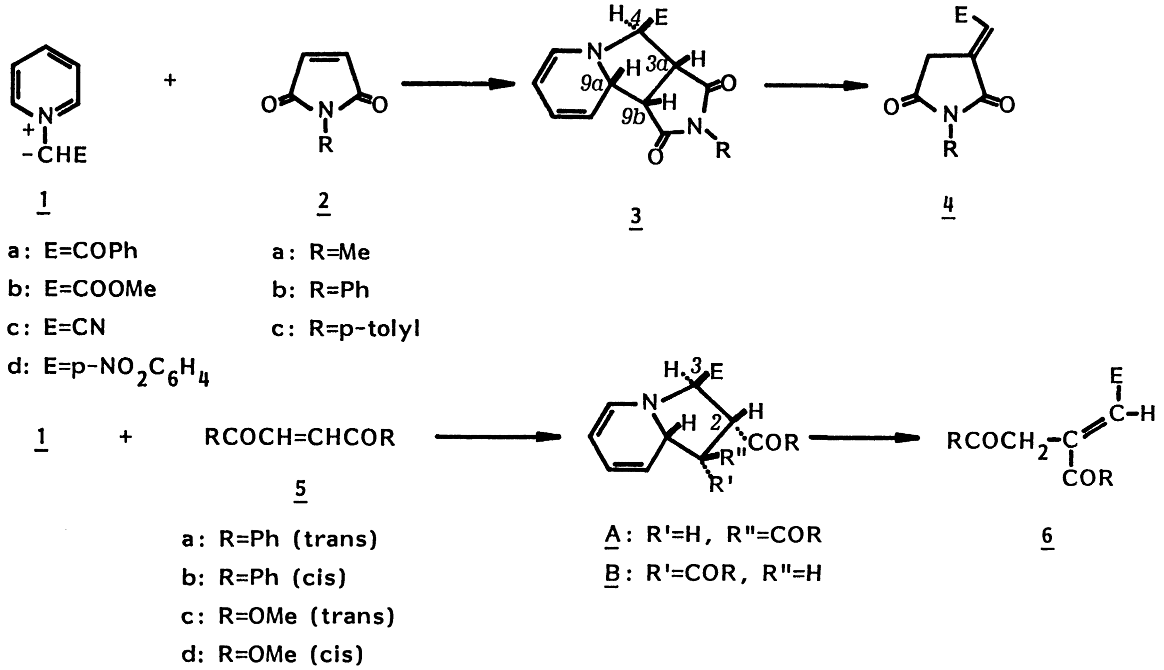
STEREOSELECTIVE HYDROALKYLIDENATION OF OLEFIN WITH PYRIDINIUM METHYLIDES

Otohiko TSUGE,* Shuji KANEMASA, Shigeori TAKENAKA, and Satoru KURAOKA
Research Institute of Industrial Science, and Department
of Molecular Science and Technology, Interdisciplinary
Graduate School of Engineering Sciences, Kyushu University,
Kasugakoen, Kasuga 816

Acid-catalyzed elimination of pyridine from the stereoselective [3+2] cycloadducts between electron-deficient olefins and pyridinium methylides with ylide-stabilizing substituents offers a new type of C-C bond formation.

Hydromethylenation of olefin, first discovered in reactions between nonstabilized pyridinium methylides and olefinic dipolarophiles, is not only a new reaction type of N-ylide but also a new functional group interconversion.$^{1)}$ It has been suggested this reaction involves the formation of intermediary cycloadducts. On the other hand, the similar reactions of stabilized pyridinium methylides gave the stereoselective [3+2] cycloadducts as rather stable products, where no pyridine elimination occurred.$^{2)}$ A new general strategy will be opened if the cycloadducts successfully eliminate pyridine, as the stabilized methylides are more readily available than the parent ones.

This communication presents the first example of stereoselective hydroalkylid-



Scheme 1.

enation of olefin with stabilized pyridinium methylides.

The reaction of pyridinium phenacylide 1a with N-methylmaleimide 2a formed a quantitative yield of endo [3+2] cycloadduct 3a (E=COPh, R=Me) which was then passed through a silica gel column (Wako gel C300) to give a pyridine-eliminated 1:1 adduct 4a (Scheme 1 and Table 1). The structure of 4a was assigned as E-3-(benzoylmethylene)-1-methyl-2,5-pyrrolidinedione on the ground of the spectral data as well as the elemental analysis.3) Its E geometry was confirmed by the comparison of chemical shifts of the 4-methylene doublet (3.76 ppm) and 6-olefin triplet (7.83 ppm) with those of 1-(p-tolyl)itaconimide (the 4-methylene triplet at 3.47 ppm and two 6-terminal olefin triplets at 5.70 and 6.43 ppm).

Elimination of pyridine also took place when 3a was treated with a catalytic amount of acetic acid or when heated in ethanol, but with lower yields of 4a. Heating 3a in aprotic solvents such as benzene and chloroform resulted in the decomposition into a complex mixture of products, from which no 4a was isolated.

Under similar conditions, a variety of pyridinium methylides with electron-withdrawing substituents reacted with several maleimides to give E-itaconimides, some of which were listed in Table 1.

Table 1. Hydroalkylidenation of Olefins with Pyridinium Methylides

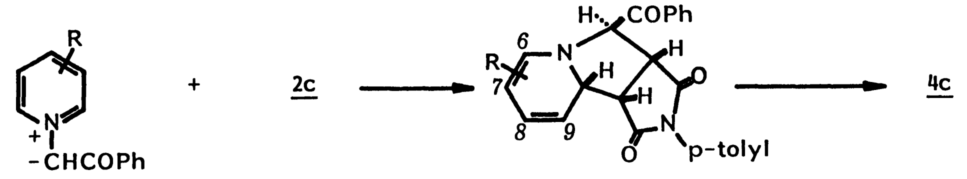
Product			Ylide	Olefin	Yield$^{a)}$	Mp or Bp	^{1}H-NMR$^{b)}$			MS (M$^+$)
	E	R			%	°C	CH$_2$^{d}	=CH^t	J	m/e
4a	COPh	Me	1a	2a	86	144	3.76	7.83	3.0	229
4b	COPh	Ph	1a	2b	85	176	3.93	7.37	3.0	291
4c	COPh	p-tolyl	1a	2c	82	180-181	3.92	7.94	2.8	305
4d	COOMe	p-tolyl	1b	2c	87	146-147	3.80	6.86	3.0	259
4e	CN	p-tolyl	1c	2c	51	147	3.66	6.43	3.0	226
4f	p-NO$_2$C$_6$H$_4$	p-tolyl	1d	2c	58	220-221	3.72	7.61	2.6	322
6a	COPh	Ph	1a	5a, 5b	$100^{c)}$, $61^{d)}$	125-127	4.88	e)	0.8	354
6b	CN	OMe	1c	5c, 5d	$65^{f)}$, $50^{g)}$	135/0.1 mmHg	3.66^s	6.48^s	0	183

a) Isolated yield based on the olefin. b) Measured in deuteriochloroform (δ ppm, Hz). c) From 5a. d) From 5b. e) Hidden in aromatic signals. f) From 5c. g) From 5d.

Since this reaction seems useful as hydroalkylidenation of olefin, some more reactions with acyclic olefins were investigated. Both reactions of 1a with trans-5a and cis-dibenzoylethene 5b provided a single product 6a (Scheme 1 and Table 1). The structure of 6a, that had been incorrectly assigned as a dihydrofuran,4) was determined as E-1,2,3-tribenzoylpropene on the basis of the spectral data as well as its chemical conversion.5) Based on the reaction mechanism discussed later, the formation of single isomer 6a indicates that each stereoselective reaction with 5a and 5b formed isomeric cycloadducts A and B, respectively, which both carry the benzoyl substituent at the 2-endo position.

Similar reactions of pyridinium cyanomethylide 1c with dimethyl fumarate 5c and maleate 5d gave again only the E isomer of dimethyl cyanoitaconate 6b.

Pyridinium phenacylides 7a-7g with a variety of substituents on the pyridine



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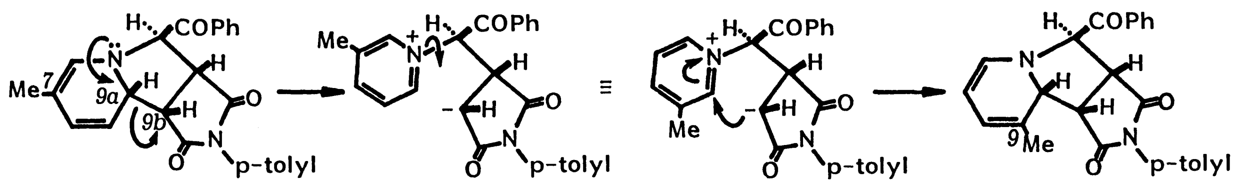
a: R=2-Me
b: R=3-Me
c: R=4-Me
d: R=3,5-diMe
e: R=4-CN
f: R=3-CF_3
g: R=3-COOMe

8a: R=6-Me
8b: R=7-Me
8b': R=9-Me
8c: R=8-Me
8d: R=7,9-diMe
8e: R=8-CN
8f: R=7-CF_3
8f': R=9-CF_3
8g: R=7-COOMe
8g': R=9-COOMe



8b (7-Me) C 8b' (9-Me)

Scheme 2.

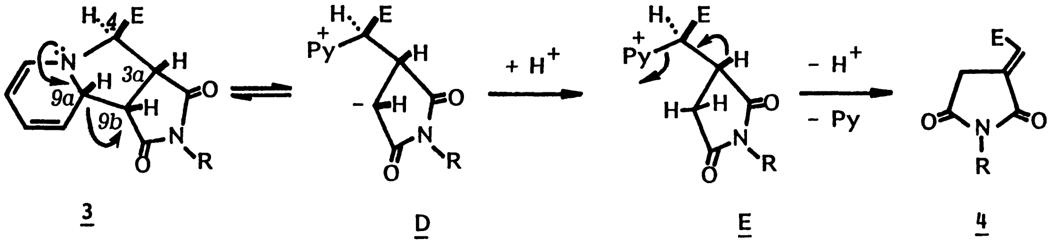
nucleus all readily reacted with 2c to give the stereoselective [3+2] cycloadducts 8a-8g in quantitative yields (Scheme 2 and Table 2).[6] When the cycloadducts 8 were subjected to a chromatography on silica gel, only the ones with electron-donating substituents succeeded in the elimination of substituted pyridines to give 4c in excellent yields (3c, 8a-8d in Table 2). Thus, the step of pyridine elimination is not critical in a hydroalkylidenation process.[7]

It was found that two regioisomers 8b and 8b' (8b:8b'=3:7) were formed in the reaction of 7b with 2c. When this mixture was chromatographed over Florisil, only the 9-methyl isomer 8b' was isolated in 96% yield, showing that the 7-methyl isomer was convertible into the 9-methyl one. The pathway for the isomerization is shown in Scheme 2: The 9a-9b bond of 8b is cleaved into a zwitterionic intermediate C and a recyclization in the other way leads to the isomer 8b'.[8]

Table 2. Reactions of Substituted Pyridinium Phenacylides with N-(p-Tolyl)maleimide

Pyridinium phenacylides		[3 + 2] Cycloadducts			Chromatography of cycloadducts over silica gel (yield/%)	
	R		R	Yield/%	Recovered cycloadducts	4c
1a	H	3c	H	100	-	82
7a	2-Me	8a	6-Me	100	-	92
7b	3-Me	8b, 8b'	7-/9-Me	100 (8b:8b'=3:7)	-	100
7c	4-Me	8c	8-Me	98	-	80
7d	3,5-diMe	8d	7,9-diMe	100	-	100
7e	4-CN	8e	8-CN	100	100	-
7f	3-CF_3	8f, 8f'	7-/9-CF_3	100 (8f:8f'=1:2)	89	-
7g	3-COOMe	8g, 8g'	7-/9-COOMe	100 (8g:8g'=5:3)	97	-

Based on the above results, the reaction mechanism for the stereoselective hydroalkylidenation of olefin is illustrated in Scheme 3. The initial reaction is a stereoselective cycloaddition leading to 3. A bond is cleaved at the 9a-9b bond to form a zwitterion D that is then protonated into E. The anti elimination of pyridine and proton gives an E isomer of 4. It should be emphasized that the high stereoselectivity is owing to the stereoselective formation of [3+2] cycloadduct. In this reaction, pyridinium methylides with electron-donating substituents on the pyridine ring are preferred because the cycloadducts having such substituents are more readily cleaved into the zwitterions.



Scheme 3.

References

1) O. Tsuge, S. Kanemasa, S. Kuraoka, and S. Takenaka, Chem. Lett., 1984, 281.
2) O. Tsuge, S. Kanemasa, and S. Takenaka, Heterocycles, 20, 1907 (1983).
3) All the new compounds reported in the present communication gave satisfactory elemental analyses.
4) B. E. Landberg and J. W. Lown, J. Chem. Soc., Perkin Trans. 1, 1975, 1326.
5) The compound 6a is convertible into 4-benzoyl-2,6-diphenylpyridine in 84% yield or 2-acetoxy-4-benzoyl-2,6-diphenyl-2H-pyran in 66% yield when treated with ammonium acetate in ethanol or acetic anhydride in the presence of pyridine, respectively.
6) All the cycloadducts except for 8d can be purified, without elimination of pyridines, by a column chromatography over Florisil using chloroform as an eluent. The elimination of 3,5-lutidine occurred so readily that the analytically pure sample of 8d was not available.
7) Although pyridines with electron-withdrawing substituents on the ring must be better leaving groups in an elimination reaction than those with electron-donating groups, the present cases have shown the reverse tendency.
8) The cycloadducts 8 with electron-donating substituents on the pyridine nucleus turn orange to red when touched to silica gel or Florisil, indicating that they are partially dissociated into the corresponding zwitterions D. The ones with electron-withdrawing groups never change their color.

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