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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

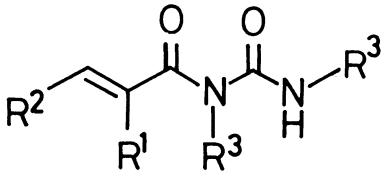
Hydrochlorination of acryloylureas was attempted using titanium tetrachloride and 2-propanol to give chloroacylureas with high yield and stereoselectivity.

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.

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]



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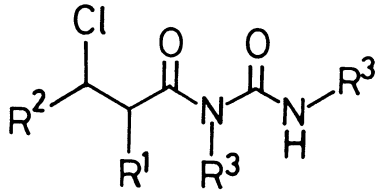

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a) Isolated yield. b) The ratio of $TiCl_4$:i-PrOH is 1:2. c) The ratio of $TiCl_4$:i-PrOH is 1:1. d) The ratios of the diastereomers were determined by ^1H NMR and HPLC analysis.

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.

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References

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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).

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