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Synthesis of Amides: An Efficient and Chemoselective Method for the Preparation of β-Lactam Derivatives Related to HLE Inhibitors

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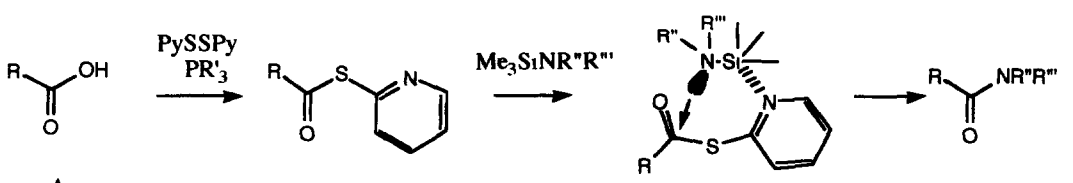
Abstract A practical method for the chemoselective synthesis of amides in presence of the β-lactam ring has been described, by an efficient coupling reaction between a reactive 2-pyridyl thiolester intermediate and a suitable N-silylamine

In 1986, researchers at Merck, Sharp and Dohme reported that suitably modified cephalosporins were able to inhibit, via a relatively stable acyl-enzyme derivative, the action of the human leukocytes elastase (HLE),[2] a serine protease enzyme responsible for the degradation of the connective tissues in inflammatory diseases [3]

It would appear that a fundamental requirement for the activity of these low-molecular weight inhibitors, is the presence of an amide, or a more lipophilic residue, at the C-2 of the cephalosporin nucleus [4-7] A number of useful methods already exist for the synthesis of amides and peptides [8] However, the presence of potentially sensitive functional groups, such as a ß–lactam ring, can affect the efficiency of the reactions. For example, in the preparation of N and N,N'- substituted C-2 carboxamides of cephalosporins, low yields and a mixture of Δ_3 and Δ_2 isomers were reported, while the corresponding primary amides have not been synthesised [5,9]

We describe herein a mild, one-pot process for the chemoselective conversion of a carboxylic acid **A** into the corresponding amide **C** *via* a highly reactive 2-pyridyl thiolester **B**,[10] using an N-silylamine as a nucleophile (Fig 1)

Fig 1

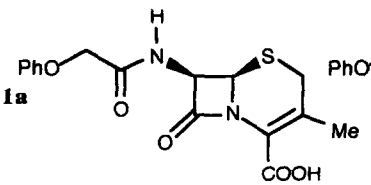
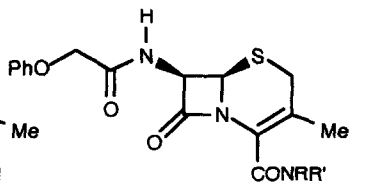
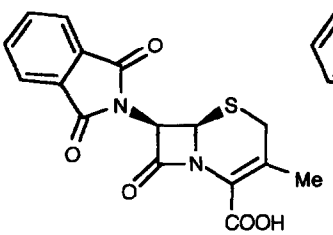
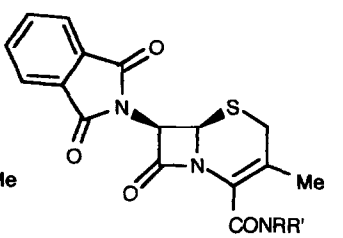
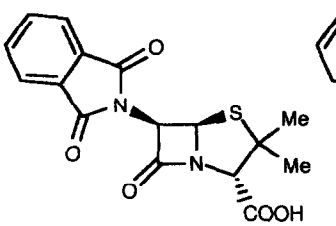
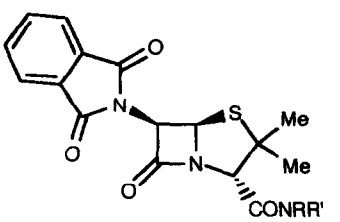


A **B** **C**

Thus, when a series of 2-pyridyl thiolesters intermediates **B**, generated *in situ* by a mild "oxidation-reduction condensation",[10a] was treated with suitable N-silylamines in dry CH_2Cl_2 or CH_3CN, efficient and rapid reactions were found to occur giving amides **C**, presumably *via* a cyclic six-membered transition state

With a series of ß-lactam substrates, the corresponding amides were isolated in good to excellent yields (Table 1) Moreover, it should be noted that even in the presence of a large excess of N-silylamines neither the Δ_2 isomers nor products deriving from ring opening of the ß-lactam were observed this can be rationalised by considering the reduced basicity and nucleophilicity of N-silylamines with respect to their isosteric carbon analogues [11]

Table 1

Entry	Acid	Amide	Product	Cond.[a]	Yield[b]	(Δ_3 Δ_2)
1a			**2a** R=R'=Me	A	98%	(100 0)
				B	98%	(78 22)
				C	82%	(100:0)
			2b R=Me R'=H	A	97%	(100 0)
			2c R=R'=H	A	86%	(100 0)
1b			**2d** R=R'=Me	A	---	(100 0)
				B	86%	(87 13)
				C	80%	(100 0)
			2e R=Me R'=H	C	58%	(100 0)
				A	---	(100 0)
			2f R=R'=H	C	57%	(100 0)
1c			**2g** R=R'=Me	A	---	
				B	86%	
			2h R=R'=H	A	---	
				B	72%	

a. Conditions, A PySSPy PPh_3, (2 eq.) B. PySSPy PBu_3, (1.7 eq.)C. PySSPy $P(OEt)_3$, (1.7 eq.)
b. Yields (overall from the acid via the corresponding 2-pyridyl thiolester) and Δ_3 Δ_2 ratios are for isolated products

Although the reaction appears to be quite general and efficient, in some cases problems were encountered in separating the resulting amides from the triphenylphosphine oxide generated as a by-product (Table 1 entries 2d-h) As a means of overcoming this potentially serious problem, the use of alternative reagents to triphenylphosphine was investigated Using tributylphosphine (Conditions B), it was possible to isolate the pure amides 2a and 2d in good yield following a simple purification by flash chromatography However in this case, a

partial Δ_3 to Δ_2 isomerisation occurred Presumably, this is due to the increased basicity of tributylphosphine compared to triphenylphosphine [12] With the less basic triethylphosphite (Conditions C), no epimerisation problems were observed while the reactions maintained their efficiency Thus, Δ_3 derivatives **2a** and **2d** were obtained in good yield

Having overcome the preparative problems of replacing PPh_3 with $P(OEt)_3$, we studied the Δ_3/Δ_2 isomerisation phenomenon, well known in the synthesis of ester derivatives of cephalosporins [13] Table 2 summarises the results for the synthesis of the N,N'-dimethylamide derivative **2a** obtained from acid **1a** with a series of phosphines and phosphites

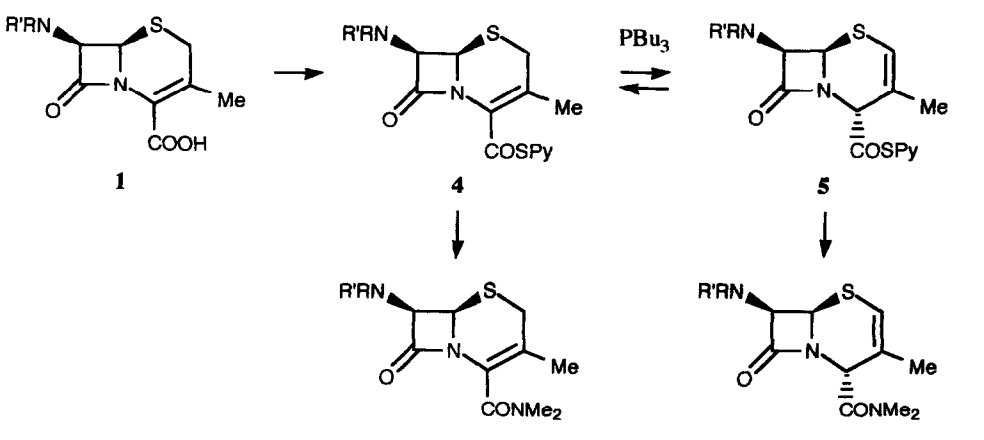
Table 2

Entry	PR_3	Yield	Ratio (Δ_3 Δ_2)	ν (cm^{-1})[a]
1	P(c-C_6H_{11})	99%	68 32	2056 4
2	P(n-Bu)$_3$	98%	78 22	2060 3
3	P(o-Tol)$_3$	97%	100 0	2066 6
4	P(C_6H_5)$_3$	98%	100 0	2060 3
5	P(OEt)$_3$	82%	100 . 0	2076 3
6	P(OC_6H_5)$_3$	-	-	2085 3

a ν_{CO} (A_1) of $Ni(CO)_3PR_3$ in CH_2Cl_2 [12], these figures are related to the electronegativity of the phosphorous atom in the PR_3 ligands which decreases from Entry 1 to Entry 6

It would appear that the Δ_3 Δ_2 ratio is dependent upon the basicity of the different phosphines or phosphites used, moreover the isomerisation of the double bond can take place only at the 2-pyridyl thiolester intermediate **4** stage (Fig 2)

Fig. 2



1 **4** **5** **2** **3**

3a R' = H R = Phenoxyacetyl
3b R' = R = Phthaloyl

In fact, as carried out in an NMR tube under conditions B and with CD_2Cl_2 as solvent, an 80 . 20 mixture of the two 2-pyridyl thiolester isomers **4** and **5** was observed. On adding the N-trimethylsilyldimethylamine, an instantaneous and quantitative reaction occurred giving the corresponding amides **2** and **3** in the same ratio, even in the presence of a large excess of the N-silylamine.

Finally it is important to stress that the mildness of the described procedure, allowed to prepare the amides **2c** , **2f** and **2h** in 86%, 57% and 72% yield, never obtained before, even though in this case the formation of these amides from the corresponding 2-pyridyl thiolester was slower (overnight, r t), reflecting the reduced silylating power[14] of the HMDS compared to the N-trimethylsilyldimethylamine

In conclusion a practical and highly efficient method for the synthesis of amides in presence of a potentially reactive ß-lactam ring has been discussed Currently the synthesis of some novel β–lactam derivatives exploiting the described procedure is in progress.

Experimental Section

Infrared spectra were recorded on a Bruker IFS 48 spectrometer ^1H NMR spectra were recorded on a Varian Unity 400 (400 MHz); the data are reported as follow chemical shift in ppm from the internal standard Me_4Si on δ scale, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling constant (Hz). Optical rotation were determined at l=589 nm (sodium lamp, D line) on a Perkin-Elmer Model 241 polarimeter. Chromatography was carried out with the use of Merck Silica Gel 60 (230-400 mesh) as described by Still *et al* [15] Mass spectra were recorded on a VG-4 Triple Quadrupole Fisons Instrument Melting points were determined on a Kofler apparatus and are uncorrected All the reactions were carried out under an atmosphere of argon in flame dried glassware. CH_2Cl_2 and CH_3CN were used after distillation from P_2O_5 Reactions were monitored by analytical thin-layer chromatography (TLC) using Merck Silica Gel 60 F-254 glass plates (0.25 mm).

General Procedures.

Conditions A :

To a magnetically stirred solution or suspension of 0 43 mmoles of starting material in 20 ml of dry CH_2Cl_2 or CH_3CN, were added, at room temperature over argon atmosphere, PPh_3 (0.22 g, 0.86 mmoles) and 2,2'-dipyridyl disulphide (0 19 g, 0 86 mmoles) portiowise over 1h, monitoring the disappearance of the starting material by TLC (EtOAc).

A-1 N-Trimethylsilyldimethylamine (0 083 ml, 0 52 mmoles) was added dropwise to the yellow-colored solution and the reaction mixture stirred at room temperature for additional 10 min The solvent was removed by evaporation and the residue poured into a mixture of EtOAc (100 ml) and HCl 5% (20 ml) The organic layer was separated and washed with NaOH 1N (2x20 ml), then with brine (3x20 ml) and finally dried over Na_2SO_4 The solvent was evaporated and the residue purified by flash chromatography (Hexanes/EtOAc 8 2 to EtOAc,

gradient) to give the pure final compound.

A-2 Hexamethyldisilazane (0 18 ml, 0 86 mmoles) or N,N'-bis(trimethylsilyl)methylamine (0 19 ml, 0 86 mmoles) were added dropwise to the reaction mixture and the solution was stirred overnight at room temperature If the final amides were partially insoluble in the reaction solvent, the white precipitate was filtered, washed twice with Et_2O and the mother liquors were processed as in the case A-1, to give a second portion of final amide

Conditions B:

To a magnetically stirred solution or suspension of 0 43 mmoles of starting material in 20 ml of dry CH_2Cl_2 or CH_3CN, were added over 1h, PBu_3 (0 18 ml, 0 73 mmoles) and 2,2'-dipyridyl disulphide (0.16 g, 0 73 mmoles), at room temperature under an argon atmosphere. The disappearance of the starting material was monitored by TLC (EtOAc)

B-1 N-Trimethylsilyldimethylamine (0 083 ml, 0.52 mmoles) was added dropwise to the reaction mixture and the solution was stirred for a further 10 min The solvent was removed by evaporation and the residue was worked up as in the case A-1

B-2 Hexamethyldisilazane (0 27 ml, 1 29 mmoles) or N,N'-bis(trimethylsilyl)methylamine (0 28 ml, 1 29 mmoles) were added dropwise to the reaction mixture and the reaction mixture was stirred at room temperature overnight, then processed according to the conditions A-2

Conditions C:

To a magnetically stirred solution or suspension of 0 43 mmoles of starting material in 20 ml of dry CH_2Cl_2 or CH_3CN were added, at room temperature under argon atmosphere over 1 h, $P(OEt)_3$ (0 12 ml, 0 73 mmoles) and 2,2'-dipyridyl disulphide (0 16 g, 0 73 mmoles), checking the disappearance of the starting carboxylic acid derivative by TLC (EtOAc).

C-1 N-Trimethylsilyldimethylamine (0 083 ml, 0 52 mmoles) was added into the reaction mixture and the solution was stirred for additional 10 min The solvent was removed by evaporation and the residue was processed as in the case A-1

C-2 Hexamethyldisilazane (0 27 ml, 1 29 mmoles) or N,N'-bis(trimethylsilyl)methylamine (0 28 ml, 1 29 mmoles) were added dropwise to the solution and the reaction mixture was stirred at room temperature overnight The CH_2Cl_2 was removed by evaporation and the residue was worked up according to the reaction conditions A-2

(6R)-N,N'-Dimethyl-3-(methyl)-7b-(phenoxy-2-acetamido)-8-oxo-5-thia-1-azabicyclo [4.2.0.] oct-2-ene-2-carboxamide 2a mp 178-180° C, $[\alpha]_D$ -19° (c 0 7, $CHCl_3$), IR (nujol) 1775, 1678, 1645, 1642 cm^{-1}, MS m/e 376 (M+1), 185, 141, ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 2H), 7 04 (dt, 1H), 6 94 (dd, 2H), 5 81 (dd, 1H, J_1 = 9 2 Hz, J_2 = 4.8 Hz), 5.06 (d, 1H, J = 4.8 Hz), 4 57 (s, 2H), 3 51 (d, 1H, J = 17 6 Hz), 3 07 (d, 1H, J = 17 6 Hz), 3.08 (s, 3H), 3.07 (s, 3H), 1 79 (s, 3H)

(6R)-N-Methyl-3-(methyl)-7b-(phenoxy-2-acetamido)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct -2-ene-2-carboxamide 2b. mp 245-247° C, $[\alpha]_D$ +91 3° (c 0 7, DMF), IR (nujol) 3287, 3269, 1763, 1678, 1647 cm^{-1}, MS m/e 362 (M+1), 171, ^1H NMR (400 MHz, CDCl3) δ 7 33 (dt, 2H), 7 04 (m, 1H), 6.93 (dd, 2H), 6 97 (bs, 1H), 5.81 (dd, 1H, J_1= 9 4 Hz, J_2 = 4 9 Hz), 5 01 (d, 1H, J = 4.9 Hz), 4.57 (s, 2H), 3 45 (d, 1H, J = 18 4 Hz), 3 13 (d, 1H, J = 18.4 Hz), 2.91 (d, 3H, J = 4 9 Hz), 2.13 (s, 3H)

(6R)-3-(Methyl)-7b-(phenoxy-2-acetamido)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxamide 2c mp 216-218° C, $[\alpha]_D$ +100° (c 0 7, DMF), IR (nujol) 3410, 3300, 3273, 1763, 1670 cm^{-1}; MS m/e 348 (M+1), 157, ^1H NMR (400 MHz, $CDCl_3$) δ 7 34 (m, 2H), 7.05, (m, 1H), 6.93 (dd, 2H), 5 85 (dd, 1H, J_1 = 9 2 Hz, J_2 = 4 9 Hz), 5 55 (bs, 1H), 5 03 (d, 1H, J = 4 9 Hz), 4 58 (s, 2H), 3 51 (d, 1H, J = 18 6 Hz), 3 18 (d, 1H, J = 18 6 Hz), 2 18 (s, 3H)

(6R)-N,N'-Dimethyl-3-(methyl)-7b-(phthalimido)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxamide 2d mp 112-114° C, $[\alpha]_D$ +20 1° (c 0 7, $CHCl_3$), IR (nujol) 1800, 1720, 1608 cm^{-1}, MS m/e 372 (M+1), 371, 326,185, 141, ^1H NMR (400 MHz, $CDCl_3$) δ 7 88 (m, 2H), 7 77 (m, 2H), 5 72 (d, 1H, J = 4 8 Hz), 5 16 (d, 1H, J = 4 8 Hz), 3 51 (d, 1H, J = 17 4 Hz), 3 25 (s, 3H), 3 12 (s, 3H), 3 11 (d, 1H, J = 17 4 Hz), 1 80 (s, 3H)

(6R)-N-Methyl-3-(methyl)-7b-(phthalimido)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxamide 2e: mp 99-101° C, $[\alpha]_D$ +31 4° (c 0 8, DMF), IR (nujol) 1778, 1767, 1720 cm^{-1}, MS m/e 372 (M+1), 187, 185; ^1H NMR (400 MHz, $CDCl_3$) δ 7 92-7 88 (m, 2H), 7 81-7 77 (m, 2H), 6.88 (m, 1H), 5 70 (d, 1H, J = 4 4 Hz), 5 13 (d, 1H, J = 4 4 Hz), 3 60 (d, 1H, J = 15 4 Hz), 3 00 (d, 1H, J = 15 4 Hz), 2 92 (d, 3H, J = 4 8 Hz), 2 50 (s, 3H)

(6R)-3-(Methyl)-7b-(phthalimido)-8-oxo-5-thia-azabicyclo [4.2.0] oct-2-ene-2-carboxamide 2f mp 236-238° C, $[\alpha]_D$ +10° (c 0 7, DMF), IR (nujol) 3402, 3169, 1799, 1780, 1750, 1718, 1655 cm^{-1}, MS m/e 345 (M+2), 344 (M+1), 343, 298, 157, ^1H NMR (400 MHz, $CDCl_3$) δ 7 90 (m, 2H), 7 79 (m, 2H), 6 94 (bs, 1H), 5 72 (d, 1H, J = 4 3 Hz), 5 48 (bs, 1H), 5 15 (d, 1H, J = 4 3 Hz), 3 65 (d, 1H, J = 15 4 Hz), 3 01 (d, 1H, J = 15 4 Hz), 2 34 (S, 3H)

(5R) - N,N'-Dimethyl-3,3-(dimethyl)-6b-(phthalimido)-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2α-carboxamide 2g mp 218-220° C, $[\alpha]_D$ +277 6° (c 0 8, $CHCl_3$), IR (nujol) 1784, 1769, 1728, 1657 cm^{-1}, MS m/e 375 (M+2), 374 (M+1), 346, 187, ^1H NMR (400 MHz, $CDCl_3$) δ 7 88 (m, 2H), 7 75 (m, 2H), 5 81 (d, 1H, J= 4 3 Hz), 5 67 (d, 1H, J = 4.3 Hz), 5 05 (s, 1H), 3 14 (s, 3H), 3 00 (s, 3H), 1 90 (s, 3H), 1 50 (s, 3H)

(5R) - 3,3-(Dimethyl)-6b-(phthalimido)-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2α-carboxamide 2h mp 223-225° C, $[\alpha]_D$ + 289 4° (c 0 8, DMF), IR (nujol) 3485, 3333, 1798, 1760, 1728, 1713 cm^{-1}, MS m/e 346 (M+1), 159, ^1H NMR (400 MHz, $CDCl_3$) δ 7 88 (m, 2H), 7 76 (m, 2H), 6 42 (bs, 1H), 5 50 (bs, 1H), 5 67 (d, 1H, J = 4 3 Hz), 5 45 (d, 1H, J = 4 3 Hz), 4 51 (s, 1H), 1 80 (s, 3H), 1.57 (s,

3H)

(6R)- N,N' -Dimethyl -3-(methyl)-7b-(phenoxy-2-acetamido)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-3-ene-2α-carboxamide 3a mp 55-57° C; $[\alpha]_D$ + 313° (c 0.8, $CHCl_3$); IR (nujol) 3450, 1772, 1693, 1657, 1601 cm^{-1}, MS m/e 376 (M+1), 185, ^1H NMR (400 MHz, $CDCl_3$) δ 7 41 (m, 1H), 7.32 (dt, 2H), 7 03 (dt, 1H), 6.92 (d, 2H), 5 98 (m, 1H), 5 73 (dd, 1H, J_1 = 9 8 Hz, J_2= 4 1 Hz), 5 29 (d, 1H, J = 4 1 Hz) 5 10 (bs, 1H), 4 55 (dd, 2H), 3 23 (s, 3H), 3 00 (s, 3H), 1 79 (bs, 3H)

(6R)-N,N'-Dimethyl-3-(methyl)-7b-(phthalimido)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2α-carboxamide 3b mp 246-248° C, $[\alpha]_D$ + 550° (c 0 5, $CHCl_3$), IR (nujol) 1786, 1772, 1728, 1655 cm^{-1}, MS m/e 358 (M+1), 187, 171, ^1H NMR (400 MHz, $CDCl_3$) δ 7 88 (m , 2H), 7.76 (m, 2H), 5.97 (m, 1H), 5 61 (d, 1H, J = 3 90 Hz), 5 41 (d, 1H, J = 3 90 Hz), 5 28 (bs, 1H), 3 30 (s, 3H), 3 03 (s, 3H), 1 85 (bs, 3H)

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