CHEMISTRY LETTERS, pp. 1583-1586, 1985.

STEREOCHEMISTRY OF AMINE-CATALYZED KNOEVENAGEL REACTIONS

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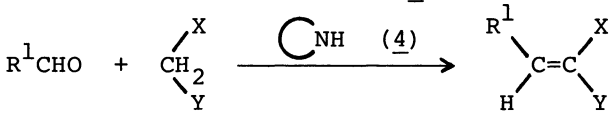
The amine-catalyzed Knoevenagel reactions of aldehydes and active methylene compounds containing two activating groups were found to involve many reversible steps, and the diastereomeric intermediary condensation compounds yielded thermodynamically stable products *via* carbanionic intermediates stabilized and sterically affected by two activating groups.

The amine-catalyzed aldol condensations referred to as the Knoevenagel reactions are one of the simplest methods for forming carbon-carbon double bonds, but little is known concerning the stereochemistry of the reaction.[1-3] The condensation of cyanoacetic esters or methylsulfonylacetic esters with aldehydes give alkenes, in which the β-alkyl or β-aryl group is *cis* to a small cyano group,[4,5] or *trans* to a large methylsulfonyl group.[6] Recently we have reported the stereoselective synthesis of (2*E*)-2-arylsulfinyl-2-alkenoic esters from arylsulfinylacetic esters and aldehydes in the presence of a catalytic amount of piperidine,[7] but the reaction mechanism remains unknown.

Here we report the mechanistic elucidation of the stereochemical problems in the Knoevenagel reactions of active methylene compounds (1) containing two activating groups (X and Y) with aldehydes (2).



2 1 3

In order to evaluate the steric effects of the functions X and Y on the formation of alkenes (3), a solution of 1 (10 mmol) and 2 (12 mmol) in acetonitrile (100 ml) was treated with piperidine (1 mmol) as previously described.[7] The

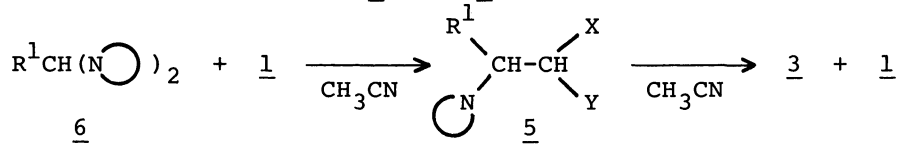
alkenes (3) thus obtained were found to be thermodynamically stable isomers as shown in Table 1. Interestingly, the formation of 3 is affected by slight differences in the steric requirements between two functions X and Y, except that X, Y, and R^1 are rather small (Run 5), or X and Y are comparable in size (Run 7).

Table 1. Reactions of the compounds (1) with aldehydes

				Conditions			
Run	R^1	X	Y	Temp/°C	Time/h	Yield/%	E/Z[a]
1	C_6H_5	CO_2CH_3	$S(O)C_6H_4Cl$-*p*	60	6	88	100/0
2	*n*-C_3H_7	CO_2CH_3	$S(O)C_6H_4Cl$-*p*	0	24	70	100/0
3	C_6H_5	COC_6H_5	$S(O)C_6H_5$	60	6	70	100/0
4	C_6H_5	CO_2CH_3	COC_6H_5	20	10	91	0/100
5	*n*-C_3H_7	CO_2CH_3	$COCH_3$	20	10	77	31/69
6	*n*-C_3H_7	$COCH_3$	COC_6H_5	20	10	70	100/0
7	*n*-C_3H_7	COC_3H_7-*i*	COC_6H_5	20	10	63	63/37

a) The ratio was determined by HPLC and/or ^{1}H-NMR.

When equimolar amounts of 1, 2, and secondary amines (4) were dissolved in a minimum quantity of acetonitrile and kept standing at 0 °C for a few days, colorless solids precipitated.[8] These intermediary condensation compounds (5) were separated by filtration, washed with cold hexane, and dried under vacuum. Similarly, 5 were obtained in 75-90% yields from 1 and the compounds (6) prepared by condensation of 2 and 4. The NMR spectra indicate that 5 contain *threo*- and *erythro*-isomers, ratios of which are explained on the rational basis of relative bulkiness of R^1 and ◯N, or X and Y (X<Y). The compounds (5), though stable in solid form, are susceptible to elimination in an acidic medium even on silica gel, yielding a mixture of *E*- and *Z*-alkenes (3). For example, 5c (*threo/erythro*=15/85) in acetic acid underwent *anti*-elimination within 10 min at 20 °C to afford the corresponding *E*- and *Z*-3c (*E/Z*=13/87) in a 81% yield. On the other hand, dissolving 5 (5 mmol) in acetonitrile (50 ml), that is, under the Knoevenagel reaction conditions resulted in another type of elimination to give thermodynamically stable products (3) and 1 as shown in Table 2.



6 5

Table 2. Reactions of the compounds (5) under Knoevenagel reaction conditions[a)]

5	R^1	X	Y		*threo/erythro*[b)]	3 Yield/%	3 *E/Z*	1 Yield/%
5a	C_6H_5	CO_2CH_3	$S(O)C_6H_4Cl$-*p*	$(CH_3)_2N$	0/100	69	100/0	29
5b	C_6H_5	CO_2CH_3	$S(O)C_6H_4Cl$-*p*		0/100	63	100/0	27
5c	C_6H_5	CO_2CH_3	$S(O)C_6H_4Cl$-*p*		15/85	58	97/3	26
5d	C_6H_5	CO_2CH_3	$S(O)C_6H_4Cl$-*p*		30/70	51	100/0	38
5e	*i*-C_3H_7	CO_2CH_3	$S(O)C_6H_4Cl$-*p*		60/40	60	100/0	27
5f	C_6H_5	COC_6H_5	$S(O)C_6H_5$		40/60	55	100/0	40
5g	C_6H_5	CO_2CH_3	COC_6H_5		61/39	70	0/100	11
5h	C_6H_5	CO_2CH_3	COC_6H_5		71/29	90	0/100	-

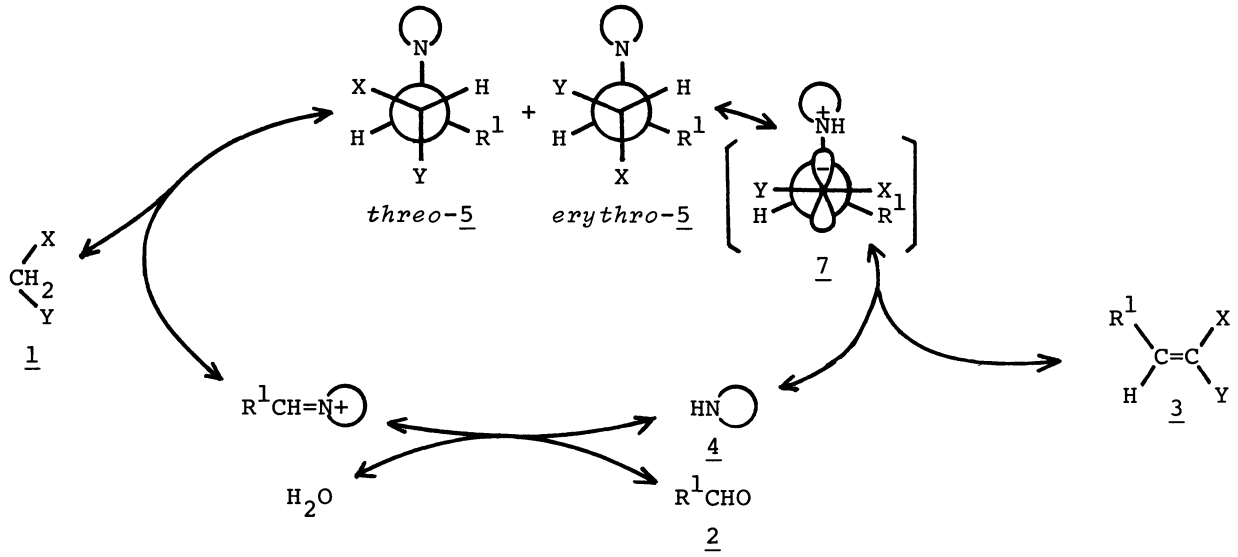
a) The same reaction temperature and time as shown in Table 1 were employed.
b) The ratio was determined by ^{1}H-NMR. The OCH_3 and R^1CH protons of *threo*-5 exhibit their absorptions in the lower field than those of *erythro*-5.

The formation of 1 as well as 3 suggests that amine-catalyzed aldol reactions are reversible. The elimination may proceed *via* a carbanionic intermediate (7) stabilized by two functions X and Y, and the stereochemistry of 3 may be controlled mainly by the steric requirements among the groups X, Y, and R^1 as shown in scheme 1. Similar reactions were reported in base-catalyzed elimination of sulfones[9)] and nucleophilic substitution (addition-elimination) of vinylic compounds.[10)] The present findings, however, show that slight differences in the steric requirements are much effective on elimination *via* stable carbanions. Although our results provide no conclusive proof concerning electronic effects, the steric ones may play a more important role than the electronic interaction between the group Y and the hydrogen atom at a nonpolar C-H bond.

Under activation by carbanion-stabilizing groups, base-catalyzed elimination and nucleophilic addition on vinylic system are known to proceed *via* similar intermediates.[10,11)] In fact, the formation of 5 by treatment of 3 with piperidine suggests that elimination step is also reversible. The elimination steps could be followed by the NMR measurement, and thereby both *threo*-5 and *erythro*-5 were found to disappear simultaneously, forming thermodynamically controlled products. On standing in a NMR tube for 1 h 5e in $CDCl_3$ gave *E*-3e in a 40% yield, and during that time no *Z*-3e was detected by the NMR observation. On the other hand, treatment of *Z*-3e with piperidine under the similar conditions resulted in *E-Z*

isomerization affording *E*-3e in a 5% yield. This finding suggests that the stereochemistry of products (3) is controlled primarily in the elimination step, although *E*-*Z* isomerization may be slightly operative.

In conclusion, the amine-catalyzed Knoevenagel reaction involves many reversible steps, and usage of a catalytic amount of an amine may force this thermodynamically controlled reaction to completion giving the most stable product.



Scheme 1.

References

1) R. L. Reeves, "The Chemistry of the Carbonyl Group," ed by S. Patai, Interscience, London (1966), p. 593.
2) G. Jones, Org. React., 15, 204 (1967).
3) J. Mathieu and J. Weill-Raynal, "Formation of C-C Bonds," Georg Thieme Publishers, Stuttgart (1975), Vol. 2, p. 513.
4) J. Zabicky, J. Chem. Soc., 1961, 683.
5) M. Schwarz, J. Chem. Soc., Chem. Commun., 1969, 212.
6) D. A. R. Happer and B. E. Steenson, Synthesis, 1980, 806.
7) R. Tanikaga, Y. Nozaki, T. Tamura, and A. Kaji, J. Chem. Soc., Chem. Commun., 1984, 87.
8) The compounds (5) were not always obtained as pure solids, and purification by chromatography was impossible because a solution of 5 was liable to produce 3.
9) R. P. Redman, P. J. Thomas, and C. J. M. Stirling, J. Chem. Soc., Chem. Commun., 1978, 43, and references cited therein.
10) Z. Rappoport, Acc. Chem. Res., 14, 7 (1981).
11) C. J. M. Stirling, Acc. Chem. Res., 12, 198 (1979).

(Received August 5, 1985)