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CATALYTIC ASYMMETRIC DARZENS CONDENSATION IN THE PRESENCE OF BOVINE SERUM ALBUMIN.

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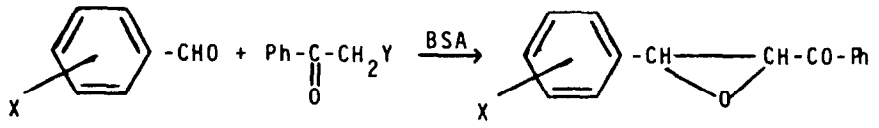
ABSTRACT: Darzens condensation of aromatic aldehydes with phenacyl halides in the presence of a catalytic amount of bovine serum albumin afforded the corresponding epoxyketones in up to 62% e.e.

Almost any compound with an organic radical of appreciable size, especially if it also contains a negative charge, has been observed to bind to bovine serum albumin (BSA), a carrier protein in biological systems. Substitution of ligand with relatively simple groups can cause great changes in the ligand-protein interaction; and, more important, the ligand binding is in some instances stereospecific.[1] For these reasons BSA is a very attractive chiral catalyst successfully used in the asymmetric synthesis of sulfoxides,[2] alcohols[3] and cis diols.[4]

In this communication we describe its application to the preparation of optically active epoxyketones by the Darzens condensation.

The reaction was performed by stirring in the dark, under nitrogen, the aldehyde (1.2 mmol) and the phenacyl halide (1 mmol) in 12.5 ml pH 11 buffer solution containing 0.05 molar equivalents of BSA. Extraction with diethyl ether and evaporation of the organic layer gave the crude product, which was purified by column chromatography, on silica gel using mixtures of petroleum ether-diethyl ether as eluant, in order to eliminate impurities from the catalyst capable of affecting the rotation measurements.

The use of a higher amount of protein (0.1 molar equivalent) did not increase the chemical and the optical yield, in agreement with the results previously found by us in the oxidation of functionalized sulphides with $NaIO_4$.[2] Reaction time, chemical and optical yield are reported in the Table.



(1-4) (5) Y = Cl (6) Y = Br (7-10)

(1); (7a, 7b) X = p-NO_2
(2); (8a, 8b) X = o-NO_2
(3): (9a, 9b) X = m-NO_2
(4); (10a, 10b) X = p-Cl

The highest stereoselectivity was observed starting from p-nitrobenzaldehyde (1) and phenacyl chloride (5); indeed epoxyketone (7a) had 62% e.e. It dropped sharply in the ortho and meta derivatives (8a), (9a), 2 and 8% e.e. respectively. p-Chlorobenzaldehyde (4) gave the corresponding epoxide (10a) in poor chemical yield (28% e.e.).

With phenacyl chloride (5) the Darzens condensation is 100% diastereoselective, since compounds (7-10) were obtained only as E isomers.

In the absence of aldehyde selfcondensation of (5) took place, affording the adduct (11) as a diastereomeric E, Z mixture in a ratio 1:6. The e.e. of Z epoxyketone (11b) was 28%.

Both the enantioselectivity and the diastereo- selectivity decreased on passing from the phenacyl chloride (5) to the bromide (6); indeed p-nitrobenzaldehyde (1) with (6) gave a diastereomeric mixture of epoxides (7a,7b) in $\sim$ 1:1 ratio, the e.e. of E (7a) being 35%.

The dependence of the optical purity of adducts (7a-10a) on the position of the substituent in the aromatic ring is not surprising; Burkhard and coworkers have observed that isomeric compounds can interact with bovine serum albumin in different ways.[5]

The nature of the starting aldehyde also plays an important role. Only aromatic aldehydes bearing electron withdrawing groups gave the condensation with phenacyl chloride; benzaldehyde was recovered unchanged. The reactivity sequence (pNO_2 > pCl > Ph) is similar to that found for the reaction performed in homogeneous conditions.[6]

The enantioselectivity with bovine serum albumin is much higher than that obtained with onium salts as chiral catalysts under phase-transfer conditions (0.8-8.6 e.e.).[7]

As the reaction involves hydrophobic molecules , it seems likely that the BSA not only favours the solubilisation of the substrates, but also their localisation on its binding sites, thus enhancing asymmetric induction.

It is worthy of note that the molecular organisation and compartmentalisation, determined by the globular protein, does not alter substantially the reaction rate of the Darzens condensation, but affects its diastereoselectivity. When p-nitrobenzaldehyde (1a) was treated with phenacyl chloride (5) under the usual conditions, a diastereomeric mixture of epoxyketones (7a, 7b) was obtained in 30% yield, in E/Z ratio 5:1.

We are now successfully exploiting these properties of the bovine serum albumin for diastereoselectivity control in the oxidation of organic sulphides with aqueous $NaIO_4$[8].

Few examples of chiral condensations are known, though very recently enantiomerically pure benzyl cis,α,β epoxycarboxylates have been prepared by a modified Darzens procedure.[9] Although the enantioselectivity described in this communication is far from that achieved in enzymatic controlled reactions, this is, to the best of our knowledge, the first example of a catalytic Darzens reaction carried out in an aqueous medium.

Table Enantioselective Darzens condensation in a buffer solution (pH 11) containing bovine serum albumin at 25°C

Substrate	Phenacyl halide	Compound	Reaction time (h)	Yield (%)	e.e.±2%
(1)	(5)	(7a)	24	43	62[a]
(2)	(5)	(8a)	5	35	2[a]
(3)	(5)	(9a)	6	26	8[a]
(4)	(5)	(10a)	44	5	24[a]
(1)	(6)	(7a,7b)	7	10	35a,b
	(5)	(11a,11b)	216	21	29[a,b]

[a] Determined in the presence of $Eu(tfc)_3$ as chiral shift reagent.
[b] For the E isomer (7a).
[c] For the Z isomer (11b).

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