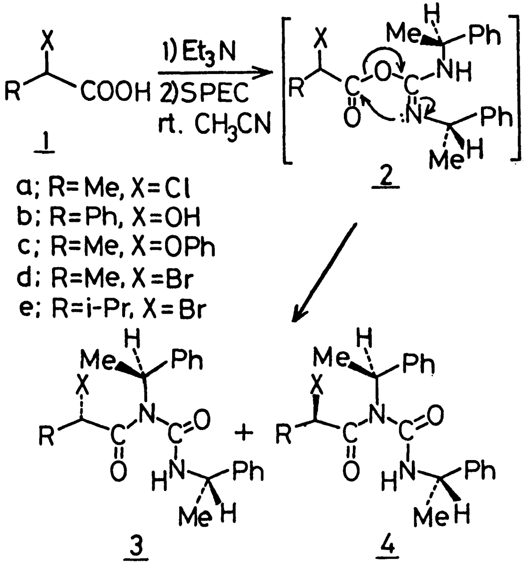
CHEMISTRY LETTERS, pp. 351-352, 1988.

Stereoselective Rearrangement of Chiral Acylisoureas and a Model for the Transition State

Kazutoshi YAMADA,* Keiki KISHIKAWA, Shigeo KOHMOTO,
and Makoto YAMAMOTO
Department of Industrial Chemistry,
Chiba University, Chiba 260

A first transition state model for the rearrangement of acylisoureas is proposed from the stereoselectivity of the reaction with chiral acylisoureas.

An unstable acylisourea intermediate rapidly rearranges to an acylurea via four-center transition state.1) However the precise transition state model has not been reported yet. In this paper we will propose the first model which could clearly explain the diastereoselectivity in the rearrangement of acylisoureas 2a-e. The chiral acylisourea intermediates 2a-e were generated in situ by the reaction of a chiral carbodiimide, N,N'-di-((S)-1-phenylethyl)carbodiimide (SPEC) with α-substituted carboxylic acids (Scheme 1). If the concept of the Felkin-Anh model2) is adapted to this rearrangement, two models (A) and (B) (Fig. 1) are possible transition states for the corresponding diastereomers of acylisourea 2, (2S)- and (2R)-forms respectively (X is a polar group. $L>S$). The nitrogen atom approaches from the least hindered side in the model(A). In the conformation(B), the nucleophilic group would encounter large steric interaction. Accordingly the diastereomer(A) rearranges faster than the other one, thus acylurea 3 would be the major product in the beginning of the reaction. Based of this assumption, the reaction was stopped on the early stage (4 h) to ensure the proposed mechanism.



Scheme 1.

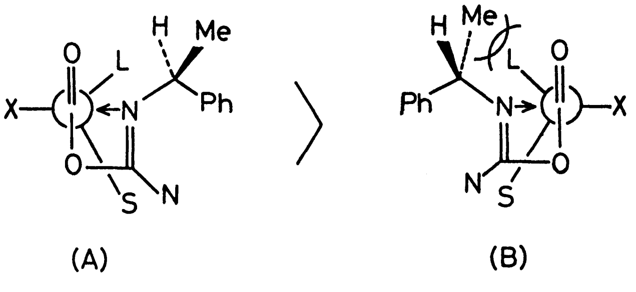


Fig. 1.

Table 1. Stereoselectivity of the rearrangement of acylisoureas

No.	Starting material	Yield/%$^{a)}$	Prod. ratio of 3:4$^{b)}$
1	1a	24	55 : 45
2	1b	14	33 : 67
3	1c	31	71 : 29
4	1d	3	>95 : 5
5$^{c)}$	1d	9	>95 : 5
6	1e	14	>95 : 5

a) Isolated yield of 3+4; the starting material was completely recovered and the byproduct was not observed. b) Determined by ^{1}H-NMR. See Ref. 3. c) Two equivalent of SPEC was used.

In all experiments,$^{4)}$ acylureas were generated stereoselectively (Table 1). In the reaction of 1a, acylurea 3a was obtained as the major product with moderate selectivity. The reaction of 1b gave a cyclic product(N-1-phenylethyl-5-phenyloxazolidine-2,4-dion). In these cases, the interaction between two phenyl groups makes the transition state model(A) unfavourable. To increase the stereoselectivity, we investigated the reaction with carboxylic acids bearing bulkier groups(X=OPh, Br). A significant improvement of stereoselectivity was observed. Especially in the reaction of α-bromocarboxylic acids (1d and 1e), corresponding single isomers 3d and 3e were obtained because of the bulkiness of the bromine atom, supporting the transition state model(A).

From the stereoselectivity observed, we conclude that the mechanism of the intramolecular rearrangement of acylisoureas could be best explained by our transition state model.

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

References

1) D. F. Detar and R. Silverstein, J. Am. Chem. Soc., 88, 1020 (1966); A. F. Hegarty, M. T. McCormack, G. Ferguson, and P. T. Roberts, ibid., 99, 2015 (1977); A. F. Hegarty and T. Bruice, ibid., 92, 6561 (1970).

2) M. Cherest, H. Felkin, and N. Prudent, Tetrahedron Lett., 1968, 2199.

3) Determined by the comparison of integrals of α-protons(^{1}H-NMR(CCl_4, 60 MHz)) : 3a 4.50(q, J=6 Hz), 4a 5.05(q, J=6 Hz), 3b 5.35(s), 4b 5.30(s), 3c 5.13(q, J=6.5 Hz), 4c 5.47(q, J=6.5 Hz), 3d 4.80(q, J=6 Hz), 3e 4.05(d, J=8 Hz), 4e 4.65(d, J=8.5 Hz).

4) A typical experiment was performed as follows. To a mixture of racemic acid (2 mmol), triethylamine(2 mmol) and 20 ml of acetonitrile, a solution of the chiral carbodiimide(2 mmol) in 10 ml of acetonitrile was added. The solution was stirred at room temperature for 4 h. The reaction was quenched by the addition of hydrochloric acid(2 mol dm^{-3}) and the solvent was replaced by 20 ml of ethyl acetate. The solution was washed with water and then with aqueous sodium hydrogencarbonate. The products were separated by column chromatography (EtOAc-hexane, 1:4) on silica gel. The ratio of the diastereomers was determined by ^{1}H-NMR study. Absolute configuration of these products was identified by the comparison of physical data with those of the chiral acylurea which was prepared from the chiral carbodiimide and an optically pure acid.$^{5)}$

5) S. J. Fu, S. Birnbaum, and J. P. Greenstein, J. Am. Chem. Soc., 76, 6054 (1954); G. Kircher, M. P. Scollar, and A. M. Klibnov, ibid., 107, 7072 (1985); B. Sjoeberg and S. Sjoeberg, Arkiv. Kemi., 22, 447 (1964).

(Received November 21, 1987)