CHEMISTRY LETTERS, pp. 1123-1124, 1990. © 1990 The Chemical Society of Japan

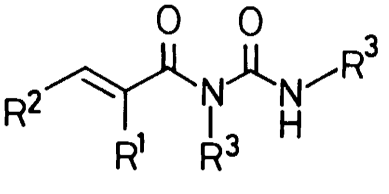
Hydrochlorination of Acryloylureas Using Titanium Tetrachloride and 2-Propanol

Keiki KISHIKAWA,† Makoto YAMAMOTO, Shigeo KOHMOTO,
and Kazutoshi YAMADA*
Department of Materials Science, Faculty of Engineering,
Chiba University, Chiba 260
†Graduate School of Science and Technology, Chiba University,
Chiba 260

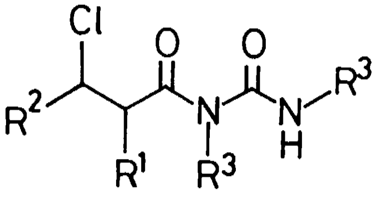
Hydrochlorination of acryloylureas was attempted using titanium tetrachloride and 2-propanol to give chloroacylureas with high yield and stereoselectivity.

Hydrochlorination of acrylic acid derivatives using hydrogen chloride is a well known and an important reaction in industrial chemistry.[1] However, to the best of our knowledge hydrochlorination of acryloylureas[2] using transition metal halides and alcohols has not been reported yet. This paper represents the first example of diastereoselective hydrochlorination of acrylic acid derivatives by titanium tetrachloride with 2-propanol.

After addition of titanium tetrachloride to acryloylureas 1 in toluene at room temperature, 2-propanol was added to give chloroacylureas 2 in high yield. In the absence of 2-propanol the hydrochlorination does not proceed at all.



1



2

Table 1. Hydrochlorination of acryloylureas 1[3]

No.	Acryloylurea	R^1	R^2	R^3	Yield[a]/%
1	1a	H	H	i-Pr	89[b]
2	1b			c-Hexyl	98[b]
3	1c			(S)-1-phenylethyl	84[c]
4	1d			(R)-1-phenylethyl	70[c]
5	1e			Ph	0[b]
6	1f	Me	H	i-Pr	0[b]
7	1g	H	Me	(S)-1-phenylethyl	100[b](45:55)[d]
8	1h		Et	(S)-1-phenylethyl	86[b](17:83)[d]
9	1i		Pr	(S)-1-phenylethyl	72[b](45:55)[d]
10	1j		i-Pr	(S)-1-phenylethyl	68[b](40:60)[d]
11	1k		Ph	i-Pr	0[b]

a) Isolated yield. b) The ratio of $TiCl_4$:i-PrOH is 1:2. c) The ratio of $TiCl_4$:i-PrOH is 1:1. d) The ratios of the diastereomers were determined by ^1H NMR and HPLC analysis.

In the case of R^1 = H (except R^3 = Ph) the reaction takes place in high yield. The reaction of **1f** does not occur, because the chelation of the titanium atom with the carbonyl oxygen atoms would be sterically prevented by the methyl group at the α -carbon. Under the same reaction conditions the hydrochlorination of benzyl acrylate and N-benzylacrylamide does not occur. This indicates that the carbonyl of the urea part plays an important role in the reaction. The reaction quantitatively proceeds in non-polar solvents (toluene and benzene), but does not in polar solvents (chloroform and dichloromethane).

The hydrochlorination of 1c quantitatively proceeds even at -20 °C. To complete the reaction, more than 1 equivalent of 2-propanol is necessary to 1 equivalent of titanium tetrachloride. Furthermore, we found that both 0.5 equivalent of titanium tetrachloride and 2-propanol (= 1:1) to **1** were enough to complete the reaction. From the above results we postulate the following mechanism for the hydrochlorination of 1c. Titanium atom makes chelation with each carbonyl oxygen atoms of acyl and urea parts of acryloylureas to cause activation of the β -carbon.4) The attack of 2-propanol on the titanium atom triggers the migration of chlorine atoms to the β -carbon of an acrylyurea.

In the case of R^2 = Me, Et, Pr, or i-Pr the reaction proceeds even at room temperature. A good diastereoselectivity was observed in the hydroclorination of **1h** (R^2 = Et). These results indicate that the hydrochlorination seems to proceed via a rigid transition state. The size of ethyl group would be the most suitable in the diastereoselective reaction. In the case of **1h** the hydrochlorination was attempted using various alcohols (methanol, ethanol, 2-propanol, and t-butanol). The reactivity order of these alcohols is 2-propanol > t-butanol > ethanol > methanol. Acylurea **1g** was reacted with titanium tetrachloride and ethanol-d_6 in benzene-d_6. From 400 MHz-^{1}H NMR analysis, 96% deutrium incorporation was observed at the α -proton. It is undoubtedly that one of the α -proton comes from alcohol.

Further investigation of the hydrochlorination using transition metal halides is now in progress.

We thank the fund of Mitsui Petrochemical Industries, Ltd., for a fellowship (K. K).

References

1) Mitsui Toatsu Chemicals, Inc., *Jpn. Kokai Tokkyo Koho*, JP 58124738; H. Erpenbach, K. Gehrmann, H. Joest, and W. Lork., *Ger. Offen.*, 2555043.

2) K. Kishikawa, M. Yamamoto, S. Kohmoto, and K. Yamada, *Chem. Lett.*, **1988**, 1623; *J. Org. Chem.*, **54**, 2428 (1989).

3) Procedure; to a solution of acryloylurea 1c (0.155 mmol) in toluene (5 ml) was added $TiCl_4$ (0.232 mmol) and the suspended solution was stirred for 20 min at room temperature. After addition of a solution of i-PrOH (0.229 mmol) in toluene the solution was stirred at room temperature for 1 h. Water (3 ml) was added to quench the reaction. The organic phase was separated, dried over $MgSO_4$ and concentrated to give a chloroacylurea 2c.

4) T. Poll, J. O. Metter, and G. Helmchen, *Angew. Chem., Int. Ed. Engl.*, **24**, 112 (1985); W. Oppolzer, I. Rodriguez, J. Blagg, and G. Bernardinelli, *Helv. Chim. Acta*, **72**, 123 (1989).

(Received April 4, 1990)