Tetrahedron Letters,Vol.25,No.31,pp 3365-3368,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

N,N-DIMETHYLCHLOROSULFITEMETHANIMINIUM CHLORIDE ($SOCl_2$-DMF) A VERSATILE DEHYDRATING REAGENT[1].

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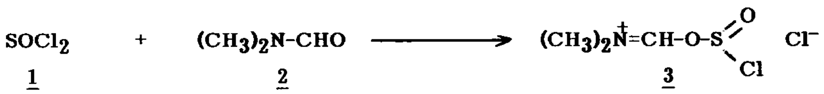
Summary : N,N-dimethylchlorosulfitemethaniminium chloride formed from thionyl chloride and dimethylformamide was found and efficient reagent for the synthesis of acyl azides from carboxylic acids and nitriles from oximes. It is also highly efficient for the direct synthesis of beta-lactams from carboxylic acids and imines avoiding the use of acid chlorides.

Since the discovery of N,N-dimethylchlorosulfitemethaniminium chloride 3, its reactivity and its synthetic applications has been little investigated[2]. This reagent has been used for the activation of carboxylic group[2d-2g] and for the preparation of alkyl chlorides[2c] and gem-dichlorides[2h]. The structure 3 of this complex has been well established by two independent authors[2a,2b,2g] and we now report its use in a variety of transformations.



$$\underset{\mathbf{1}}{SOCl_2} + \underset{\mathbf{2}}{(CH_3)_2N\text{-}CHO} \longrightarrow \underset{\mathbf{3}}{(CH_3)_2\overset{+}{N}{=}CH\text{-}O\text{-}S(=O)Cl}\ \ Cl^-$$

Preparation of 3

The reagent is prepared as follows : in a 25 ml dropping funnel, benzene (5 ml), dimethylformamide (1 ml, 10.2 mmol) and thionyl chloride (0.8 ml, 11 mmol), are consecutively added, after 3-5 min two phases were separated and the reagent (lower layer) was added to the corresponding substrates.

Preparation of Acyl azides

Acyl azides were obtained by adding the reagent prepared as above to a suspension of the carboxylic acid (10 mmol), sodium azide (20 mmol), tetrabutylammonium bromide (1 mmol) and pyridine (20 mmol) in dichloromethane as solvent. After work-up, the corresponding acyl azides were isolated in fairly pure form (Table 1).

Preparation of oximes

Oximes are rapidly dehydrated into nitriles in high yields under mild conditions. In this case two equivalents of pyridine were also used in order to neutralize the hydrochloric acid formed (Table 1).

Preparation of beta-lactams

Carboxylic acids together with Schiff bases and triethylamine react with 3 at room temperature to give beta-lactams in excellent yields. A typical example is given as follows : to a suspension of phthalimido acetic acid (2.05 gr, 10 mmol) in dichlormethane (20 ml) was added at 0ºC the reagent (10 mmol) prepared as above, after stirring at 5-10ºC for 10 min, 4-methoxybenzalaniline (2.11 gr, 10 mmol) was added and then triethylamine (4.2 ml, 30 mmol) in dichloromethane (10 ml) was dropwise added. The resulting mixture was stirred overnight at room temperature, and washed with water

TABLE 1

Substrate	time	Product	Yield (%)[a]	mp or bp /torr(ºC)
$PhtCH_2COOH$	15h	$PhtCH_2CON_3$	75	109-110
$3,5(NO_2)_2C_6H_3COOH$	20h	$3,5(NO_2)_2C_6H_3CON_3$	84	104-105
$4\text{-}CH_3OC_6H_4COOH$	20h	$4\text{-}CH_3OC_6H_4CON_3$	96	67-70
$PhtCH(CH_3)COOH$	20h	$PhtCH(CH_3)CON_3$	80	70-71
$4\text{-}ClC_6H_4CH{=}NOH$	15min	$4\text{-}ClC_6H_4CN$	80	91-92
$4\text{-}CH_3OC_6H_4CH{=}NOH$	15min	$4\text{-}CH_3OC_6H_4CN$	90	59-60
$C_6H_5CH{=}NOH$	10min	C_6H_5CN	90	190-192/760

a. Yield of pure products isolated by distillation or recrystallization ; purity $\geqslant$ 98% by tlc and glc analysis. Pht : Phthalimido group.

(50 ml), the organic layer separated and dried with sodium sulphate. Evaporation of the solvent gives trans 1-phenyl-3-phthalimido-4-(4'-methoxyphenyl)azetidine-2-one (2.78 gr, 70%) m.p. 236-237ºC (ethanol) (lit m.p. 236-237ºC)[5f] ; pmr ($CDCl_3$)δppm : 7.62(m,4H,arom.), 7.05 (m,9H, arom.), 5.25 (d,1H,CH, J=1.5 Hz), 5.18 (d,1H,CH), 3.75(s,3H,CH_3) ; i.r.($CHCl_3$)νcm^{-1} : (C=O) 1780,1770,1725 ; the use of different carboxylic acids and imines permits the preparation of a wide range of beta-lactams. The results are compiled in Table 2. As can be seen from the table, this reagent provides a short and convenient route avoiding the use of acid chlorides to synthesise beta-lactams.

We suggest that the reaction proceeds through the formation of an activated carboxylic acid species such as 4. Under the reaction conditions used, carboxylic acid chlorides were not formed ; but when the reaction between carboxylic acids and the reagent 3 was carried out in boiling dichloromethane intermediate 4 losses hydrogen chloride and sulfur dioxide giving carboxylic acid chlorides in high yields such as proposed by earlier workers[2] and by Boshard et al.[5g].

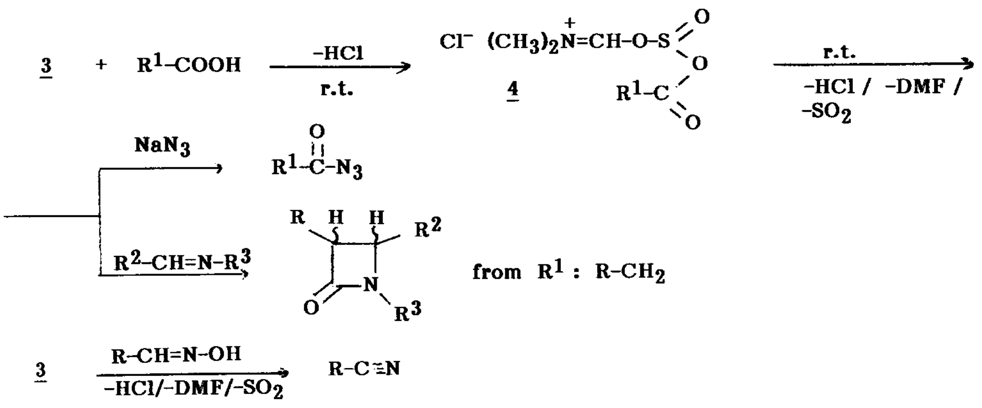
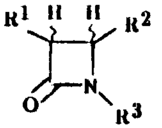


TABLE 2. beta-lactams prepared



	R^1	R^2	R^3	Yield (%)^c	Conf.^{d}	m.p.(ºC) found	m.p.(ºC) lit^4
1	**Pht^a**	**ϕ**	**ϕ**	50	trans	229-230.5	230-231^{4a}
2	**ϕO**	**4-$CH_3O\phi$**	**4-$CH_3\phi$**	61	(50%)cis^e		
					(50%)trans^e		
	ϕO	**4-$CH_3O\phi$**	**4-$CH_3\phi$**	74^g	(65%)cis	180-183	182-183^{4b}
					(35%)trans		
3	**Pht**	**4-$CH_3O\phi$**	**4-$CH_3\phi$**	74	trans^f	189-190	
4	**Cl_2^{h}**	**ϕ**	**ϕ**	60	———	164	164^{4d}
5	**4-$CH_3O\phi$**	**ϕ**	**ϕ**	35	trans	200-204	200-204^{4e}
6	**ϕO**	**ϕ**	**ϕ**	48	(57%)cis	192-193	192-195^{4e}
					(43%)trans	111-112	110-113^{4e}
7	**Pht**	**4-$CH_3O\phi$**	**ϕ**	70	trans	236-237	236-237^{4f}
8	**Pht**	**4-$CH_3O\phi$**	**-$C_{10}H_7$**	75	trans	222-223	222-223^{4f}
9	**Pht**	**4-$CH_3O\phi$**	**ϕCH_2**	60	trans	181-183	———

a) Pht : Phthalimido group . b) All compounds were identified by their physical and spectral characteristics . c) Yield of isolated pure product (before recrystallization) . d) Configuration of C-3 and C-4 protons in all these monocyclic beta-lactams was determined by pmr spectroscopy. e) percentaje determined by pmr analysis . f) m.p. 172-174ºC reported in ref. **4c** g) Addition of triethylamine at -13ºC . h) 1,4-diphenyl-3-dichloro-azetidine-2-one

REFERENCES AND NOTES

1.- Considered as Reagents and Synthetic Methods **39** . This work was financially supported by GEMA S.A. (Spanish) and LONZA A.G. (Swiss). Patent applications submited by GEMA S.A.

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(Received in UK 23 May 1984)