

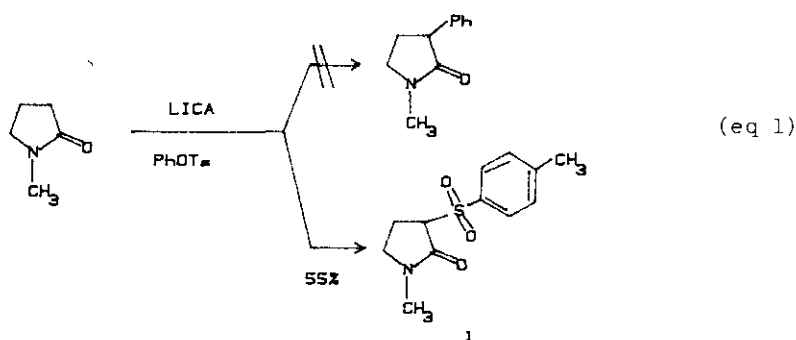
PREPARATION OF α -ARYLSULFONYL LACTAMS¹

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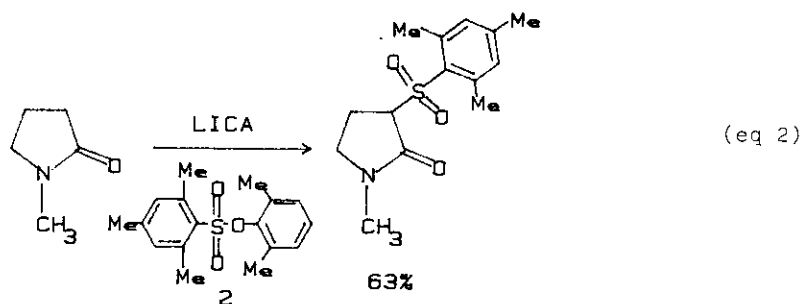
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Abstract—Lactam enolates are efficiently converted into α -arylsulfonyl lactams by aryl sulfonate esters.

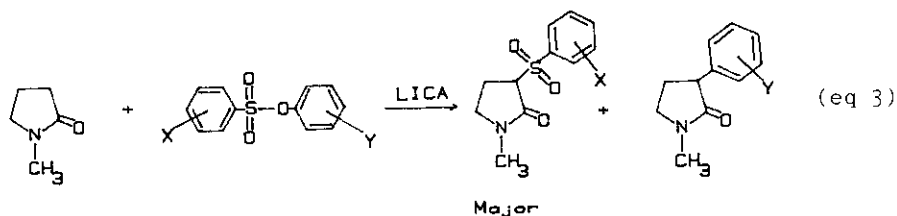
The total synthesis of several alkaloids requires α -aryl lactams as key intermediates.² These have been made by allowing lactam enolates to react with aryl halides in the presence of excess strong base and involves the formation of benzyne³ which are trapped by the enolates.⁴ The yields from this process sometimes are not high, so an alternate arylation was attempted with the tosylate of phenol⁵ as a model system. This unexpectedly produces not the α -phenyl lactam but rather the α -sulfonyl lactam **1** (eq 1).



This novel reaction⁶ is general for a variety of aryl sulfonates and several amides. The enolates of N-methylpyrrolidinone and N,N-dimethylacetamide react with phenyl tosylate to give products analogous to sulfone **1** in 55% and 29% yields, respectively. N-Benzylpyrrolidinone fails to react under similar conditions. Substituents in both rings of the aryl sulfonate are tolerated. Even very hindered systems like compound **2** give a good yield of the sulfone (eq 2). Table 1 summarizes the sulfonyl lactams which have been prepared from the reaction with N-methylpyrrolidinone.

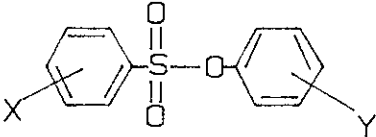


This conversion is selective for lactam and amide enolates. Anions from diethyl malonate, cyclohexanone, acetophenone, ethyl acetoacetate, ethyl phenylacetate and ethyl acetate all fail to react with phenyl tosylate under the usual conditions. Both the tosylate and the carbonyl compound are recovered upon workup. In contrast, aryl thiosulfonate esters are well-known to react with various enolates to give α -thioaryl derivatives.⁷ Aryl sulfonyl chlorides do not react with lactam enolates in the same manner. For example, the anion of N-methylpyrrolidinone reacts with tosyl chloride to give di-p-tolyl disulfide and thiophenol tosylate as the only observed products. Similar results were found for 2,5-dimethylbenzenesulfonyl chloride. This suggests that the reactions of Table 1 do not involve a simple displacement process. The ease of the conversion of eq 2, where the sulfur is very hindered to direct attack, also illustrates the complex nature of this reaction. Although formation of an α -sulfonyl amide is the predominant reaction, some benzyne-derived product (α -aryl lactam) is observed as a competing process in some systems. This latter pathway is the one which was sought when this study began. Ironically, the presence of this α -aryl lactam greatly complicates the purification of the lactam sulfones (eq 3) rendering these systems of little synthetic value.



Consequently, none of these are shown in Table 1 where little, if any, of the α -aryl lactam is formed. The benzyne process can be avoided by using sulfonate esters derived from 2,6-dimethylphenol.

Table 1. Reaction of N-Methylpyrrolidinone with Aryl Sulfonates^a

		% Yield of α -Arylsulfonyl Lactams ^b
X	Y	
p-Me	H	85
H	H	48
2,5-dimethyl	H	43
2,4,6-trimethyl	H	61
2,4,6-trimethyl	2,6-dimethyl	63
p-Cl	p-Me	23
p-Br	H	54
p-Br	p-Me	58
p-I	p-Me	50
p-OMe	2,6-dimethyl	43
p-Me	H	29
p-Me	o-(2-(1,3-dioxolanyl))	54

^aExcess amide base was used in all cases.^bIsolated yields of pure products.

Further studies of these reactions are underway. This includes extension of the scope of the reactions as well as mechanistic aspects of these conversions.

REFERENCES

It is with great pleasure that this communication is dedicated to Professor Gilbert Stork in celebration of his 65th birthday.

1. Presented in part at the 19th Middle Atlantic Regional Meeting of the American Chemical Society, May 21, 1985, West Long Branch, N.J..
2. For example, our synthesis of mesembrine uses α -(3,4-di-methoxyphenyl)-N-methylpyrrolidinone: K. S. Kochhar and H. W. Pinnick, Tetrahedron Lett., 1983, 4785.
3. R. W. Hoffmann, 'Dehydrobenzene and Cycloalkynes,' Academic Press, New York, 1967.
4. S. C. Fields, K. S. Kochhar, J. D. Stewart and H. W. Pinnick, submitted to J. Org. Chem..
5. (a) o-Bromophenyl tosylate undergoes metal-halogen exchange to give benzyne which has been trapped in a 2 + 4 cycloaddition: see Reference 3, p. 66.
(b) Phenyl benzenesulfonate reacts with lithium 2,2,6,6-tetramethylpiperide to give benzyne but trapping with nucleophiles gives products in lower yields than that possible from bromobenzene as the benzyne source: I. Fleming and T. Mah, J. Chem. Soc., Perkin Trans. I, 1577 (1976).
6. Organometallics react with sulfonate esters to give sulfones although the yields often are poor:
(a) W. H. Baarschers, Can. J. Chem., 1976, 54, 3056.
(b) A. I. Meyers, A. Nabeya, H. Adickes and I. Politzer, J. Am. Chem. Soc., 1969, 91, 763.
(c) M. A. Sabol and K. K. Anderson, J. Am. Chem. Soc., 1969, 91, 3603.
7. Phenyl benzenesulfonate is an efficient thiophenyl transfer agent for enolates: B. M. Trost and G. S. Massiot, J. Am. Chem. Soc., 1977, 99, 4405.

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