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A MILD AND EFFICIENT METHOD FOR THE PREPARATION OF N-TOSYL AMIDES AND LACTAMS

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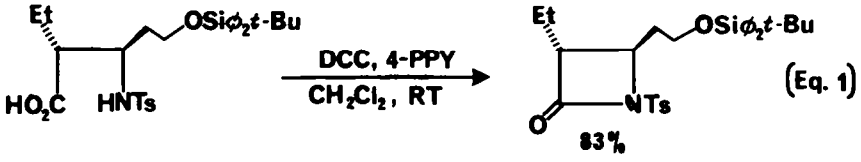
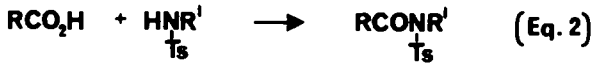
Abstract - N-tosyl amides and lactams can be prepared easily and under mild conditions by the inter- or intramolecular condensation of carboxylic acids and secondary sulfonamides. The coupling reagent used is dicyclohexyl-carbodiimide (DCC) in the presence of 4-pyrrolidinopyridine (4-PPY) and the reactions proceed readily, usually in high yield, at room temperature.

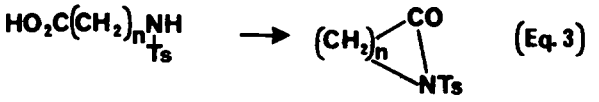
In the course of our work on the synthesis of β-lactam antibiotics[1] we recently made the serendipitous discovery that the β-sulfonamido carboxylic acid shown in Eq. 1 could be cyclised rapidly (15 min. at RT) to the corresponding N-tosyl β-lactam in excellent yield. This reaction was one of the key steps in the enantioselective route to the carbapenem antibiotic (+)-PS-5 which is described in the following paper[2], while the present report deals with the scope and limitations of the inter- and intramolecular varieties of this novel coupling reaction (Eq. 2 and 3).



(Eq. 1)



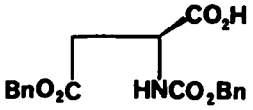
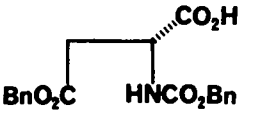
(Eq. 2)



(Eq. 3)

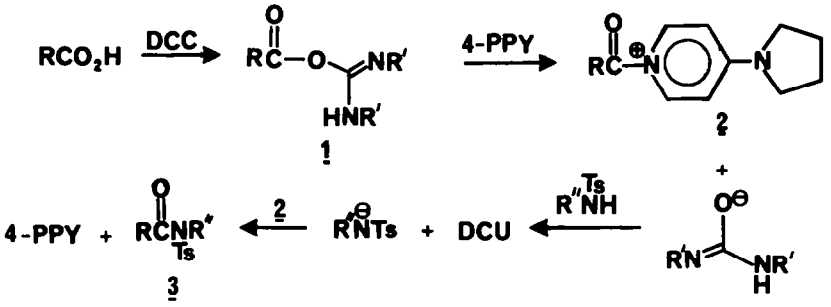
The general procedure for the coupling reaction is simple and differs little from the related Hassner esterification protocol[3]. Thus, the carboxylic acid (1.2 eq.) is added to a stirred CH_2Cl_2 solution of DCC (1.1 eq.), 4-PPY (0.1 eq.) and the sulfonamide (1.0 eq.). Upon completion of the reaction (a few minutes to several hours) the precipitated DCU is filtered off, excess acid is washed out with dilute base, and the crude N-tosyl amide obtained from the organic phase is purified by recrystallisation. The p-toluenesulfonamide from p-toluidine was chosen arbitrarily to test the coupling reaction with a variety of carboxylic acids (see Table 1).

Table 1. Coupling of p-TolNHTs with various carboxylic acids RCOOH

Entry	Acid	% Isolated yield of N-tosyl amide, 3	
1	acetic	92	
2	benzoic	78	
3	pivalic	no reaction	
4	phenylacetic	84	
5	crotonic	76	
6	9-anthroic[a]	--	
7	acetic anhydride	80	
8		63	$[\alpha]_D$ +2.8°
9		65	$[\alpha]_D$ -2.8°

[a] The relevant N-acyl urea was isolated. No coupling product observed.

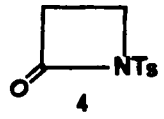
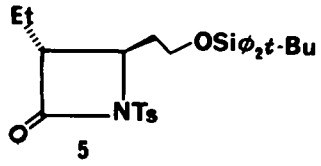
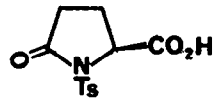
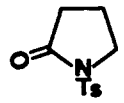
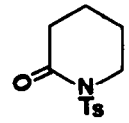
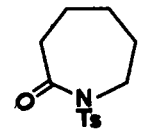
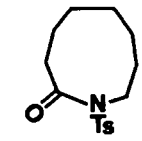
As shown in Table 1, the condensation reaction usually proceeds readily and in good to excellent yield, provided that the acid is not too sterically hindered. Pivalic acid did not react at all at room temperature, while with 9-anthroic acid the only isolable product was the N-acyl urea formed by rearrangement of the initially-formed O-acyl species. The presence of 4-PPY is essential for the desired coupling reaction, and in line with the reasoning presented by Hassner[3] to explain the mechanism for the esterification of carboxylic acids using DCC/4-PPY the acid component can be replaced by its anhydride (see entry 7 in Table 1). This may imply that anhydrides are intermediates in the coupling reactions of the carboxylic acids, but the alternative mechanistic rationale presented below is also plausible:



Thus, the initially-formed species 1 is attacked by the "super-nucleophilic"[4] 4-PPY to form the acylpyridinium ion 2. The anion of dicyclohexylurea (DCU) thus released acts as a base to generate the sulfonamide anion which then intercepts 2 to give the observed product 3, the 4-PPY catalyst being recycled. It may be recalled that Rebek and Feitler[5], in an elegant mechanistic study of DCC-mediated peptide coupling, have shown that two different reaction pathways are available, one of which does not require the intermediacy of anhydrides. We have also noted that the reactions involving "preformed" anhydrides tended to be more sluggish than the condensations which employed the acids themselves.

The results from the intramolecular coupling reactions of ω-sulfonamido carboxylic acids are shown in Table 2.

Table 2. N-tosyl lactams from the intramolecular coupling of ω-sulfonamido carboxylic acids

Entry	Product	% Isolated yield	
1	 4	20[a]	
2	 5	83	$[\alpha]_D$ - 15.2°
3	 6	63	$[\alpha]_D$ - 27.5°
4	 7	77	
5	 8	89	
6	 9	42	
7	 10	23	

[a] Estimated by ^{1}H NMR spectroscopy.

Not surprisingly, the formation of 5- and 6-membered rings presents no problem and in favourable cases (entry 2) β-lactams can also be obtained in excellent yield. As expected, the 7- and 9-membered rings were formed in only modest yields even at high dilution. In attempts to prepare an α-lactam from the N-tosyl derivative of phenylalanine, a double condensation occurred to give the relevant 2,5-diketopiperazine derivative in low yield. The use of the present methodology in the total synthesis of macrocyclic spermidine alkaloids is presently under investigation.

Finally, it may be noted that entries 8 and 9 in Table 1 and entry 3 in Table 2 imply that little or no racemisation is occurring under these conditions, the optical rotation data for compound 6 being in excellent accord with the literature value[6]. This contention is further supported by the fact that the chiral β-lactam 5 (entry 2 in Table 2) has been elaborated to a

known key intermediate for the total synthesis of the carbapenem antibiotic (+)-PS-5, as described in the following paper.

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EXPERIMENTAL

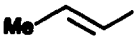
All reactions were performed under argon using oven-dried, septum-capped glassware. Methylene chloride was distilled from calcium hydride under nitrogen immediately before use. The ω-sulfonamido carboxylic acids used in the intramolecular coupling reactions were prepared by standard procedures from commercially available ω-amino acids. The synthesis of the precursor to β-lactam 5 (entry 2 in Table 2) is described in the following paper. The intermolecular condensation reactions were carried out as described in the text, the solutions being initially 0.1M with respect to the sulfonamide. For the intramolecular cases shown in Table 2, entries 2, 3, 4, and 5 were carried out at 0.1M concentration, while entries 1, 6, and 7 were run at 0.01M.

Physical data for 

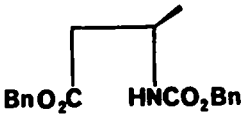
R = Me: m.p. 126 - 128°C. IR: 1700(s) 1365(s) 1170(s) cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$/TMS): δ 7.91 and 7.33 (each 2H, AA'BB'-m) 7.29 and 7.15 (each 2H, AA'BB'-m) 2.46 (3H, s) 2.42 (3H, s) 1.89 (3H, s).

R = Ph: m.p. 158 - 159°C. IR: 1690(s) 1370(s) 1170(s).
NMR: 7.83 and 7.31 (each 2H, AA'BB'-m) 7.45 and 7.05 (each 2H, AA'BB'-m) 7.29 (2H, apparent d, J = 8 Hz) 7.19 (2H, apparent t, J = 8) 7.04 (1H, m) 2.45 (3H, s) 2.30 (3H, s).

R = $PhCH_2$: m.p. 140 -142°C. IR: 1700(s) 1365(s) 1165(s).
NMR: 7.90 and 7.32 (each 2H, AA'BB'-m) 7.25 and 7.05 (each 2H, AA'BB'-m) 7.20 (3H, m) 6.90 (2H, m) 3.39 (2H, s) 2.45 (3H, s) 2.42 (3H, s).

R = 

m.p. 137 - 138°C. IR: 1690(s) 1365(s) 1170(s).
NMR: 7.91 and 7.31 (each 2H, AA'BB'-m) 7.27 and 7.13 (each 2H, AA'BB'-m) 6.95 (1H, dq, J = 15, 7.8) 5.51 (1H, dq, J = 15, 1.5) 2.45 (6H, s) 1.69 (3H, dd, J = 7.8, 1.5).

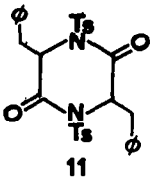
R = 

m.p. 147 - 148°C. IR: 3350, 1730(b, s) 1370(s) 1180(s).
NMR: 7.89 and 7.29 (each 2H, AA'BB'-m) 7.35 - 7.09 (14H, complex m) 5.41 (1H, bd, J = 9, -NH) 5.00 (4H, 2 x AB-m, benzylic) 4.52 (1H, ddd, J = 9, 6.5, 6, methine) 2.71 (1H, dd, J = 16, 6, methylene) 2.55 (1H, dd, J = 16, 6.5, methylene) 2.42 (3H, s) 2.39 (3H, s).
$[\alpha]_D$ = + 2.8° (c = 1, CH_2Cl_2).

The data for the enantiomer are identical, except for the sign of rotation.

Physical data for the N-Tosyl lactams.

Exposure of the N-tosyl derivative of (D,L)-phenylalanine to the usual coupling conditions (0.01M in CH_2Cl_2, RT) did not lead to formation of the desired α-lactam. Rather, a compound to which we assign the 2,5-diketopiperazine structure 11 was isolated in low yield:



11

11 : m.p. 215°C (dec.)
IR: 3015, 3000, 1705(s) 1370(s) 1175(s) cm^{-1}.
NMR: 7.98 and 7.39 (each 4H, AA'BB'-m) 7.13 (2H, apparent t, J = 8 Hz) 7.00 (4H, apparent t, J = 8) 6.61 (4H, apparent d, J = 8) 4.65 (2H, dd, J = 7, 3, methine) 3.33 (2H, dd, J = 14, 3 methylene) 3.00 (2H, dd, J = 14, 7, methylene) 2.49 (6H, s).

4: Despite several attempts, β-lactam 4 could not be obtained pure by chromatography or recrystallisation. The yield was estimated to ca. 20% by integration of the NMR spectrum of the crude product.

5: See following paper.

6: m.p. 128 - 129°C (lit.[6] 130°C).
IR: 3500 - 2500(vb) 1750 (b,s) 1360(s) 1165(s).
NMR: 8.00 and 7.35 (each 2H, AA'BB'-m) 5.55 (1H, b, -COOH) 4.93 (1H, m, methine) 2.60 (2H, m) 2.45 (3H, s, Me) 2.22 (2H, m).
$[\alpha]_D$ = -27.5° (c =1.5, EtOAc). Lit.[6] -28° (c = 1.5, EtOAc).

7: m.p. 142 - 143°C (lit.[7] 144 - 145°C).
IR: 1730(s) 1370(s) 1170(s).
NMR: 7.92 and 7.32 (each 2H, AA'BB'-m) 3.90 (2H, apparent t, J = 7) 2.41 (3H, s) 2.40 (2H, apparent t, J = 8) 2.09 (2H, m).

8: m.p. 143 - 144°C (lit.[8] 144 - 145°C).
IR: 1690(s) 1350(s) 1165(s).
NMR: 7.91 and 7.30 (each 2H, AA'BB'-m) 3.91 (2H, apparent t, J = 6) 2.40 (3H, s) overlapping (2H, apparent t, J = 6.8) 1.92 (2H, m) 1.78 (2H, m).

9: m.p. 123 - 124°C (lit.[9] 123 - 124°C).
IR: 1695(s) 1350(s) 1165(s).
NMR: 7.90 and 7.30 (each 2H, AA'BB'-m) 4.o5 (2H, m) 2.55 (2H, m) 2.40 (3H, s) 1.90 - 1.60 (6H, complex m).

10: m.p. 185°C (dec.).
IR: 1695(s) 1350(s) 1170(s).
NMR: 7.75 and 7.32 (each 2H, AA'BB'-m) 3.82 (2H, apparent t, J = 7) 2.60 (2H, apparent t, J = 7) 2.41 (3H, s) 1.60 (4H, complex m) 1.30 (6H, complex m).

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