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A NEW AND CONVENIENT METHOD FOR THE PREPARATION OF ß-LACTAMS AND UNSATURATED AMIDES USING N-[[(CHLOROSULFINYL)OXY] METHYLENE]-N-METHYLMETHANAMINIUM CHLORIDE

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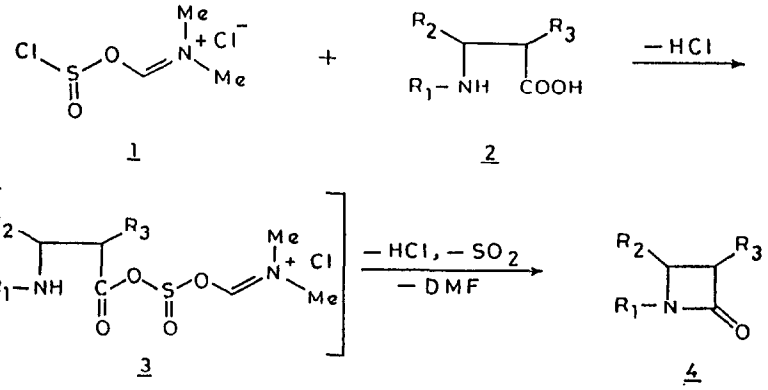
Summary: N-[[(Chlorosulfinyl)oxy]-N-methylmethanaminium chloride 1 is a highly reactive condensing agent which provides an efficient route to azetidinones 4a-f from ß-amino acids 2 and unsaturated amides 6a-d from a variety of carboxylic acids 5. The products were obtained in good purity and high yields.

Azetidin-2-ones have been important synthetic target molecules particularly because of their presence in the penicillin family of antibiotics. The four membered ring in these compounds is strained, hard to form and also susceptible to either acidic, or basic hydrolysis. Although numerous methods have been reported already,[1] there still exists ongoing needs to develop general and convenient methods for the synthesis of ß-lactams.[2]



4	R_1	R_2	R_3
a	CH_2Ph	H	H
b	CH_2	Me	H
c	H	Me	H
d	CH_2Ph	H	Me
e	CH_2Ph	Ph	H
f	H	H	H

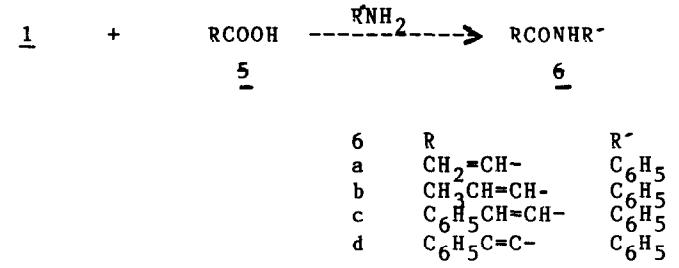
The major routes are through cycloaddition or ring closure reactions. The cycloaddition reaction used is necessarily a (2+2) cycloaddition[3] since the

desired product is a four membered ring. The cyclisation of ß-amino acids, through the use of reagents such as AcCl, PCl_3, $SOCl_2$ $MeSO_2Cl$ under phase-transfer conditions and bis(5-nitro-2-pyridyl)trichloroethyl phosphate has been accomplished in a limited number of cases. The DCC method is most commonly applied to azetidinone formation, but the yields markedly depends upon the structural feature and solvents employed.[5] More recently the Ph_3P-$(PyS)_2$ method is employed, but according to this reaction, rather high reaction temperature and tedious purification of the product are necessary[6]. Application of these known reagents to 2a, did not give any good results, yielding 4a only in poor yields, therefore a systematic investigation of the condensing system was carried out. Here we now wish to report an improved one-pot methodology using N,N-dimethylchlorosulfitemethaniminium chloride[7] 1 as an acid activating agent with triethylamine as the base to synthesize various ß-lactams, under mild conditions.

In a typical case, to a dry dichloromethane (30 mL) suspension of 3-benzylamino propionic acid (10 mmol) and 1 (15 mmol) was added in one portion, a dichloromethane solution (5 mL) of Et_3N (30 mmol) and the reaction mixture was stirred first at (0-5°C) for 20 min and then at room temperature 5h. After usual work-up followed by purification of the residue by silica gel thin layer chromatography, afforded the corresponding ß-lactam 4a in 70% yield. To explore the generality of this reaction substituted and unsubstituted ß-amino acids were subjected to the cyclodehydration conditions. The corresponding ß-lactams 4b-f were isolated in moderate to good yields. The yields were generally poor when the amino group is primary. In order to improve the yield of ß-lactams (4c and 4f) the reaction was carried out at reflux temperature, while reagent 1 is lossing hydrogen chloride, sulphur dioxide and polymeric materials separating out.

Reagent 1 was also found to be equally effective in one-pot methodology, when we attempted for various unsaturated amides under mild conditions. Recently, Laszlo et al reported a new two step route for 2-alkenamides using phosphazo compound[8]. The direct conversion of esters to amides is potentially a useful synthetic operation, but the practical application of this method has been somewhat limited for a number of reasons.[9] In general, aminolysis of esters required high temperature and/or long reaction times,[10] the strong alkali metal catalysts used are not compatible with sensitive functionality.[11] Our method appears to be quite convenient and in most of the instances the present procedure is a substantial improvement over the existing methods.

In a typical experiment, to a solution of acrylic acid (10 mmol) in absolute dichloromethane (25 mL) was added at 0-5°C, reagent 1 (15 mmol). After stirring at this temperature for 10 min, freshly distilled aniline (10 mmol) was added,followed by dropwise addition of dry triethylamine (20 mmol) in dichloromethane (10 mL). The resulting mixture was then stirred at room temperature for 5h (monitored vide tlc). After usual work-up N-phenyl-2-propenamide 6a (R=CH_2=CH, R´=Ph), mp 103-104°C (lit[8] mp 103-104°C) was obtained in 85% yield. Similarly phenylpropiolic acid was obtained in 80% yields (Table).



6	R	R´
a	CH_2=CH-	C_6H_5
b	CH_3CH=CH-	C_6H_5
c	C_6H_5CH=CH-	C_6H_5
d	C_6H_5C=C-	C_6H_5

Table: Reaction times and yields for compounds 4a-f and 6a-d

Acid	Isolated product[12]	Yield[a] (%)	Time (h)
3-Benzylamino propionic acid	4a	70	5
3-Benzylamino butyric acid	4b	71	6
3-Amino-3-methyl propionic acid	4c	25	8
3-Benzylamino-3-methyl propionic acid	4d	70	7
3-Benzylamino hydrocinnamic acid	4e	55	7
β-Alanine	4f	15	9
Acrylic acid	6a	85	4
Crotonic acid	6b	80	3
Cinnamic acid	6c	85	4
Phenylpropiolic acid	6d	80	5

[a]The yields refer to isolated products.

In conclusion, the present method offers several adventages over previous methods, the reagent is readily available, the azetidinones and unsaturated amides are obtained in high yields under mild reaction conditions. The synthetic extension of this methodology to current β-lactam antibiotics of interest and to further explore the scope of the reagent is in progress.

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