Scope and Limitations of Oxidative Decarboxylation of α-(Acylamino) Acids by Peroxy Acids: Conversion of a 2-Azetidinone-4-carboxylic Acid to a Carbapenem

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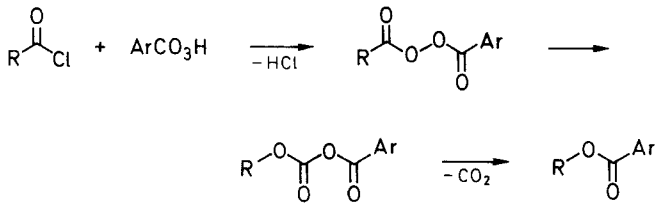
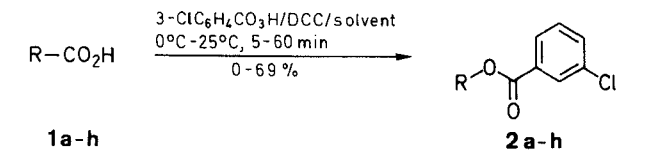
Oxidative decarboxylation of α-(acylamino) acids by peroxy acids was investigated. An application of this reaction for the conversion of the 2-azetidinone-4-carboxylic acid **1h** to a carbapenem **8** is described.

The mode of decomposition of acyl aroyl peroxides has been examined and found to give decomposition products in the cases of mixed peroxides derived from 3-chloroperoxybenzoic acid (Scheme **A**).[1] Some of these diacyl, diaroyl or acyl aroyl peroxide (R = alkyl or aryl) are occasionally fairly stable in thermolysis.[2] However, there is only one example for the conversion of an α-(acylamino) acid to acyloxy derivative with retention of configuration.[3] The author reports now on the oxidative decarboxylation of various α-(acylamino) acids via the corresponding acyl aroyl peroxides and describes the scope and limitations of this reaction.

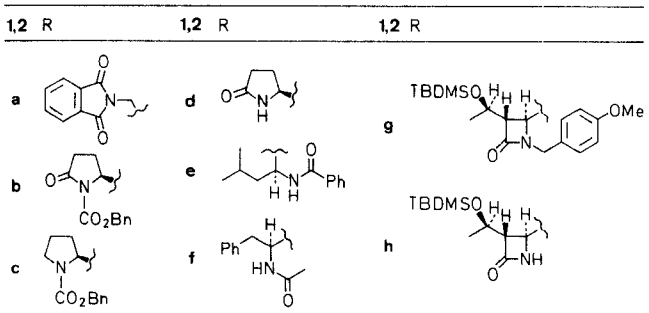


Scheme **A**

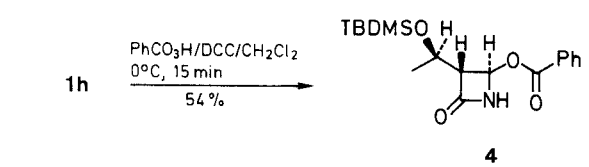
α-(Acylamino) acids, **1a–h** were prepared and treated with 3-chloroperoxybenzoic acid in the presence of 1,3-dicyclohexylcarbodiimide (DCC). Compounds **1a,b,g** and **h** gave the oxaaminal analogues **2a,b,g** and **h**, respectively, while decomposition was observed for **1d–f**. Compound **1c** gave *N*-benzyloxycarbonyl-2-hydroxypyrrolidine (**3**) instead of the expected **2c**. In the case of **1h**, oxidation with peroxybenzoic acid gave the benzoate **4**. (Scheme **B**).



1a-h **2a-h**

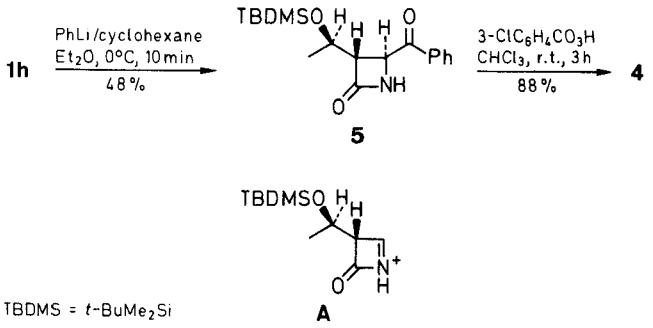


Bn = CH_2Ph; TBDMS = *t*-$BuMe_2Si$



Scheme **B**

The reaction proceeds under mild conditions below room temperature without the use of base. It is obvious that, (i) the α-substituted nitrogen atom of carboxylic acid assists the oxidative decarboxylation of acyl aroyl peroxides, (ii) *N*-substituted α-(acylamino) acids usually yield the expected products, (iii) α-(acylamino) acids possessing hydrogen on the nitrogen atom, except the β-lactam carboxylic acid **1h**, usually undergo spontaneous degradation via their iminium salts derived from normal products, and (iv) the ring strain of β-lactam spurs the reaction. The reaction conditions are mild enough not to produce the iminium ion **A** from compounds **2h** and **4**. The results are listed in Table. The melting point and $[\alpha]_D$ of **4** were found to be different from that reported in the literature.[4] Therefore, **4** was alternatively prepared from **1h** in two steps (Scheme **C**) and shown to be identical with that obtained from **1h** by oxidative decarboxylation in all respects.



TBDMS = *t*-$BuMe_2Si$ **A**

Scheme **C**

In the field of β-lactam antibiotics, 3-(1-hydroxyethyl)-4-acetoxy-2-azetidinone is an important intermediate for the syntheses of thienamycin (**9**) and 1-methylcarbapenems. A number of syntheses of 4-acetoxy-2-azetidinone have appeared in the literature. Two of these are the oxidative decarboxylation of 2-azetidinone-4-carboxylic acid by lead tetraacetate,[5] and by the electrochemical method.[6] Another is the Baeyer–Villiger oxidation of 4-acyl-2-azetidinone derivatives,[7] which was also obtainable from 2-azetidinone-4-carboxylic acid and other sources. The compound **2h** is expected to be useful as an intermediate in carbapenem synthesis. Therefore, conversion of **2h** to thienamycin intermediate **8** was attempted, and it became obvious that **2h** was also a suitable intermediate for the synthesis of carbapenems.

Compound **1h**, obtained by saponification of *tert*-butyl (3*S*,4*S*)-3-[(*R*)-1-(*tert*-butyldimethylsiloxy)ethyl]-2-azetidinone-4-carboxylate (**6**) synthesized from L-threo-

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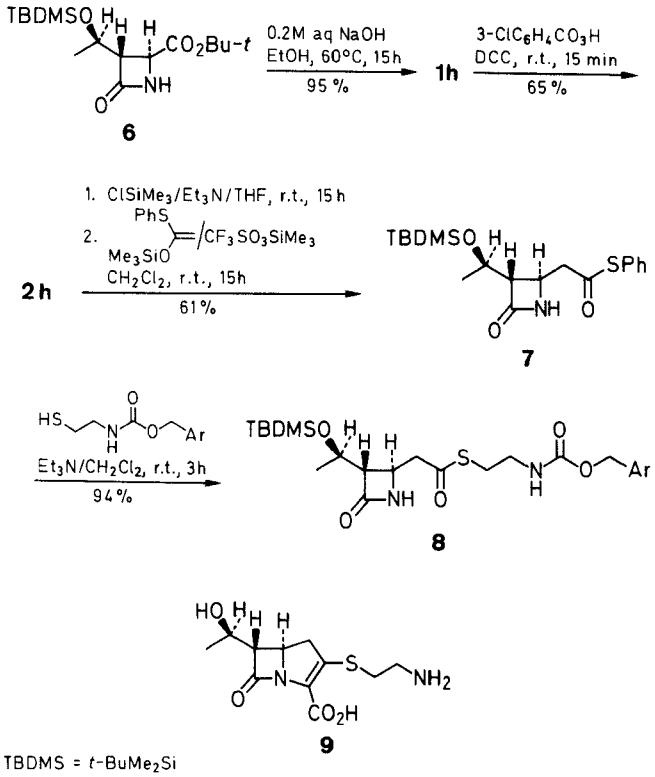
nine,[8] yielded **2h** by oxidative decarboxylation with 3-chloroperoxybenzoic acid. *N*-Silylation of **2h**, followed by C–C bond formation[9] with 1-phenylthio-1-trimethylsiloxyethylene using trimethylsilyl trifluoromethanesulphonate gave **7** which on treatment with 2-mercapto-*N*-(4-nitrobenzyloxycarbonyl)ethylamine using triethylamine as a catalyst gave **8**, a key intermediate to thienamycin (**9**)[10] (Scheme **D**).



Scheme **D**

All melting points are uncorrected. ^{1}H-NMR spectra were recorded at 60 or 270 MHz using TMS as an internal standard. Column chromatography was carried out on columns packed with Merck silica gel 60 (230–400 mesh ASTM) using a slightly increased pressure (1.2 atm) for elution. α-(Acylamino) acids **1a–f** were commercially available. Compounds **1g,h** were prepared from the corresponding *tert*-butyl esters.[7]

(3*S*,4*S*)-3-[(*R*)-1-(*tert*-Butyldimethylsiloxy)ethyl]-2-azetidinone-4-carboxylic Acid (1h):

A solution of *tert*-butyl (3*S*,4*S*)-3-[(*R*)-1-*tert*-butyldimethylsiloxy)-ethyl]-2-azetidineone-4-carboxylate (**6**;[8] 659 mg, 2.0 mmol) in EtOH (40 mL) and 0.2 N NaOH (12 mL) is warmed at 60 °C for 15 h. The reaction mixture is concentrated *in vacuo*, acidified with dil HCl, and extracted with EtOAc. The extract was washed with H_2O and brine and dried ($MgSO_4$). After filtration, the solvent is removed *in vacuo* to give **1h**; yield: 521 mg (95 %); mp 143–145 °C (hexane).

$C_{12}H_{23}NO_4Si$	calc.	C 52.72	H 8.48	N 5.12	
(273.2)	found	52.54	8.31	5.06	

IR (Nujol): ν = 3320, 3200–2400, 1760, 1733, 1710 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.07 (s, 6H, $2CH_3$), 0.86 (s, 9H, *t*-C_4H_9), 1.26 (d, 3H, J = 6.5 Hz, CH_3), 3.35 (m, 1H, H-3), 4.25 (m, 1H, CHOSi), 4.43 (d, 1H, J = 2.5 Hz, H-4), 6.79 (br s, 1H, NH), 8.68 (br s, 1H, CO_2H).

Oxidative Decarboxylation of α-(Acylamino) Acids 1a–h; General Procedure:

To a solution of the substrate **1a–h** (1.0 mmol) in a solvent (2–10 mL) cooled in an ice bath is added peroxy acid (3-chloroperoxybenzoic acid or peroxybenzoic acid) (1.1 mmol) and then 1,3-dicyclohexylcarbodiimide (227 mg, 1.1 mmol) with stirring. After evolution of CO_2 has ceased at 0 °C or r.t. (see Table for reaction conditions), the mixture is filtered and chromatographed on a silica gel column (eluent: cyclohexane/EtOAc (3:1) (Table).

N-Benzyloxycarbonyl-2-hydroxypyrrolidine (**3**); mp 45 °C (Lit.[11,12] mp 45–46 °C).

IR (film) ν = 3420, 1690 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.8–2.1 (m, 4H, H-3 + H-4), 3.15 (s, 1H, OH), 3.3–3.7 (m, 2H, NCH_2), 5.13 (s, 2H, CH_2Ar), 5.52 (s, 1H, CHOH), 7.53 (s, 5H_{arom}).

(3*S*,4*R*)-4-Benzyloxy-3-[(*R*)-1-(*tert*-butyldimethylsiloxy)ethyl]-2-azetidinone (4) (cf. Scheme C):

To a solution of **1h** (273 mg, 1 mmol) in Et_2O/cyclohexane (3:1, 8 mL) is added a 2 M solution of PhLi in cyclohexane/Et_2O (2.0 mL) at 0 °C with stirring under N_2. After 10 min, the mixture is quenched with H_2O (5 mL), and extracted with EtOAc. The organic layer is washed with H_2O and brine, dried ($MgSO_4$), concentrated *in vacuo* to give a crude solid, which is chromatographed on a silica gel column. Elution with cyclohexane/EtOAc (4:1) affords **5** as a crystalline solid; yield: 159 mg (48 %); mp 173.5–174.5 °C (EtOAc/hexane); $[\alpha]_D^{25}$ – 20.1° (c = 1.15, $CHCl_3$); (Lit.[4] mp 158–160 °C; $[\alpha]_D$ – 28.2° ($CHCl_3$)).

Baeyer–Villiger Oxidation of **5** *to* **4**: Ketone **5** is dissolved in $CHCl_3$ (6 mL), and treated with 3-chloroperoxybenzoic acid (500 mg). After keeping 3 h in the dark, the mixture is diluted with EtOAc. The organic layer is separated, washed with 10 % $NaHSO_3$ (2 × 20 mL), sat. $NaHCO_3$ (2 × 20 mL), brine, and concentrated to give a crude solid, which is chromatographed on silica gel. Elution with cyclohexane/EtOAc (4:1) gives **4**; yield: 147 mg (88 %); mp 123–124.5 °C (hexane); $[\alpha]_D^{25}$ + 69.1° (c = 1.0, $CHCl_3$); (Lit.[4] mp 100–102 °C, $[\alpha]_D$ – 66° ($CHCl_3$)). This compound was identical in all respects with **4** obtained in the general procedure.[13]

(3*S*,4*R*)-3-[(*R*)-1-(*tert*-Butyldimethylsiloxy)ethyl]-4-[(phenylthiocarbonyl)methyl]-2-azetidinone (7):

To a stirred solution of **2h** (192 mg, 0.50 mmol) in THF (2 mL) is added Et_3N (76 mg, 0.76 mmol) and chlorotrimethylsilane (82 mg, 0.76 mmol) at r.t. After 15 h, the mixture is filtered and concentrated *in vacuo* to give an oily residue, which is dissolved in CH_2Cl_2 (3 mL). To this solution is added 1-phenylthio-1-trimethylsiloxyethylene (224 mg, 1.0 mmol) and then trimethylsilyl trifluoromethanesulfonate (222 mg, 1.0 mmol) at r.t. with stirring. The mixture is stirred for 15 h at r.t., diluted with CH_2Cl_2, washed with H_2O and brine, dried ($MgSO_4$), and the concentrated to give a residue. Purification by column chromatography on silica gel gives **7** as crystalline solid; yield: 115 mg (61 %); mp 95–96 °C (hexane); $[\alpha]_D^{24}$ + 41.7° (c = 1.6, $CHCl_3$).

$C_{19}H_{29}NO_3SSi$	calc.	C 60.12	H 7.70	N 3.69	S 8.45
(379.5)	found	60.06	7.82	3.70	8.37

IR (Nujol): ν = 3175, 3110, 1765, 1725, 1698 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.08 (s, 6H, $2CH_3$), 0.87 (s, 9H, *t*-C_4H_9), 1.19 (d, 3H, J = 6 Hz, CH_3), 2.55–3.25 (m, 3H, H-3 + H-4), 3.7–4.33 (m, 2H, H-4 + CHOSi), 6.20 (bs, 1H, NH), 7.35 (s, 5H_{arom}).

(3*S*,4*R*)-3-[(*R*)-1-(*tert*-Butyldimethylsiloxy)ethyl]-4-{[2-(*p*-nitrobenzyloxycarbonylamino)ethylthiocarbonyl]methyl}-2-azetidinone (8):

A solution of phenylthioester **7** (191 mg, 0.50 mmol), *N*-(*p*-nitrobenzyloxycarbonyl)cysteamine (144 mg, 0.56 mmol), and Et_3N (10 mg) in CH_2Cl_2 (5 mL) is stirred for 3 h at r.t. The mixture is diluted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), concentrated, and chromatographed on a silica gel column. Elution with cyclohexane/EtOAc (1:2) affords **8** as gum; yield: 247 mg (94 %).

$C_{23}H_{35}N_3O_7SSi$	calc.	C 52.55	H 6.71	N 7.99	S 6.10
(525.7)	found	52.50	6.58	7.94	6.13

MS (70 eV): m/z = 468 (M^+-*t*-Bu).

IR (Nujol): ν = 3300, 1752, 1720, 1690 (sh) cm^{-1}.

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Table. Oxidative Decarboxylation of α-(Acylamino) Acids via Diacyl Peroxides

Product	Peroxy Acid[a]	Reaction Conditions: Solvent	Reaction Conditions: Temp (°C)/ Time (min)	Yield (%)	mp (°C) (solvent)	Molecular Formula[b] or Lit. mp (°C)	IR (film/ Nujol) ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
2a	A	EtOAc	25/60	46	167–169 (EtOAc)	$C_{16}H_{10}ClNO_4$ (315.7)	3065, 1785, 1720	6.00 (s, 2H, CH_2), 7.2–8.1 (m, 8H$_{arom}$)
2b	A	$CHCl_3$	25/60	42[c]	74–75 (EtOAc/ hexane)	$C_{19}H_{16}ClNO_5$ (373.8)	1790, 1727, 1708	2.14–2.23 (m, 1H, H-4), 2.35–2.63 (m, 2H, H-3 + H-4), 2.76–2.91 (m, 1H, H-3), 5.17, 5.35 (ABq, 2H, J = 12.1, CH_2Ar), 6.96 (d, 1H, J = 5.5, H-5), 7.18–7.40 (m, 6H$_{arom}$), 7.53–7.58 (m, 1H$_{arom}$), 7.78–7.88 (m, 2H$_{arom}$)
2c	A	CH_2Cl_2	0/5	0[d]	–	–	–	–
2d	A	DMF	25/60	0	–	–	–	–
2e	A	CH_2Cl_2	0/5	0	–	–	–	–
2f	A	EtOAc	0/10	0	–	–	–	–
2g	A	CH_2Cl_2	0/5	69	oil	$C_{26}H_{34}ClNO_5Si$ (504.1)	1770, 1725	0.04 (s, 3H, CH_3), 0.08 (s, 3H, CH_3), 0.85 (s, 9H, t-C_4H_9), 1.29 (d, 3H, J = 6.6, CH_3), 3.25 (d, 1H, J = 3.3, H-3), 3.37 (s, 3H, OCH_3), 4.26 (m, 1H, CHOSi), 4.26, 4.48 (ABq, 2H, J = 14.9, CH_2Ar), 6.33 (s, 1H, H-4), 6.75 (d, 2H$_{arom}$, J = 8.8), 7.20–7.77 (m, 6H$_{arom}$)
2h	A	CH_2Cl_2	0/15	65	133–135 (hexane)	$C_{18}H_{26}ClNO_4Si$ (383.9)	3175, 3020, 1775, 1727	0.09 (s, 3H, CH_3), 0.10 (s, 3H, CH_3), 0.88 (s, 9H, t-C_4H_9), 1.32 (d, 3H, J = 6.2, CH_3), 3.37 (dd, 1H, J = 1.1, 3.4, H-3), 4.29 (dq, J = 3.4, 6.2, CHOSi), 6.10 (d, 1H, J = 1.1, H-4), 6.54 (br s, 1H, NH), 7.3–8.1 (m, 4H$_{arom}$)
4	B	CH_2Cl_2	0/15	54	121–122 (hexane)	100–102[4]	3180, 1775, 1742, 1722	0.10 (s, 6H, 2CH_3), 0.90 (s, 9H, t-C_4H_9), 1.32 (d, 3H, J = 6.5, CH_3), 3.34 (dd, 1H, J = 1, 3, H-3), 4.28 (m, 1H, CHOSi), 6.12 (d, 1H, J = 1, H-4), 6.70 (br s, 1H, NH), 7.3–7.7 (m, 3H$_{arom}$), 7.9–8.2 (m, 2H$_{arom}$)

[a] A = 3-chloroperoxybenzoic acid, B = peroxybenzoic acid.
[b] Satisfactory microanalyses obtained: C ±0.20, H ±0.13, N ±0.09, Cl ±0.30.
[c] $[\alpha]_D^{24}$ −66.1° (c = 2.3, $CHCl_3$).
[d] *N*-Benzyloxycarbonyl-2-hydroxypyrrolidine **(3)**[11,12] instead of **2c** was obtained in 43% yield.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.06 (s, 3H, CH_3), 0.07 (s, 3H, CH_3), 0.87 (s, 9H, t-C_4H_9), 1.20 (d, 3H, J = 6.4 Hz, CH_3), 2.74–2.84 (m, 2H, CH_2CO), 2.94–3.17 (m, 3H, SCH_2 + H-3), 3.37–3.46 (m, 2H, CH_2N), 3.99 (ddd, 1H, J = 2.4, 3.9, 9.8 Hz, H-4), 4.17 (quintet, 1H, J = 5.7 Hz, CHOSi), 5.20 (s, 2H, CH_2Ar), 5.33 (t, 1H, J = 5.9 Hz, $NHCO_2$), 6.39 (s, 1H, CONH), 7.51 (d, 2H$_{arom}$, J = 8.8 Hz), 8.22 (d, 2H$_{arom}$, J = 8.8 Hz).

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(1) Denney, D.B.; Sherman, N. *J. Org. Chem.* **1965**, *30*, 3760.
(2) Shiozaki, M.; Ishida, N.; Sato, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3950.
(3) Barton, D.H.R.; Coates, I.H.; Sammes, P.G. *J. Chem. Soc., Perkin 1* **1973**, 599.
(4) Hanessian, S.; Bedeschi, A.; Battistini, C.; Mongelli, N. *J. Am. Chem. Soc.* **1985**, *107*, 1438.
(5) Reider, P.J.; Grabowski, E.J.J. *Tetrahedron Lett.* **1982**, *23*, 2293.
(6) Mori, M.; Kagechika, K.; Tohjima, K.; Shibasaki, M. *Tetrahedron Lett.* **1988**, *29*, 1409.
(7) Shiozaki, M.; Ishida, N.; Hiraoka, T.; Maruyama, H. *Tetrahedron Lett.* **1981**, *22*, 5205.
(8) Shiozaki, M.; Ishida, N.; Hiraoka, T.; Maruyama, H. *Tetrahedron* **1984**, *40*, 1795.
(9) Barrett, A.G.M.; Quarle, P. *J. Chem. Soc., Chem. Commun.* **1981**, 1076.
(10) Yoshida, A.; Tajima, T.; Takeda, N.; Oida, S. *Tetrahedron Lett.* **1984**, *25*, 2793.
(11) Lucente, G.; Pinnen, F.; Zanotti, G. *Tetrahedron Lett.* **1978**, 3155.
(12) Nagasaka, T.; Tamano, H.; Maekawa, T.; Hamaguchi, F. *Heterocycles* **1987**, *26*, 617.
(13) Author can not explain the difference in the $[\alpha]_D$ value between the value of **4** and that of the compound reported in the literature.[4]

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