Stereoselective Synthesis of 3-*p*-Tolylsulphinyl-4-aryl-β-lactams

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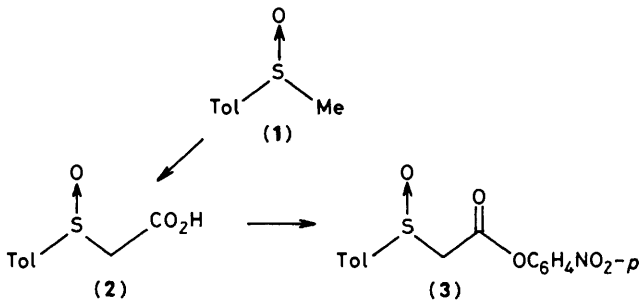
3-*p*-Tolylsulphinyl-4-aryl-β-lactams (**4**) have been synthesised in moderate yield and with good overall stereoselectivity by the condensation of aryl aldimines with derivatives of 2-*p*-tolylsulphinylacetic acid (**2**).

Although a large number of methods for the synthesis of β-lactams has been made available in the last three decades,[1] only few reports dealing with their asymmetric synthesis *via* chiral auxiliaries have appeared,[2] and total syntheses of optically active β-lactam antibiotics still heavily rely upon the use of chiral starting materials derived from natural sources.

In the course of our studies[3] on sulphoxide-mediated asymmetric synthesis,[4] we explored the feasibility of a synthesis of β-lactams based on the condensation between an imine and a derivative of 2-*p*-tolylsulphinylacetic acid (**2**).

The base-catalysed reaction between imines and acyl chlorides is one of the most direct routes to β-lactams and has been extensively used.[1] In some cases other activated carboxylic compounds like 1-methyl-2-halogenopyridinium salts,[5] mixed anhydrides,[6] and *p*-nitrophenyl esters[7] were used instead of the acyl chloride.



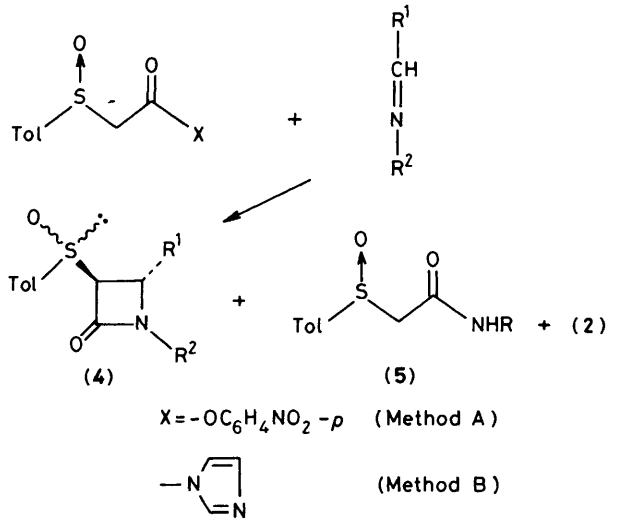
2-*p*-Tolylsulphinylacetic acid (**2**) was synthesised by the reaction of lithium (±)-*p*-tolyl methyl sulphoxide[8] with CO_2 in tetrahydrofuran at −78 °C (70% yield). Condensation of (**2**) with *p*-nitrophenol (dicyclohexylcarbodi-imide, AcOEt, 90%) gave the activated ester (**3**). Cyclisation of this ester with aryl aldimines proceeds in the presence of imidazole [dimethylformamide (DMF), room temp.] to give β-lactams (**4**) in moderate yields (method A). The principal by-products were the amide (**5**) and the acid (**2**) (Scheme 1).†

Imidazole and DMF were chosen after experiments with numerous bases and solvents had indicated that: (a) catalysts that are more basic and less nucleophilic than imidazole (*e.g.* Et_3N, Pr^i_2NEt, NaH, or diazabicyclo[5.4.0]undecene) give very low yields of β-lactams, furnishing mainly the acid (**2**), probably *via* a ketene pathway; (b) yields of (**4**) are increased with more polar solvents.

In all cases, in accord with the results of other authors for a similar reaction,[9] a moderate amount of the amide (**5**) was obtained and all attempts to avoid its formation were unsuccessful. Moreover it is noteworthy that under the same conditions alkyl aldimines, as well as 2-phenyl-4,5-dihydro-1,3-thiazole, appear to be unreactive (see entries 5 and 12, Table 1).

Later we found that the same synthesis could be more advantageously carried out in 'one pot', by directly treating 2-*p*-tolylsulphinylacetic acid (**2**), activated with carbonyl

† Here only one enantiomeric form is arbitrarily shown although a racemate was used.



Scheme 1

Table 1. Synthesis of 3-*p*-tolylsulphinyl-4-aryl-β-lactams (Scheme 1).[a]

Entry	Method[b]	R^1	R^2	% Yield (4)[c]	% Yield (5)[c]	Diastereoisomeric ratio[d]
1	A	Ph	Ph	34	38	82:18
2	A	Ph	*p*-MeO-C_6H_4	38	41	73:27
3	A	Ph	*p*-ClC_6H_4	30	38	87:13
4	A	Ph	CH_2Ph	40	43	47:53
5	A	$Me[CH_2]_5$	Ph	—	—	—
6	B	Ph	Ph	44	30	84:16
7	B	Ph	*p*-MeO-C_6H_4	38	41	80:20
8	B	Ph	*p*-ClC_6H_4	30	35	87:13
9	B	Ph	CH_2Ph	45	26	44:56
10	B	*p*-ClC_6H_4	Ph	15	24	36:64
11	B	*p*-AcNH-C_6H_4	Ph	31	[e]	87:13
12	B	2-Phenyl-4,5-dihydro-1,3-thiazole		—	—	—

[a] All reactions were performed on a 0.3 mmol scale. [b] Method A: (**3**), imine, imidazole, DMF, room temp., 1 day. Method B: (**2**), carbonyldi-imidazole, imine, DMF, room temp., 1 day. [c] After preparative t.l.c. [d] Determined by ^1H n.m.r. (80 MHz): the first diastereoisomer is the one whose C^3-*H* and CH_3-aryl resonate upfield. [e] Not determined because inseparable from starting imine.

di-imidazole, with the imine (method B). Although in this case yields are only slightly higher, the esterification step is avoided and the absence of *p*-nitrophenol as by-product renders purification of β-lactams easier. The results are summarised in Table 1.

With regard to the stereoselectivity of the process, it is interesting that only two of the four possible diastereoisomeric pairs were detected. Both of them were recognized as 3,4-*trans* by their vicinal *CH–CH* coupling constants (ranging from 2.0 to 2.4 Hz.).[10] Moreover, the ratio between these two diastereoisomeric pairs was in some cases fairly good (up to 6.7 : 1) meaning that the reaction proceeds not only with very high 'internal asymmetric induction', affording exclusively *trans* products, but also with good 'relative asymmetric induction'.[11]

This diastereoselective synthesis of functionalised β-lactams using racemic *p*-tolyl methyl sulphoxide (**1**) should be capable of extension to enantioselective condensations by employing the easily available optically pure (+)-(*R*)-(**1**).[8]

We thank Miss Delia Bertoia for her collaboration in this work and C. N. R. and Ministero della Pubblica Istruzione for financial support.

Received, 12th March 1984; Com. 319

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