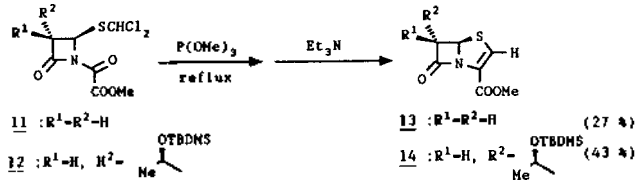
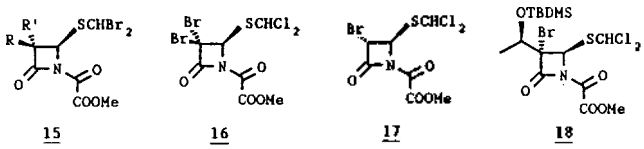
Thus, heating of a solution of oxalimie **11** and $P(OMe)_3$ in toluene to reflux for 5 h generated two polar compounds, one minor (less polar) and major one (more polar), both of which were quite unstable enough to resist numerous attempts for isolation and characterization. However, treatment of the reaction mixture with an amine such as Et_3N or i-Pr_2NEt at rt for 12 h transformed the major one directly into methyl ester of the known penem **13**[4] devoid of chlorine, isolated in 27% yield after aqueous work-up and chromatography, which was rather surprising. The same behavior was noted for the silyloxyethyl oxalimide **12** (yield of **14**, 43%).

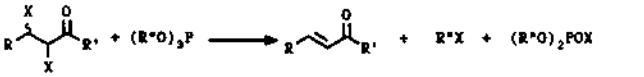


It was subsequently found that, understandably, 4-dibromomethylthio azetidinone oxalimides, **15**, regardless of substitution pattern at the C-3 position and those with halogen atom(s) at 3-position of the azetidinone ring, **16**–**18**, gave complex mitures under the same reaction condition. Also,



the phosphorus reagent for this reaction had to be specific: Among many phosphines and phosphites (PPh_3, $P(n\text{-}Bu)_3$, $P(OMe)_3$, $P(OEt)_3$, $P(OPh)_3$, $P(O\text{-}i\text{-}Pr)_3$, $P(OSiMe_3)_3$) examined so far, only trimethyl phosphite behaved properly.

Among the many possibilities, the mechanistic rationale at the moment may be outlined as described below: Initially, the oxalimide **9**(X = Cl) is converted to an α-alkoxycarbonyl carbene, which is eventually transformed into the 2,3-dichloropenam **10**(X = Cl) through the ensuing intermediacy of a chloronium ylide (analogous to **4**) and a 1,5-dipole (similar to **5**[2b]). Since trialkyl phosphite is known to dehalogenate α,β-dihalo carbonyl compounds (Eq. 6)[5], the dichloride **10** may well be reduced by trimethyl phosphite, eventually to



the corresponding penem. But the fact that the penems were not generated until the base treatment does suggest that the overall reaction occurred in a stepwise sense or the Perkow-type reaction somehow intervened during the process.

Regardless of the mechanistic details of the present reaction, herein is reported a new annulation of penem rings.

Acknowledgement. This work was generously supported by the Korea Science and Engineering Foundation.

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Rapid Ketonization of 2-Methylprop-1-en-1-ol in Chloroform: Reinvestigation of Stabilization with a Rhodium(I) Complex

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Kinetic studies for ketonization of enols have been carried out in aqueous solutions[1] as well as in some nonaqueous solvents.[2] But there has not been a report on kinetics for the ketonization in chloroform probably because it could not be clearly explained why the rate of ketonization in chloroform is unusually fast compared with those in H_2O[1] and in nonaqueous solvents.[1a,2] According to the mechanism suggested for ketonization of enols whose pK_a values are smaller than those of solvents (Eq. 1),[1,2] observed rate constants ($K_S \times k_{SH^+}$) are closely related with pK_a values of both solvents (S) and protonated solvents (SH^+).

$$R^1R^2C{=}C(OH)R^3 + S \overset{K_S}{\rightleftharpoons} R^1R^2C{=}C(O^-)R^3 + SH^+ \xrightarrow{k_{SH}^+} R^1R^2CHCOR^3 + S \quad (1)$$

The pK_a value of $CHCl_3$ (25)[3] is somewhat comparable with those of H_2O (15.7), CH_3OH (16), CH_3COCH_3 (20) and C_6H_6 (37)[4] and the ketonization is considerably slower in H_2O, CH_3OH, CD_3OD, CD_3COCD_3 and C_6D_6 than in $CDCl_3$.[2] (No

Table 1. Observed Rate Data for the Ketonization of 2-Methylprop-1-en-1-ol (1) at 27 °C under Argon

Solvent	Rate, k_{obs}, s^{-1}[a]
$CDCl_3$[b]	$t_{1/2}$ = 2–3 min, varies with $CDCl_3$[c]
$CDCl_3$[b,d]	$t_{1/2}$ = *ca.* 7 min[e]
$CDCl_3$[f]	$t_{1/2}$ = *ca.* 120 min[g]
$CDCl_3$[h]	$(1.6–4.0) \times 10^{-5}$ ($t_{1/2}$ = 720–290 min)
$CDCl_3$[d,h]	$(1.0–5.5) \times 10^{-4}$ ($t_{1/2}$ = 110–20 min)
C_6D_6[i]	2.2×10^{-5} ($t_{1/2}$ = 530 min)
C_6D_6[j]	$(4.0–5.9) \times 10^{-5}$ ($t_{1/2}$ = 290–200 min)

[a]Observed first-order rate constant. At least 10 experiments were carried out to obtain each value in this table. [b]Without treatment with molecular sieves. [c]From Fluka 31330 to Aldrich 23,691-8. [d]In the presence of $[Rh(CO)(PPh_3)_3]ClO_4$ (2) ([Rh] = 0.04 M, 1/2 = 30).[5a] [e]Reference 5a. [f]Treated with molecular sieves which were filtered off.[6] [g]Rate data do not conform to first-order kinetics. Rate increases gradually (see text). [h]Treated with molecular sieves and decanted without filtration.[7] Rate constant seems to vary with the amount of molecular sieves present in the reaction mixture (see text). [i]Reference 2. [j]In the presence of molecular sieves which were treated in the same manner as described in reference 7.

pK_a values have been reported for $CH_2Cl_3^+$). The fast ketonization rates of 2-methylprop-1-en-1-ol (1)[2] and other enols[1a] in $CDCl_3$ may not be simply explained with the pK_a values of $CHCl_3$.

In this paper, we wish to report the nature of ketonization of 1 in chloroform and the role of $[Rh(CO)(PPh_3)_3]ClO_4$ (2) in the ketonization which was reported to stabilize 1 in $CDCl_3$.[5] The enol, 1 was prepared and it's ketonization was followed in the same manner as described before.[2]

Results and Discussion

In $CDCl_3$ thoroughly treated with molecular sieves and filtered to remove small particles of molecular sieves,[6] the ketonization of 1 (Eq. 2) is remarkably slower ($t_{1/2}$ = *ca.* 2 hr) than that ($t_{1/2}$<4 min)[2,5a] in $CDCl_3$ (as puchased from Fluka (31330) or Aldrich (23,691-8)) not treated with molecular sieves at all, and it's rate increases gradually (rate data do not conform to first-order kinetics). The rate data for Eq. 2 in $CDCl_3$ in the presence of molecular sieves,[7] however, conform well to first-order kinetics for at least 4 half-lives. The reaction rate seems to vary with amounts of molecular sieves present in $CDCl_3$ (see Table 1). This observation may well be

$$(CH_3)_2C{=}CHOH \rightarrow (CH_3)_2CHCHO \qquad (2)$$

understood in terms of a impurity present in $CDCl_3$ which catalyzes the ketonization, may be removed by molecular sieve treatment, and generated and accumulated in $CDCl_3$ in the absence of molecular sieves. Such impurity is most likely DCl which is somehow produced under our experimental conditions even if extreme cautions are exercised to remove trace of oxygen in the reaction mixture and avoid exposure of the reaction mixture to light. The rate of DCl generation under our experimental conditions could be very slow since the rate of ketonization of 1 in $CDCl_3$ treated with molecular sieves[6] in the absence of molecular sieves is comparable (Table 1) with those in other nonaqueous solvents.[2]

Now, a question arises whether molecular sieves themselves affect the ketonization. Separate experiments in C_6D_6 in the presence and absence of molecular sieves revealed that the ketonization is catalyzed in some degree by molecular sieves (Table 1). Therefore the observed slow rates (Table 1) in $CDCl_3$ in the presence of molecular sieves may actually be the rates of the ketonization catalyzed by molecular sieves (and possibly very small amount of DCl) whose exact concentrations in the reaction mixture are difficult to determine since they are not soluble in $CDCl_3$.

Reasonably slow rates for Eq. 1 in $CDCl_3$ treated with molecular sieves[6,7] prompted us to reinvestigate the role of 2 in Eq. 2 since it was suggested that in $CDCl_3$ without molecular sieve treatment, 1 is stabilized by 2 so that the ketonization of 1 (Eq. 2) is slower in the presence of 2 than in the absence of 2.[5] As seen in Table 1, the rate of the ketonization of 1 is evidently faster in the presence of 2 than in the absence of 2 in $CDCl_3$ treated molecular sieves. In other words, compound 2 catalyzes the ketonization of 1 but not stabilizes 1 in $CDCl_3$. Now one can readily deduce that (1) in $CDCl_3$ without molecular sieve treatment, compound 2 mostly reacts with the impurity (DCl) present in $CDCl_3$, which consequently suppressed the rate of the ketonization and (2) in $CDCl_3$ treated with molecular sieves, 2 mostly reacts with 1 to catalyze the ketonization. A supporting evidence for the reaction of 2 with DCl has been obtained in separate experiments: compound 2 readily reacts with HCl (less than 0.01 atm) in $CHCl_3$ to give a solid which seems a mixture of rhodium complexes showing two strong carbonyl absorption bands at 1961 and 2045 cm^{-1}, and two medium absorption bands at 2102 and 2116 cm^{-1} due to Rh-H.

In conclusion it may be said that the simple enol 1 undergoes the ketonization reasonably slowly in $CDCl_3$ in the absence of DCl, and both molecular sieves and compound 2 which is so effective to generate 1[5] also catalyze the ketonization of 1.

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6. A 10 gram of molecular sieves (Aldrich 3A) was heated at 150 °C under vacuum for 1 hour and cooled to room tem-

perature under argon and added into degassed 5 ml of $CDCl_3$ (Fluka 31330 or Aldrich 23, 691-8) under argon in darkness and filtered off after 24 hours.

7. $CDCl_3$ was treated with molecular sieves in the same manner as descrived in reference 6 except that it was decanted (not filtered). Very small particles of molecular sieves were seen in decanted $CDCl_3$.

Unexpected Effect of Fluorine in Diels-Alder Reaction of 2-Fluoroacrolein with Thebaine

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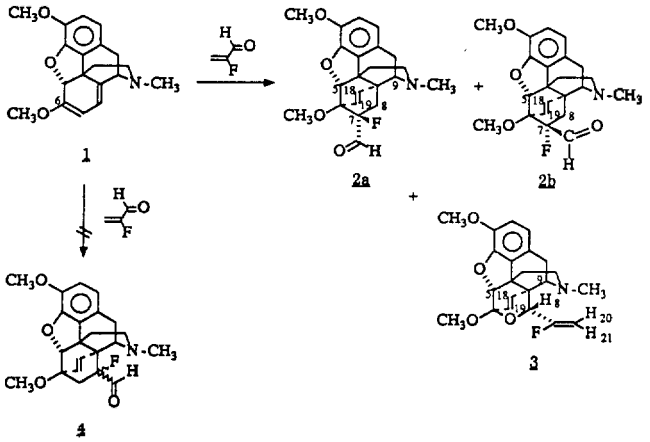
Although a number of Diels-Alder reactions of thebaine **1** with dienophilic monosubstituted[1-3] and 1,2-disubstituted[4,5] ethylenes have been previously studied, the fact that 7α-(1-hydroxy-1-methylalkyl)-6,14-endo-ethenotetrahydrooripavines[6] obtained *via* the chemical transformation of the Diels-Alder adduct prepared from the reaction of thebaine **1** with methyl vinyl ketone have shown the remarkable opioid agonist/antagonist properties has stimulated studies on the Diels-Alder reaction of thebaine **1** with 1,1-disubstituted ethylenes.[7] However, there has been no report concerning the reaction of thebaine 1 with fluoro-substituted ethylene, which should be convenient tool for the introduction of fluorine into the specific site of thebaine system.

As one of our efforts to obtain morphine alkaloid of biological interest from thebaine 1, we are interested in the introduction of fluorine into thebaine system because fluorine can have profound and unexpected results on biological activity.[8] Fluorine is the only element which can replace hydrogen without notable steric consequences. Once introduced, carbon-fluorine bond energy renders the substituent relatively resistant to metabolic transformations, and electronegativity of fluorine can have pronounced effects on the electron distribution in molecule, which cause different reaction between nonfluorinated and fluorinated compound.[9] In this communication we address the fluroine introduction into thebaine system *via* Diels-Alder reaction of thebaine **1** with 2-fluoroacrolein and effect of fluorine in that reaction.

When thebaine 1 was allowed to react with 2-fluoroacrolein (2 eq.), which is prepared from the previous method,[10] in benzene at 50 °C for 18 hours, Diels-Alder adduct **2**, mp 98-99 °C, and hetero Diels-Alder adduct **3**, mp 109-109 °C, were obtained in 75% and 11% yields, respectively. However, the reaction in acetonitrile resulted in the formation of adducts **2** and **3** in 25% and 15% yields, respectively. There was no formation of regioisomer **4**. Diels-Alder adduct **2** is a 88:12 mixture of 7β-fluorine (2a)/7α-fluorine (2b) stereoisomers which can not be separated by MPLC or HPLC. Thus, the ratio of these isomers was determined by integration ratio of aldehyde protons of two isomers in ^1H NMR spectrum. The decrease of stereoselectivity in the formation of adduct **2**, as compared to that in the reaction of thebaine **1** with acrolein[1], can be rationalized by 1,3-diaxial interaction between C-5 hydrogen and C-7 fluorine atom. The absence of the regioisomeric aldehyde adduct **4** is presumably a result of a combination of steric and electronic effects. C-6 Methoxy polarization of the dience system results in formation of only the C-7 regioisomer 2. One important feature in this reaction is the formation of hetero Diels-Alder adduct **3** which is totally unexpected product.



Since the adducts **2a** and **2b** can not be separated by MPLC or HPLC, the structures of **2a** and **2b** were also determined on the basis of spectroscopic data of the mixture of stereo-isomers. The MS spectrum showed an intense molecular ion peak at m/e 385 and IR spectrum showed characteristic absorptions at 2750 and 2850 cm^{-1} for aldehyde C-H and 1740 cm^{-1} for C=O group. The ^1H NMR ($CDCl_3$) spectrum of **2a** exhibited characteristic signals of H-5 proton at δ 5.22 (d, J = 1.0 Hz), two H-8 protons at δ 1.92 (dd, J = 21.2, 14.6 Hz, H-8α) and 2.91 (dd, J = 31.7, 14.6 Hz, H = 8β), H-9 proton at δ 3.23 (d, J = 4.9 Hz), two vinyl protons at δ 5.60 (d, J = 8.7 Hz, H-18) and 5.78 (ddd, J = 8.7, 4.5, 1.1 Hz, H-19), and aldehyde proton at δ 9.52 (d, J = 8.2 Hz). The assignment of adduct **2a** as the C-7 β fluorine compound rests on the coupling constant between C-8β proton and C-7β fluorine, since this type of coupling constant between C-8β proton and C-7β fluorine, since this type of coupling constant is usually larger than that between C-8β proton and C-7β fluorine ($J_{H\alpha F\beta}$ = 31.7 Hz *vs.* $J_{H\alpha F\alpha}$ = 21.2 Hz).[11] Since C-8β proton is shifted downfield due to the deshielding effect of the tertiary amine,[11] especially, the stereochemistry of adduct **2a** can be easily determined. Zigzag coupling (J = 4.5 Hz) between H-19 proton and fluorine also indicates that fluorine should be oriented at β-position. The ^1H NMR ($CDCl_3$) spectrum of **2b** also exhibited characteristic signals of H-5 proton at δ 4.69(s), H-8α proton at δ 1.53 (dd, J = 31.9, 14.5 Hz), two vinyl protons at δ 5.61 (d, J = 8.8 Hz, H-18) and 6.05 (d, J = 8.8 Hz, H-19), and aldehyde proton at δ 9.98 (d, J = 3.0 Hz). Other characteristic signals (H-8β and H-9 proton) of adduct can not be identified because of overlapping with signals of adduct **2a**. Upfield shift of signal for