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Communications to the Editor

Lawesson's Reagent: A New Entry in the Preparation of 2-Azetidinones

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Abstract:

Lawesson's reagent is found to be a unique reagent that provides a convenient route for the synthesis of β-lactams from Schiff's bases and alkoxy/aryloxy acetic acids. The process involves the formation of a titanium enolate of a mixed anhydride followed by condensation with imine to afford β-lactam.

Development of efficient methods for the stereoselective generation of β-lactams is an important goal, due to their utility as synthetic intermediates and to their biological activity.[1−8] Efforts have been largely directed towards the use of an acid-activating reagent that can be utilized with a diverse set of reactants while giving high yields under mild reaction conditions. Among some conceptual approaches to accomplish highly stereospecific azetidinone formation, the annelation of imino compounds with an activated acid using an oxidizing−reducing agent has received much attention during the recent years.[9] It is also worth mentioning here that we have already identified several compounds, such as phosphorus oxychloride,[10] benzenesulphonyl chloride,[11] methanesulphonyl chloride,[12] in β-lactam formation.

Lawesson's reagent, i.e., 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulphide has been used extensively as a thionation reagent[13] for the conversion of a wide variety of carbonyl compounds to thiocarbonyl compounds as well as for the synthesis of phosphorus- and sulphur-containing heterocycles.[14] Recently, it has also been described as a racemization-free coupling reagent in peptide synthesis.[15] During our studies directed towards the synthesis of β-lactam antibiotics, we became interested in exploring the use of this reagent for the construction of β-lactam rings. To our great surprise the reagent did not undergo the straightforward [2 + 2] ketene−imine cycloaddition reaction to furnish the β-lactam ring under various reaction conditions.

An alternative way to construct the β-lactam ring from the above-mentioned synthons is the enolate−imine condensation reaction. Although several ester enolates have been utilized, no attempt to prepare an enolate from our type of anhydride intermediates in generating β-lactam structure has been made. We attempted the reaction by generating the titanium enolate **5**. The mixed anhydride **4**, generated in situ,

Scheme 1

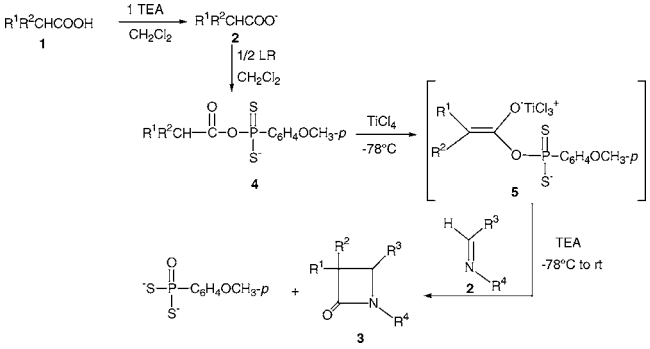

***Table 1. β*-Lactams prepared using Lawesson's reagent**

entry	R^1	R^2	R^3	R^4	config. cis:trans	yield[a] (%)
a	C_6H_5O	H	C_6H_5	$C_6H_4OCH_3$(p)	80:20	75
b	C_6H_5S	H	piperonyl	$C_6H_4OCH_3$(p)	0:100	70
c	CH_2=CH	H	piperonyl	$C_6H_4OCH_3$(p)	0:100	71
d	CH_3	CH_3	piperonyl	$C_6H_4OCH_3$(p)	−	74
e	C_6H_5	H	piperonyl	$C_6H_4OCH_3$(p)	0:100	77
f	Phth	H	C_6H_5	$C_6H_4OCH_3$(p)	0:100	78
g	PhthCH$_2$	H	C_6H_5	$C_6H_4OCH_3$(p)	0:100	74

[a] Yield refers to isolated product; all products were identified by comparing FT-IR, NMR, analytical data, and TLC with those of authentic samples.

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was treated with a dichloromethane solution of titanium tetrachloride at −78 °C under nitrogen atmosphere. After the mixture stirred for 1.5 h, triethylamine followed by the Schiff's bases were added, and the contents were stirred at −78 °C for an additional 5 h and then overnight at room temperature. Usual workup furnished the β-lactams in more than 70% yield. A plausible mechanism can be depicted as in Scheme 1.

To define the scope of this successful reaction we repeated the experiments by varying the two synthons. The procedure works with equal ease with the enolates derived from phenoxyacetic acid, thiophenoxyacetic acid, crotonic acid, isobutyric acid, phenylacetic acid, or phthaloyl propionic/acetic acids. An interesting aspect of this reaction is the stereoselectivity whereby, in most of the cases studied, the trans isomer was obtained (Table 1). Ths cis:trans ratios are based on the ^{1}HNMR spectrum of the crude reaction products in each case. The formation of the cis product in the case of **3a** can be explained in terms of the coordination of aryl oxygen with the oxophilic titanium in the enolate **5**,[16] whereas in the other case the more stable trans product is obtained.

Since the reagent is readily accessible and also commercially available, the reaction conditions mild, the procedure simple, and the yields generally high, we believe that this method provides a convenient route especially for the synthesis of useful and variously functionalized monocyclic 2-azetidinones.

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