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SYNTHETIC UTILITY OF AZETIDINE-2,3-DIONES: A NEW APPROACH TO 3-HYDROXYETHYL- β-LACTAMS AND α-AMINOACID DERIVATIVES[1]

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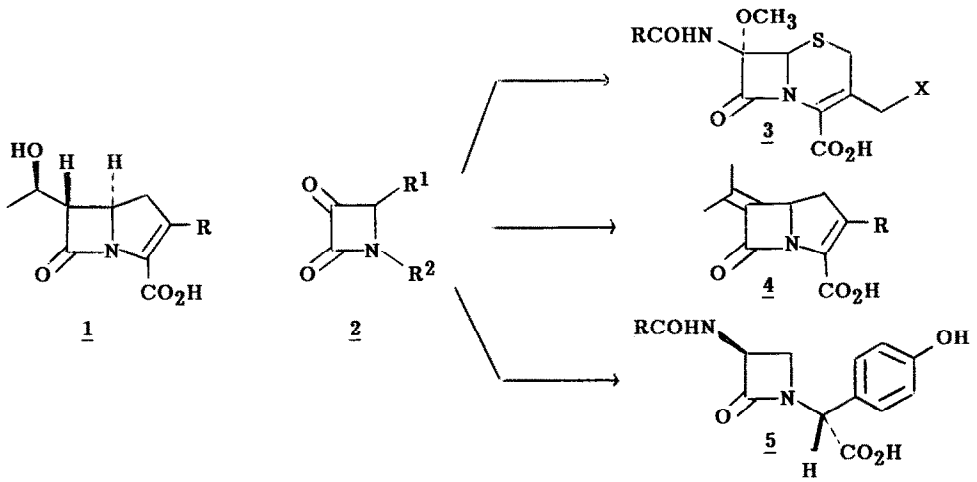
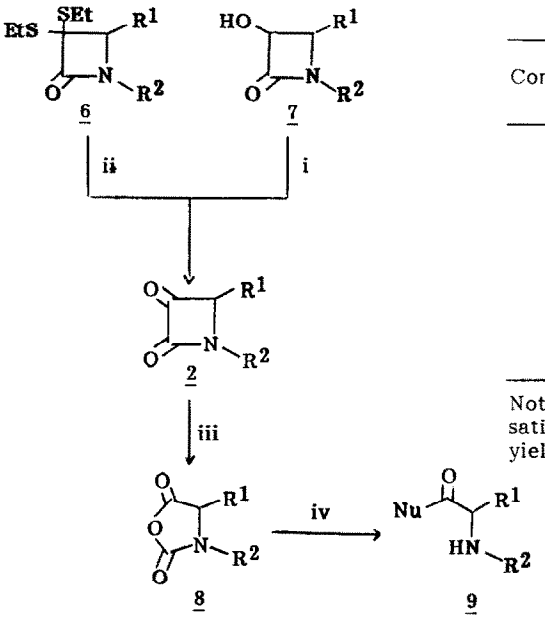
Abstract: Baeyer-Villiger oxidation of azetidine-2,3-diones provides a new route to α-aminoacid-N-carboxy-anhydrides. Conversion of azetidine-2,3-diones into 3-acetyl- β-lactams is also described.

Functionalyzed monocyclic azetidin-2-ones are an important sort of compounds not only for their interest in β-lactam antibiotic synthesis[2] but also for their conversion into diverse types of heterocycles[3]. The carbapenem family of antibiotics 1 is often characterized by the presence of hydroxyethyl side chains adjacent to the β-lactam carbonyl[4]. Several research groups have shown that azetidine-2,3-diones 2 are useful synthetic targets for the construction of β-lactams with the cephamycin[5] 3, asparenomycin[6] 4 and nocardicin[7] 5 type side chains. In this note we would like to show the utility of azetidine-2,3-diones for the preparation of 3-acyl- β-lactams as well as their synthetic potential in peptide chemistry.



We first prepared azetidine-2,3-diones 2 by oxidative hydrolysis of 3-bis(ethylthio)-β-lactams[8] 6. Now, we have found that oxydation of 3-hydroxy- β-lactams[9] 7 by means of Me_2SBr_2-NEt_3 reagent[10] provides a better way to azetidine-2,3-diones in nearly quantitative yields[11].

We found (scheme 1) that reaction between 2 and m-chloroperbenzoic acid (MCPBA) in methylene chloride afforded α-aminoacid-N-carboxyanhydrides[12] 8, which upon treatment with nucleophiles gave the expected α-aminoacid derivatives 9 in good to excellent yields. The general procedure is exemplified as follows : To a solution of MCPBA (5 mmol) in methylene chloride (25ml) the azetidine-2,3-dione 2 (3.5mmol) was added at -20ºC. After 5-10min of stirring at such temperature a white precipitate was appeared and stirring was



Scheme 1: Reagents and conditions: i, Me_2SBr_2, NEt_3, CH_2Cl_2, 60min., r.t.; ii, NBS, CH_3CN-H_2O; iii, MCPBA, CH_2Cl_2, -20°C, 60min.,; iv, NuH, C_5H_5N, 3.5h, r.t.

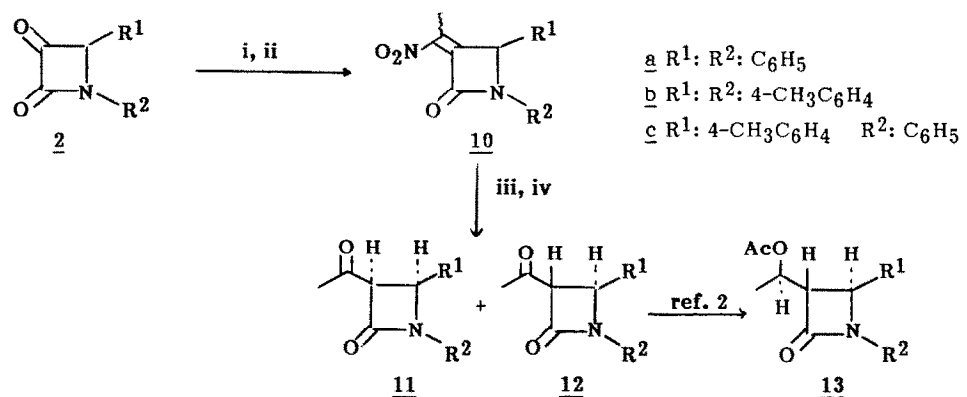
Table 1. α-Aminoacid derivatives 9 prepared [a]

Compound 9	NuH	Yield,%[b]	m.p.,°C
a	MeOH	60	78-79
b	MeOH	50	90-92
	t-$BuNH_2$	70	101-103
c	MeOH	65	114-116
d	MeOH	52	syrup
	$PhCH_2NH_2$	77	131-133

Notes: a) All compounds were racemic and gave satisfactory spectral and analytical data. b) Overall yields from 2.

a R^1: R^2: Ph
b R^1: R^2: 4-CH_3OPh
c R^1: 4-CH_3Ph, R^2: 4-BrPh
d R^1: R^2: 4-CH_3Ph

continued until the substrate could not longer be detected by tlc analysis of the crude mixture (60min). Then, a solution of the corresponding amine (4mmol) and pyridine (6.4mmol) in methylene chloride was dropwise added and the mixture was stirred at room temperature for 70min, washed with water (20ml) and then with HCl 0.1N (2x15ml). The organic layer was separated and dried with $MgSO_4$. Evaporation of the solvent gave a brown syrup which was purified by column chromatography or crystallized from ethanol. Some examples



Scheme 2: Reagents and conditions: i, $MeCH_2NO_2$, KOBu-t, THF; ii, $MeSO_2Cl$, NEt_3, CH_2Cl_2; iii, nBu_3SnH, CH_2Cl_2, r.t., 24h; iv, O_3, -70°C, CH_2Cl_2, then Me_2S.

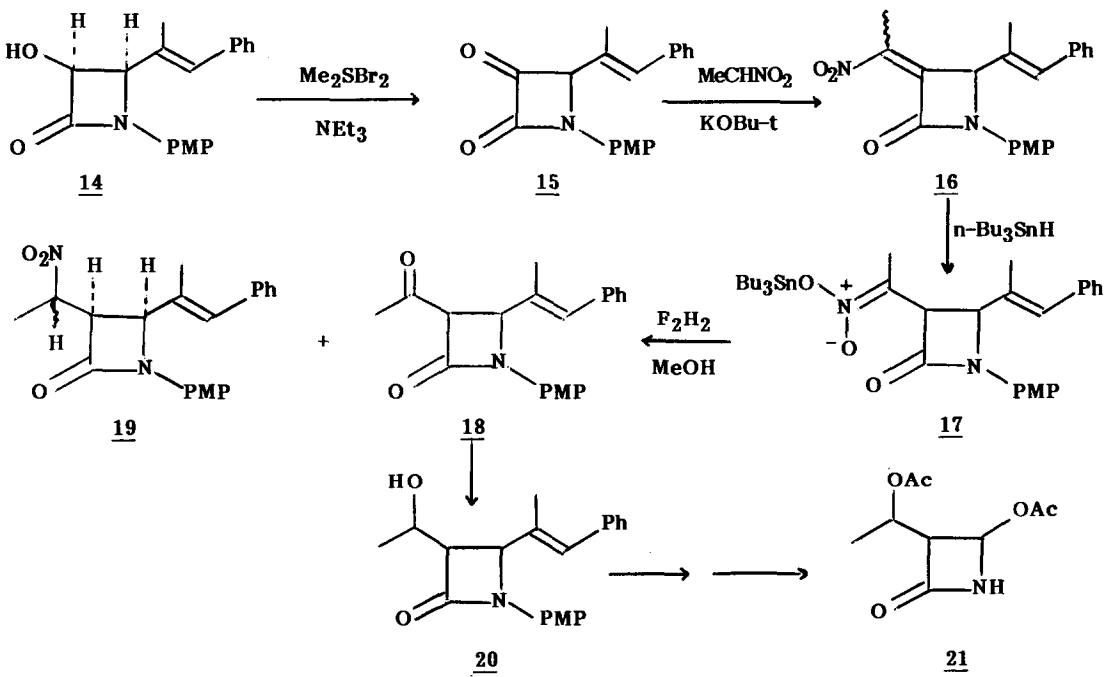
a R^1: R^2: C_6H_5
b R^1: R^2: 4-$CH_3C_6H_4$
c R^1: 4-$CH_3C_6H_4$ R^2: C_6H_5

Table 2. Compound prepared[a]

Product[b]	Yield (%)[c]	m.p.,ºC	^{1}H-NMR ($CDCl_3$,δ)[d]
10a	57	190(d)	5.9, s
10b	50	171-174	5.7, s
10c	60	172-174	5.7, s
11a	17	206(d)	6.05, 5.55 (d, J= 5 Hz)
12a	66	103-105	5.30, 3.95 (d, J= 3 Hz)
11b	80	188(d)	5.75, 5.30 (d, J= 6 Hz)
12b	—	—	
11c	14	191-193	5.75, 5.25 (d, J= 5 Hz)
12c	77	—	5.15, 3.75 (d, J= 3 Hz)

[a]All compounds were racemic and gave satisfactory analytical data. [b]Compounds **10** were isolated by crystallization from EtOH; compounds **11** and **12** were isolated by column chromatography silica gel 70-230 mesh, CH_2Cl_2/n-hexane as eluent.[c] Yields based on weight of isolated product. [d]Only C_3 and C_4 protons are given.

are listed in Table 1 to illustrate the present method. We also have found that reaction of **2** with nitrocompounds[13] followed by dehydration of the resulting nitroaldol[14] and sequential treatment[15] of **10** with tributyltin hydride and then with O_3 in methylene chloride at -70ºC afforded **11** in good yield. Although the configuration of the double bond in **10** was not determined, the stereoselectivity of the hydride addition reaction seems to be dependent of the bulkness of N-1 and C-4 substituents. Thus, while compound **10c** upon treatment with tributyltin hydride gave a mixture of cis **11c** and trans **12c** in a ratio 1/5 respectively, **10b** afforded **11b** as single isomer. In a similar way compound **10** furnished a mixture of cis-**11a** and trans-**12a** in a ratio 1/4 respectively. Since compounds of type **12** can be transformed into **13** in a stereospecific manner[2,16] our method provides a new approach to 3-hydroxyethyl β-lactams.



14 15 16 17 18 19 20 21

- scheme 3 -

At this stage we concentrated on the preparation of an appropriate substituted β-lactam as synthetic tool for the thienamycin synthesis. For this purpose we selected the β-lactam **14** depicted in scheme 3. Thus, the β-lactam **14** (m.p. 175ºC, EtOH) obtained following our procedure[9] was oxidized by means of Me_2SBr_2-NEt_3 system in methylene chloride at 0ºC for 45 min. affording **15** (m.p. 114-115ºC, $CHCl_3$-hexane) in 90% yield. Treatment of **15** with $MeCH_2NO_2$-KOBu-t in THF as solvent followed by dehydration ($MeSO_2Cl$, NEt_3,CH_2Cl_2) of the resulting crude product afforded **16** (m.p. 133-135ºC, EtOH) in 65% yield. Reaction between **16** and tributyltin hydride (molar ratio 1:1.2) in methylene chloride for 20h followed by addition of a 5N solution of H_2F_2 in methanol gave **19** as main product in 45% yield, together with traces of the carbonyl compound **18**. Compound **19** was obtained as a mixture of diastereomers (1:6) epimeric about the nitro group. Although the corresponding diastereomers were not isolated the 5Hz coupling constant between the C_3-H and C_4-H protons in both of them was indicative of the cis-stereochemistry. Since compound **19** can be transformed into **18** via Nef reaction and this one into **21** by further elaboration of the styryl and p-methoxyphenyl groups[17] the present procedure constitutes a new synthetic application of azetidine-2,3-diones in β-lactam chemistry.

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