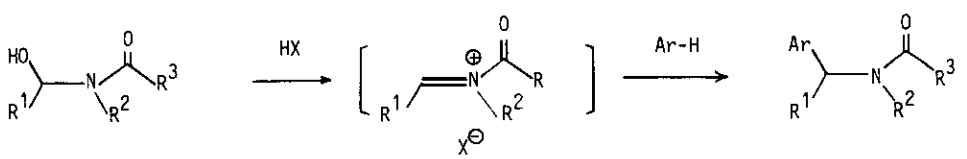
SYNTHESIS AND REACTION OF 3-HYDROXYENAMIDES

Shunsaku Ohta,* Motoshige Sumino, Tsutomu Sasaki, and
Nobuyuki Yamagami
Kyoto Pharmaceutical University
Misasagi Nakauchi-cho 5, Yamashinaku, Kyoto 607, Japan

Abstract —— 3-Hydroxyenamides (7) were prepared starting from 1,3-dicarbonyl compounds (4), and the enamides (7) readily reacted with π nucleophiles in the presence of trifluoroacetic anhydride to give 3-arylketones (11) in moderate yields.

N-Acyliminium salt (2) has been well-known as an important reactive intermediate especially for an intramolecular C-C bond formation, and the salt (2) has been prepared in situ mainly by treating N-(1-hydroxy- or 1-alkoxyalkyl)amide (1) with an appropriate acid.[1] Although the methodology seems to be useful in preparation of amide- or lactam-containing compounds (3), removal of the amide moiety after the C-C bond construction has not been almost considered. In this communication, we would like to report a new C-C bond forming reaction via the N-acyliminium intermediate analogues, the amide function of which can be removed in a hydrolytic manner after the reaction.



1 2 3

1,3-Dicarbonyl compound reacts with a primary or secondary amine readily to give the 3-enaminoketone,[2] whereas reaction of 1,3-dicarbonyl compound with amide has not been common. We found that 1,3-dicarbonyl compound (4) readily reacts with primary or secondary amide (5) as well as amine under azeotropically dehydrative conditions in the presence of an acid catalyst (p-toluenesulfonic acid; TsOH) to give the 3-

enamidocarbonyl compound (6). The carbonyl function of the enamides (6) was reduced by lithium borohydride ($LiBH_4$) to give the corresponding 3-hydroxyenamide (7) in moderate yields.

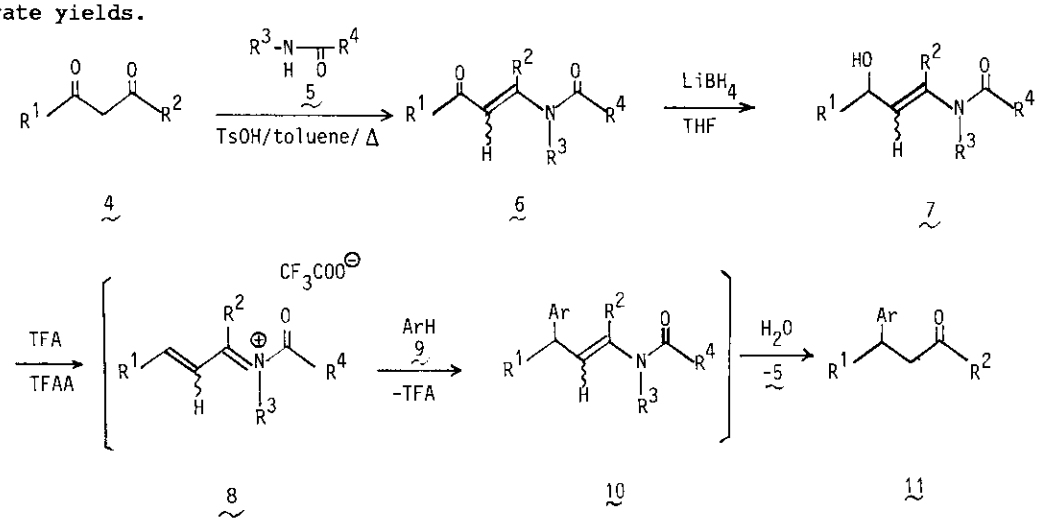
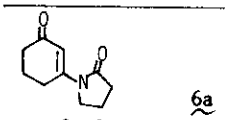
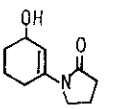
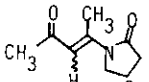
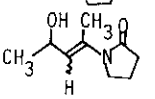
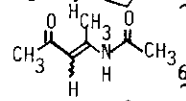
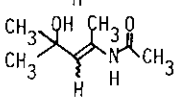
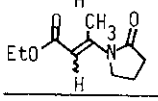


Table I. 3-Enamidoketone (6) and 3-Enamidoalcohol (7) Prepared

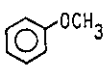
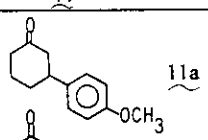
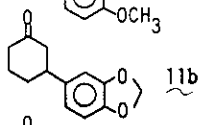
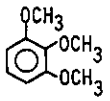
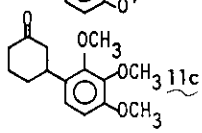
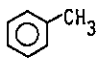
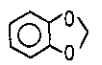
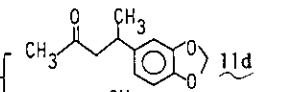
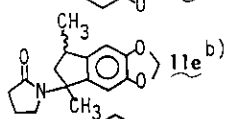
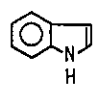
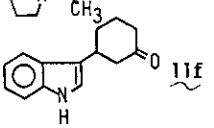
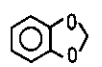
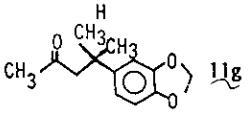
Compound	mp or bp (℃)	Yield (%)	Compound	mp or bp (℃)	Yield (%)
 6a	mp 70-71	54.3	 7a	oil[b]	32.3
 6b	mp 65-66	35.2	 7b	oil[b]	35.9
 6c	mp 40-42 bp_2 73-75	64.9	 7c[a]	bp_1 75-78	56.7
 6d	mp 51-52 bp_1 122-125	36.5			

a) prepared by treatment of 6c with CH_3Li in THF at -78℃.
b) purified by silica gel chromatography.

The hydroxyenamide (7a) was treated at room temperature with trifluoroacetic anhydride (TFAA) in trifluoroacetic acid (TFA) in the presence of anisole (Entry 1 in Table II). The hydroxyenamide (7a) was disappeared within several hours. Silica gel chromatography of the crude product gave an oily compound in 40.0 % yield, of which spectral and analytical data indicated that the product was 3-(4-anisyl)cyclohexanone (11a). The reaction might proceed via a nucleophilic attack of anisole to the conjugated iminium intermediate (8) to produce the enamide (10),

which was hydrolyzed to the ketone (11a) during the work-up procedure. Several applications of the present reaction to other reaction systems are listed in Table II.

Table II. 3-Arylketones (11) Obtained

Entry	Starting Materials		Product		
	7	9	11	mp or bp (℃)	Yield (%)
1	7a		 11a	mp<30[a]	40.0
2	7a		 11b	mp 57-58	43.4
3	7a		 11c	mp 76-77	34.1
4	7a		(no reaction)	-	-
5	7b		 11d	oil[a]	10.1
			 11e[b]	oil[a]	7.6
6	7a		 11f	mp 105-106	42.1
7	7c		 11g	bp, 150-155	25.2

a) purified by silica gel chromatography.
b) Stereochemistry of the product was not determined, but hrms and ^{1}H-nmr supported the plane structure.

The reaction of the enamide (7b) with 1,2-methylenedioxybenzene (entry 5) afforded a normal product (11d) and an interesting doubly attacked product (11e). Generally speaking, the yields of the present C-C bond forming reaction are moderate or low. Typical procedure (entry 1 in Table II): A solution of anisole (0.5 ml, 4.60 mmol) in dry dichloromethane (0.5 ml) was added at 0 ℃ under N_2 atmosphere to a mixture of the hydroxyenamide (7a, 181 mg, 1 mmol), TFA (1 ml) and TFAA (141 μl, 1 mmol). The mixture was stirred at ambient temperature for 2 h. The reaction mixture was

neutralized by addition of water (10 ml) and solid K_2CO_3. The product was extracted with ethyl acetate. Removal of the solvent gave anoily residue, which was purified by silica gel chromatography ($CHCl_3/CH_3OH$ = 20/1) to give colorless prisms of 11a. Yield, 82 mg (40.0 %). Ir ($CHCl_3$): 1715 cm^{-1} (C=O). ^{1}H-Nmr (80MHz in $CDCl_3$) δ : 1.61-2.61 (m, 8H, CH_2 x 4), 2.83 - 3.05 (m, 1H, CH-Ar), 3.79 (s, 3H, OCH_3), 6.76-7.25 (m, 4H, Ar-H). High-Resolution ms m/z for $C_{13}H_{16}O_2$ Calcd : 204.1151 ; Found : 204.1146.

Improvement of the yield and further applications of the present methodology are now under investigation.[3]

ACKNOWLEDGEMENT

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1) For review : W.N.Speckamp and H.Hiemstra, Tetrahedron, 1985, 41, 4367.

2) S.A.Grickman and A.C.Cope, J. Am. Chem. Soc., 1945, 67, 1017; N.H.Cromwell, Chem. Reviews, 1946, 38, 83.

3) An outline of the present work was presented at The 38th Annual Meeting of Japan Pharmaceutical Society, Kinki-Branch (November 6, 1988, Higashiosaka; Paper, p 36).

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