Tetrahedron Letters,Vol.28,No.17,pp 1945-1948,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

N,N-DIMETHYLPHOSPHORAMIDIC DICHLORIDE : A CONVENIENT REAGENT FOR THE PREPARATION OF β-LACTAMS FROM ACETIC ACIDS AND IMINES [1]

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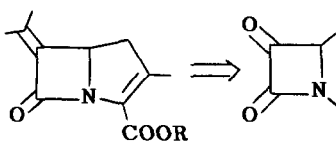
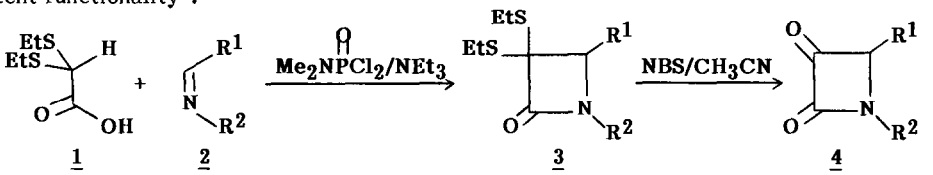
Abstract : A convenient reagent for the preparation of β-lactams from acetic acids and imines is described. A new route to α-keto- β-lactams from 3-bis(ethylthio)β-lactams is also reported. Reaction of 4-acethyl-β-lactams with diazomethane is also made.

The synthesis of functionalized monocyclic β-lactams is one of the key features of several synthetic approaches to β-lactam antibiotics. These strategies often involve as first step the construction of the azetidinone ring followed by an appropriate functionalization at N-1, C-3 and C-4 positions[2]. Despite of numerous suitable methods for the synthesis of β-lactams, the annelation of imino compounds with an activated acetic acid has proven to be a versatile procedure for the construction of the azetidinone ring[3]. Recently azetidine-2,3-diones **4** have been shown by several research groups to be useful intermediates for the introduction of carbon chains in β-lactams[4]. Unfortunately from the acetic acid-imine approach the direct disconnection of α-keto-β-lactams leads to an unsuitable synthon. To our knowledge, from this approach only a method has been appeared concerning the synthesis of azetidine-2,3-diones[5]. The recent paper by Abramski et al[6], on the reaction between 2-chloro-carbonyl-1,3-dithiane and imines, has prompted us to report our own related studies on α-keto-β-lactams. In our approach, bis(ethylthio)acetic acid was the synthetic equivalent of choice which involves the expected α-keto- latent functionality[7].

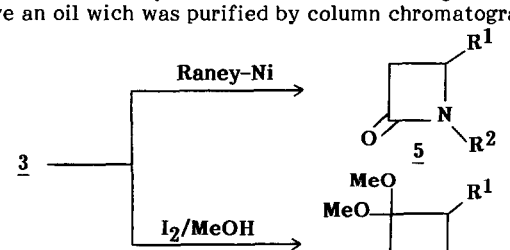


- Scheme 1 -



1 **2** **3** **4**

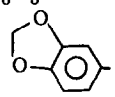
The key to our approach is the use of an efficient activating agent of the carboxyl group. Liu et al.[8] have revealed that N,N-dimethylphosphoramidic dichloride is an excellent reagent for the activation of carboxylic acids greater than the corresponding monochloro compounds. However, no application of this reagent to the synthesis of β-lactams has been given. This encouraged us to investigate the full-potential of this readily available reagent for the preparation of β-lactams[9]. First, the reaction was examined from bis(ethylthio)acetic acid, thus, a mixture of an imine **2** (10 mmol), bis(ethylthio)acetic acid **1** (1.8 g, 10 mmol) and triethylamine(4.2 ml, 30 mmol) in dichloromethane (25 ml) was stirred at 0ºC and N,N-dimethylphosphoramidic dichloride (1.2 ml, 10 mmol) was added. The resulting mixture was stirred at room temperature for 24 h and then washed with water (25 ml) followed by 1N HCl (25 ml) and the organic layer was dried with Na_2SO_4 and evaporation of the solvent gave an oil wich was purified by column chromatography (silica gel, eluent hexane/AcOEt 4:1) to give the corresponding β-lactam **3**. These β-lactams upon treatment with 7.5 fold excess of N-bromosuccinimide[10] in acetonitrile : water (4:1 v/v) cleanly afforded the expected α-keto- β-lactam in good yield. Some results are listed in Table 1 to illustrate the efficiency of the present method. Particularly, β-lactams **3b** and **4b** can be regarded as key compunds for bicyclic β-lactams because they can be easily convertible into the corresponding N-H azetidin-2-ones by means of Kronenthal's method[11] and the styryl moiety in these β-lactams can be oxidized to a carbonyl function. A further synthetic application of 3-bis(ethylthio) β-lactams **3** is that these compounds can be transformed into 3-unsubstituted β-lactams **5** by treatment with Raney-Ni. For example, β-lactam **5a** (mp. 93-95ºC) was prepared from **3a** (0.5 g, 1.6 mmol) and Raney-Ni (5 g) in refluxing ethanol (5 ml) for 1.5 h. On the other hand, since the thioalkyl group undergoes facile oxidation reactions we examined the conversion of this moiety into the bis-methoxy group following Trost's method[12]. Thus, 3-bis(ethylthio)-1-(4'-methoxyphenyl)-4-phenylazetidin-2-one **3a** upon treatment with iodine, molar ratio 1:2, in refluxing methanol for 48 h yielded the expected bis-methoxy derivative **6a** in 40% yield (mp. 111-113ºC). Under similar conditions the β-lactam **3b** afforded **6b** in 44% yield.



3 → **5** ; **3** → **6**

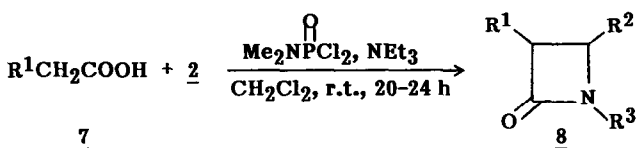
a : R^1: C_6H_5; R^2: 4-$CH_3OC_6H_4$
b : R^1: $C_6H_5CH{=}CH$; R^2: 4-$CH_3OC_6H_4$

Table 1. 3-bis(ethylthio) β-lactams 3 and α-keto- β-lactams 4 prepared

R^1	R^2	Product	Yield,%[a]	m.p.ºC	Product	Yield,%[a]	m.p.ºC	lit.m.p.ºC[5]
C_6H_5	$4\text{-}CH_3OC_6H_4$	**3a**	80	61-64	**4a**	65	129-130	130-131
$C_6H_5CH{=}CH$	$4\text{-}CH_3OC_6H_4$	**3b**	85	68-70	**4b**	65	syrup[b]	
C_6H_5	C_6H_5	**3c**	90	108-111	**4c**	50	133-135	135-137
	C_6H_5	**3d**	75	128-130	**4d**	50	137-139	139-140
$C_6H_5CH{=}C(CH_3)$	CH_2COOCH_3	**3e**	65	oil				

a) Isolated yields by column chromatography, silica gel 70-230 mesh, eluent, AcOEt/Hexane 1:4 ; all new compounds gave satisfactory elemental analyses ; b) ^{1}H-NMR ($CDCl_3$) δppm : 7.4 (m, 9H, arom), 7.1 (dd, 1H, CH=, J=8Hz), 6.9 (m, 1H, CH=, J=8Hz), 4.7 (m, 1H, CH), 3.9 (s, 3H, CH_3).

To explore the general applicability of N,N-dimethylphosphoramidic dichloride we examined the preparation of diverse β-lactams .



7 8

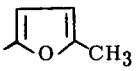
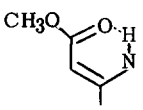
The preparation of β-lactams has been performed on a variety of structurally different acetic acids **7** to determine the scope and limitations of this reagent. Results of this study are summarized in Table 2. Phenoxyacetic acid, methoxyacetic acid and phthalimidoacetic acid (runs a-f), in the presence of imines and triethylamine, upon treatment with N,N-dimethylphosphoramidic dichloride reagent yielded the corresponding β-lactams **8** in good to excellent yields. In contrast thiophenoxyacetic acid afforded very low yields in the expected β-lactams (runs g,h). However, benzylthioglycolic acid yielded the expected β-lactam (run i) in much higher yield.

The activation of acetic acids having other functional groups such as acetoxyacetic acid, and N-(α-methyl-β-methoxycarbonylvinyl)aminoacetic acid potassium salt (Dane salt of aminoacetic acid)[13] was also examined in order to determine the synthetic effectiveness of this method. For example acetoxyacetic acid (run j) under the conditions reported here, yielded the corresponding β-lactam in good yield. Likewise, Dane salt of aminoacetic acid (runs k-n) upon treatment with N,N-dimethylphosphoramidic dichloride and triethylamine yielded the corresponding α-vinylamino-β-lactams which upon treatment with 1N HCl in methanol, followed by acylation with an acyl chloride provided the corresponding α-amido-β-lactam in 40-50% yield. From these results it is of interest to note that this reagent can be added to the narrow group of activating agents suitable for the synthesis of α-vinylamino-β-lactams[15].

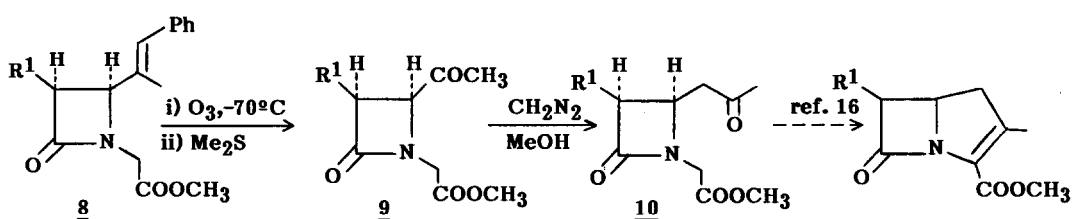
Furthermore, this method reaches a limit with N-acylamino acids such as hippuric acid and aceturic acid. Activated hippuric acid, upon treatment with benzylidene imines and triethylamine yielded the corresponding 5(4H)-oxazolone. Activation of simple aliphatic acids such as propionic acid and butyric acid did not lead to the formation of the expected β-lactams. However α-phenylacetic acids (runs o-q) such as 4-methoxyphenylacetic acid, 3,4-dimethoxyphenylacetic acid and phenylacetic acid itself yielded the respective β-lactams in moderate yields. Somewhat better yields were obtained when the reaction was carried out in refluxing benzene for 4 h.

Finally to test the potential use of the strategy depicted in scheme 1, the β-lactam **8a** was subjected to ozonolysis at -70ºC and the resulting 4-acetyl-β-lactam **9a** was treated with an ethereal solution of diazomethane in methanol as solvent ; afther 24 hr of reaction at room temperature the β-lactam **10a** was isolated by column chromatography as an oil in 43% yield. Of the solvents examined such as dichloromethane, diethylether and dioxane only methanol was found suitable for carry out diazomethane insertion. Under these conditionsβ-lactam **9b** afforded **10b** in 40% yield. Attempts to apply diazomethane insertion on β-lactam **9c** was unsuccessful probably because its extremely low solubility.

Table 2. Preparation of β-lactams 8

run[a]	R^1	R^2	R^3	yield,%[b]	m.p.[c]
a	PhO	Ph	$CH_2\overset{OH}{C}HCH_3$	40	138-141
b	PhO		$4\text{-}CH_3OC_6H_4$	50	177-179
c	PhO	$-\overset{CH_3}{C}=CHPh$	CH_2COOCH_3	60	syrup
d	CH_3O	$-\overset{CH_3}{C}=CHPh$	CH_2COOCH_3	55	syrup
e	Pht	-CH=CH-Ph	$4\text{-}CH_3OC_6H_4$	55	192-194
f	Pht	$-\overset{CH_3}{C}H=CH\text{-}Ph$	CH_2COOCH_3	50	191-194
g	PhS	Ph	Ph	12 (15)	115-116
h	PhS	Ph	$C_6H_4OCH_3\text{-}p$	15	147-148
i	$PhCH_2S$	Ph	Ph	55	147-148
j	CH_3COO	$4\text{-}CH_3C_6H_4$	$4\text{-}CH_3OC_6H_4$	50	128-130
k		$4\text{-}CH_3OC_6H_4$	$4\text{-}CH_3C_6H_4$	40	177-178
l	PhCONH	Ph	$CH_2C_6H_3(OCH_3)_2 2,4$	55[d]	147-149
m	$PhOCH_2CONH$	$-\overset{CH_3}{C}=CHPh$	$CH_2\overset{OH}{C}H\text{-}Ph$	60[d]	154-157
n	$ClCH_2CONH$	$COCH_3$	CH_2COOCH_3	30[d]	127-128
o	$4\text{-}CH_3OC_6H_4$	Ph	Ph	46 (50)	199-201
p	Ph	Ph	Ph	15 (30)	133-134
q	$3,4\text{-}(CH_3O)_2C_6H_3$	Ph	Ph	45	116-117

a) The C_3-C_4 configuration was determined by nmr spectroscopy, all products have cis-stereochemistry (J≈5Hz) except for g-i and o-q which have trans-stereochemistry (J≈2Hz) ; b) Reported yields after crystallization from athanol or ethanol-water, yield in parentheses refered to β-lactams obtained under reflux conditions ; c) All compounds were identified by their physical properties and analytical data. All the synthetic β-lactams are racemic mixtures. Pht= phthalimido group; d) overall yield from the respective α-vinylamino β-lactam.



a : PhO ; **b** : MeO ; **c** : Pht

In conclusion the present method extends the use of the readily available N,N-dimethylphosphoramidic dichloride reagent to synthesize a variety of functionalized β-lactams from acetic acids and imines[17].We are continuing to explore the diazomethane insertion on β-lactams and total synthesis of β-lactam antibiotics starting from these compounds would be presented in the near future.

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17.- Selected ^{1}H-NMR ($CDCl_3$) spectra data include : β-lactams **3** : **b,** δ ppm : 7.5-6.9(m, 9H, arom), 6.5 (d, 1H, CH, J= 8Hz), 6.2(t, 1H, CH=, J=8Hz), 4.6 (s_b, 1H, CH), 3.75 (s, 3H, CH_3), 2.9 (m, 4H, CH_2), 1.3 (m, 6H, CH_3) ; **e,** δ ppm : 7.22(s, 5H, arom), 6.35 (s_b, 1H, HC=), 4.45 (s_b, 1H,CH), 4.37(d, 1H, NCHCOO, J=-18 Hz), 3.37 (s,3H, OCH_3), 3.57 (d, 1H, NCHCOO, J=-18 Hz), 3.1-2.5 (m, 4H, $-CH_2-S$), 1.88 (s, 3H, $CH_3-C=$), 1.23 (t, 3H, CH_3-CH_2 J= 6Hz), 1.13 (t, 3H, CH_3-CH_2, J= 6Hz). β-lactam **6a** ; δ ppm : 7.1 (s, 5H, arom), 6.9(d, 2H, arom), 6.5(d, 2H, arom), 4.8 (s, 1H, CH), 3.55 (s, 3H, CH_3), 3.4 (s, 3H, CH_3), 2.9 (s, 3H, CH_3). β-lactams **8** : **run c** : δ ppm : 7.66-6.78 (m, 10 H, arom), 6.50(s_b, 1H, HC=), 5.46 (d, 1H, CH, J= 5Hz), 4.65 (d, 1H, CH, J= 5Hz), 4.45 (d, 1H, NCHCOO, J= -18 Hz), 3.72 (s, 3H, OCH_3), 3.53 (d, 1H, NCHCOO, J= -18 Hz), 1.80 (d, 3H, CH_3, J= 1.8 Hz). **run d** : δ ppm : 7.16 (s,5H, arom), 6.40 (s_b, 1H, HC=), 4.63 (d, 1H, CH, J= 5Hz), 4.20 (d, 1H, CH, J= 5Hz), 4.32 (d, 1H, NCHCOO, J= -18 Hz), 3.63-3.36((hidden), d, 1H, NCHCOO, J= -18 Hz), 3.63 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 1.83 (d, 3H, CH_3, J= 1.8 Hz). **run n** : δ ppm : 7.35 (d_b, 1H, NH, J= 8Hz), 5.50 (dd, 1H, CH, J= 5Hz, J'= 8 Hz), 4.92 (d, 1H, CH, J= 5Hz), 4.5 (d, 1H, NCHCOO, J= -18 Hz), 4.0 (s, 2H, CH_2Cl), 3.80 (d, 1H, NCHCOO, J= -18 Hz), 3.7 (s, 3H, OCH_3), 2.10 (s, 3H, CH_3). β-lactam **10a** : δ ppm : 7.5-6.8 (m, 5H, arom), 5.30 (d, 1H, CH, J= 6Hz), 4.25 (m, 1H, CH), 4.20 (d, 1H, CH, J= -18 Hz), 3.70 (s, 3H, OCH_3), 3.65 (d, 1H, CH, J= -18 Hz), 2.90 (m, 1H, CH), 2.55(m, 1H, CH), 1.35 (s, 3H, CH_3).

(Received in UK 20 February 1987)