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Base Effects on the Stereoselectivity of the Reaction of (2*R*,3*R*)-2,3-Diacetoxy- and (2*R*,3*R*)-2,3-Dibenzoyloxy-succinic Anhydrides with Racemic Alcohols

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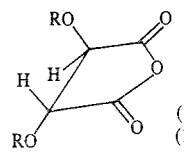
Abstract

A study has been made of the effect on the stereoselectivity of the reaction of racemic alcohols with (2*R*,3*R*)-2,3-diacetoxy- and (2*R*,3*R*)-2,3-dibenzoyloxy-succinic anhydrides, by using various pyridine derivatives as the basic catalyst.

Considerable enhancement in stereoselectivity is observed with increasing steric bulk around the basic centre, as for example in substituting 2-methylpyridine for pyridine. However, if the pK_a of the base used differs significantly from that of pyridine, a decrease in stereoselectivity results.

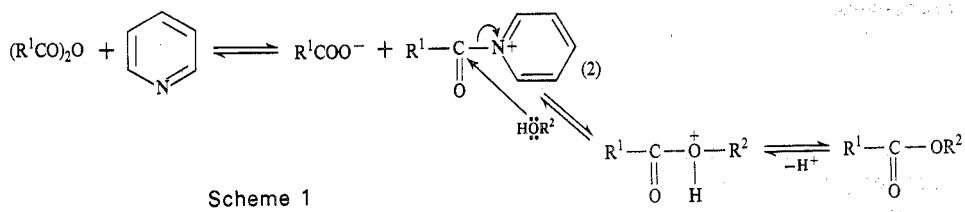
Introduction

In previous papers,[1,2] the stereoselectivity of the reaction of (2*R*,3*R*)-2,3-diacetoxy- and (2*R*,3*R*)-2,3-dibenzoyloxy-succinic anhydrides, (1a) and (1b), with racemic alcohols in the presence of pyridine was described. Acylations of this type proceed through an acylammonium ion (2) as outlined in Scheme 1.



(1a) R = Ac
(1b) R = COPh

The rates of reaction of the enantiomers of a racemic alcohol with a chiral anhydride will differ, as they proceed through diastereomeric transition states. This results in kinetic resolution. Changes in the basic catalyst could affect the stereoselectivity of the reaction in two ways. Firstly, a change in the pK_a of the base would



Scheme 1

modify its leaving group ability from the ion (2). Secondly, an alteration could be made in the steric environment around the basic centre by, for example, substitution in the pyridine ring. Both these factors could affect the rates of the subsequent diastereomeric reactions differently, and thus alter the stereoselectivity.

[1] Bell, K. H., *Aust. J. Chem.*, 1979, **32**, 65.
[2] Bell, K. H., *Aust. J. Chem.*, 1979, **32**, 2625.

The present study was undertaken to determine the effect of these two variables on the stereoselectivity of the reaction of (1a) and (1b) with racemic alcohols.

Horeau[3] has made a preliminary study of the reaction of racemic 2-phenylbutanoic anhydride with optically active 3β-hydroxy-5β-androstan-17-one in the presence of pyridine, and 2-, 3- and 4-methylpyridine. Stereoselectivities were 45, 39, 41 and 44% respectively. In this case, the slight differences appear to be attributable to changes in steric effects.

Results and Discussion

The two anhydrides (1a) and (1b) were made to react with 1-phenylethanol in the presence of various bases under a standard set of conditions (see Experimental). 1-Phenylethanol was chosen for initial studies since the large size difference in the two groups (methyl and phenyl) attached to the chiral centre would provide a sensitive probe for any steric interactions. Stereoselectivities, together with pK_a values for the bases, are shown in Table 1.

Table 1. Base effects on percentage stereoselectivity

Values for stereoselectivity are shown to the nearest percentage for an average of three runs, provided the values were within 1%. If necessary, further runs were taken until this agreement was reached

Base	pK_a value[A]	Stereoselectivity (1a)	Stereoselectivity (1b)	Rotation of recovered alcohol (1a)	Rotation of recovered alcohol (1b)
Pyridine	5·2	6	7	(+)	(+)
2-Methylpyridine	6·0	11	16	(+)	(+)
3-Methylpyridine	5·7	6	7	(+)	(+)
4-Methylpyridine	6·0	6	7	(+)	(+)
2,4-Dimethylpyridine	6·6	11	17	(+)	(+)
2,6-Dimethylpyridine	6·7	12	18	(+)	(+)
2-Phenylpyridine	4·5	4	4	(+)	(+)
Pyridine-2-carbonitrile	−0·3	0	0		
Pyridine-3-carbonitrile	1·5	2	2	(−)	(−)
Pyridine-4-carbonitrile	1·9	4	<1	(+)	(−)
Quinoline	4·9	10	15	(+)	(+)
2-Methylquinoline	5·4	10	15	(+)	(+)
Isoquinoline	5·4	7	8	(+)	(+)
N,N-Diethylethanamine	10·8	0	0		

[A] pK_a values, at 20–25°, are taken from Albert, A., in 'Physical Methods in Heterocyclic Chemistry' (Ed. A. R. Katritzky) Vol. 1, Ch. 1 (Academic Press: New York 1963).

It is clear from Table 1 that increased steric effects around the basic centre enhance the stereoselectivity, whereas changing the pK_a significantly from that of pyridine has the opposite effect. At the two extremes of the pK_a range, pyridine-2-carbonitrile was ineffective as a catalyst while the strongly basic *N,N*-diethylethanamine caused decomposition of the anhydrides.

It is noteworthy that the observed increases in stereoselectivity due to steric effects contrast to the opposite findings of Horeau[3] with alkylpyridines. The

[3] Horeau, A., in 'Stereochemistry: Fundamentals and Methods' Vol. 3, p. 51 (Thieme: Stuttgart 1977).

enhancing steric effect is shown further in the reaction of (1a) and (1b) with racemic menthol. Here, substitution of pyridine by 2-methyl- and 2,6-dimethyl-pyridine gave stereoselectivities of 41, 51 and 65% for (1a), and 49, 58 and 66% for (1b).

On the other hand, when the size difference between the two groups attached to the chiral centre is small, as in pentan-2-ol, the improvement in stereoselectivity was only marginal in changing from pyridine (15%) to 2-methyl- and 2,6-dimethyl-pyridine (both 16%).

The stereoselectivities shown in Table 1, when pyridine was used, are slightly lower than those reported previously[1] where a higher mole proportion of pyridine instead of benzene was employed as solvent. That this effect is due probably to changes in solvent polarity is shown by the increase to 8% for (1a) when acetonitrile was substituted for benzene.

The dramatic improvement in stereoselectivity resulting from the simple substitution of 2-methylpyridine for pyridine in the above reactions suggest that a higher degree of regioselectivity may be possible in the base-catalysed acylation of polyhydroxy compounds if a similar substitution is made.

Experimental

Optical rotations were measured with a Perkin–Elmer 241 spectropolarimeter in a 1-dm cell kept at 20°.

Preparation of Reagents

The anhydrides (1a) and (1b) were prepared as described previously.[1,2]

2-Phenylpyridine was prepared from pyridine and phenyllithium.[4] All the other bases were available commercially. Liquid bases were dried over KOH before distillation under nitrogen, and stored over 4A molecular sieves. Solid bases were recrystallized, and dried over P_2O_5 in a vacuum desiccator.

Standard Procedure for the Reaction of (1a) and (1b) with Racemic Alcohols in the Presence of Various Bases

A solution of the alcohol (1 mole equiv.) (usually 0·02–0·05 mol) in dry benzene (7·5 ml per 0·01 mol of alcohol) containing the basic catalyst (0·1 mole equiv.) was stirred magnetically at 0–2°. The solid anhydride (0·1 mole equiv.) was added in one lot. After 1 h at 0–2°, the ice bath was removed, and the solution was stirred at 15–20° for 6 h. Water (1 ml) was added and the mixture was stirred for an additional 30 min. A trial experiment with a solution of just the anhydride in benzene containing the basic catalyst showed that hydrolysis, as determined by titration, was complete under these conditions. Workup of the reaction and determination of stereoselectivities was carried out as described previously.[1] To ensure that no optical enrichment had taken place during the distillation of the isolated alcohols, in some instances several fractions were collected. Rotations were the same for each fraction.

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[4] Evans, J. C. W., and Allen, C. F. H., *Org. Synth.*, 1943, Coll. Vol. II, 517.