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Amide Bond Formation via Pentafluorothiophenyl Active Esters

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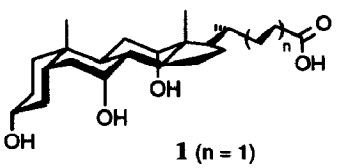
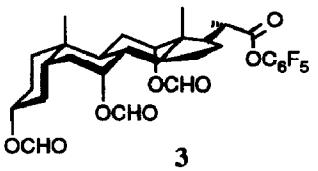
Abstract: *A number of pentafluorothiophenyl (PFTP) esters were shown to be useful acyl donors for amide bond formation, being non-polar, stable to chromatography and extended storage, but sufficiently active for use with relatively unreactive acyl groups. In particular, the synthesis of amide* **4** *via PFTP ester* **5** *proved superior to a range of alternative methods, including the use of the analogous pentafluorophenyl active ester* **3**.

The formation of amide bonds is one of the better-studied transformations in organic synthesis,[1] largely because of the importance of peptide linkages in biological chemistry. However, there may still be room for improvement, especially for situations which are somewhat removed from the coupling of common α-amino acids. We now report a new method which is generally convenient and may be uniquely useful in certain situations.

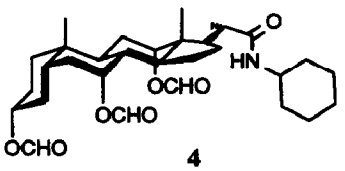
In pursuit of our studies on "cholaphanes" and related oligosteroidal receptor molecules,[2] we require high-yielding methods for coupling amines to derivatives of cholic acid (**1**) and, in more recent work, bis-nor-cholic acid (**2**). In the case of the cholic acid derivatives we have found that the well-established methodology involving pentafluorophenyl (PFP) active esters[3] is extremely effective. The PFP esters are non-polar and easily obtained pure *via* silica gel chromatography (often requiring little more than a simple filtration through flash silica). Their reactions with amines are clean and efficient, giving good results even for demanding macrolactamisations.[4]



1 (n = 1)
2 (n = 0)



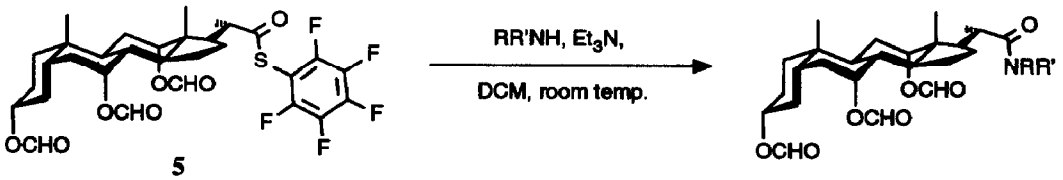
3



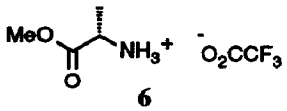
4

For the bis-nor system, the PFP esters (e.g. **3**) are again simple to obtain and purify. However, it seems that steric hindrance lowers the reactivity of the side-chain acyl carbon, such that couplings proceed sluggishly and in modest yield. Thus, the reaction of **3** with cyclohexylamine and triethylamine in dichloromethane (DCM) at room temperature occurred to give amide **4**, but was only 70 - 80% complete after 2 days. Looking for a more "forcing" method which retained the advantages of the PFP ester protocol, and noting that C_6F_5SH is quite reasonably priced,[5] we decided to investigate the potential of pentafluorothiophenyl (PFTP) esters as *N*-acylating agents.[6] The PFTP ester **5** was prepared in 93% yield by

treatment of the corresponding acid with C_6F_5SH and dicyclohexyl carbodiimide (DCC) in DCM.[7] As expected the thioester had similar polarity to its O-analogue **3**, and was fully stable to chromatography on silica gel.[8] It was also stable to storage over a period of weeks, even in the presence of moist air. However, it did indeed have the extra reactivity required to make it useful for coupling to primary and secondary amines. Thus, reaction with cyclohexylamine/Et_3N (1.1 equivalents of each) went to completion in only 8 h, resulting in an 85% yield of amide **4**.[9] Couplings with other amines proceeded smoothly as summarised in Scheme 1; conditions in all cases were analogous to those used for **4**, except for the experiment employing the alanine-derived salt **6** in which DMAP (2 eq.) was added to the reaction mixture.



5

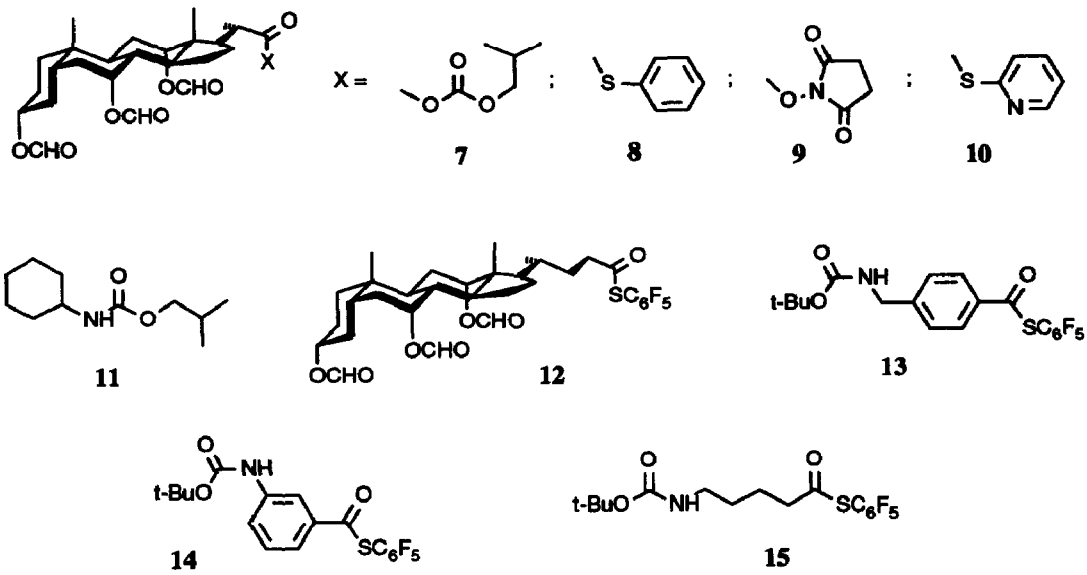
RR'NH	Reaction Time	Yield (%)
	8 h	83
	1 h	90
	1 h	95
	4 h	80

6

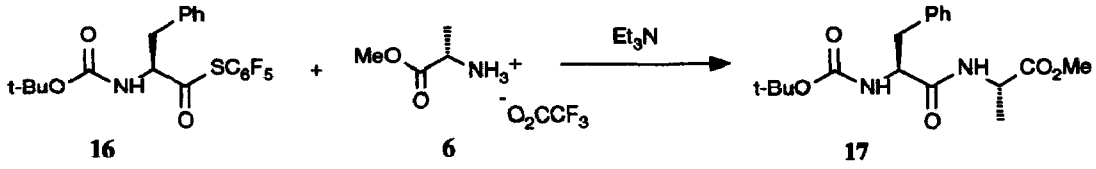
Scheme 1

To provide comparisons, a variety of other methods were applied to the synthesis of **4**. The phosphorous-based coupling reagents $(EtO)_2POCN$[10] and $(PhO)_2PON_3$[11] were unsatisfactory, giving yields of <20% after reaction times of several days. The mixed carbonic anhydride procedure, *via* intermediate **7**,[12] led only to carbamate **11** and recovered carboxylic acid. The thiophenyl ester **8** proved unreactive under the conditions, and the *N*-hydroxysuccinimide-derived active ester **9**[13] reacted at roughly the same rate as PFP ester **3**. Only the 2-pyridyl thioester **10**[14] reacted cleanly and rapidly with cyclohexylamine to give **4**. However, this derivative was more difficult to handle than **5**, being highly polar (and therefore difficult to purify by silica gel chromatography), and liable to decomposition in the presence of moist air.

Having established the value of thioester **5**, we extended our investigation to cover other acyl groups. Esters **12** to **15** were prepared in analogous fashion and, once again, were found to be stable to chromatography and extended storage. All reacted with cyclohexylamine/Et_3N in less than 1 h, under the conditions used for **5** → **4**, giving the corresponding *N*-cyclohexylamides with yields of ≥85%.



Finally we decided to examine the PFTP active ester methodology in conventional peptide synthesis. Here we encountered its first limitation, namely that *N*-BOC-α-amino acid PFTP esters could only be prepared in moderate yields, possibly due to instability to silica gel. For example, thioester **16** was obtained in 55% yield from *N*-BOC-phenylalanine, *via* our usual procedure. However, once prepared, **16** was found to be an excellent acylating agent, reacting with **6** to give dipeptide **17** in 95% yield [DMF, Et_3N (1 eq.), 0 °C, 5 min]. Davies test[15] failed to detect racemisation during coupling.



The coupling of amines with pentafluorophenyl active esters is an exceptionally convenient and effective method for amide bond formation. In applying the PFTP esters, we have developed a variant which has similar virtues (e.g. non-polar, shelf-stable intermediates) but the extra potency which may be required in certain cases. In a sense we have broadened the scope of the "PFP protocol", allowing its application to a wider range of acyl units than was previously possible.

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References and Footnotes

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2. Davis, A.P. *Chem. Soc. Rev.* **1993**, *22*, 243.
3. See e.g. Kisfaludy, L.; Schön, I. *Synthesis* **1983**, 325: Schmidt, U.; Kroner, M.; Griesser, H. *Tetrahedron Lett.* **1988**, *25*, 3057: Sheh, L.; Mokotoff, M. *Tetrahedron Lett.* **1985**, *26*, 5755.
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5. Current price from Aldrich £8.60 for 5 g; *cf.* C_6F_5OH at £7.70 for 5 g.
6. For an earlier application, in the acylation of diazoalkanes, see: Pettit, G.R.; Nelson, P.S. *Can. J. Chem.* **1986**, *64*, 2097. In this case the PFTP esters showed no particular advantages.
7. To a stirred solution of 3α,7α,12α-tris(formyloxy)-23,24-bisnorcholan-22-oic acid (0.50 g, 1.08 mmol) in anhydrous DCM (5 ml) at 0 °C was added pentafluorothiophenol (0.24 g, 1.18 mmol) and DCC (0.24 g, 1.18 mmol). The reaction mixture was left stirring at 0 °C for 1 h and at room temperature for 3 h. Precipitated dicyclohexylurea was removed by filtration and the filtrate evaporated. The residue was taken up in DCM and passed through a plug of silica, eluting with ethyl acetate-hexane (1:4), to give PFTP ester **5** (0.65 g, 93%): IR (film from DCM) 1730, 1722 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (s, 3 H, 18-Me), 0.98 (s, 3 H, 19-Me), 1.23 (d, 3 H, 21-Me), 2.72 (m, 1 H, C*H*-CO-S), 4.72 (br m, 1 H, 3β-*H*), 5.08 (m, 1 H, 7β-*H*), 5.23 (m, 1 H, 12β-*H*), 8.02, 8.10, 8.19 (3s, 3 x 1 H, O-CO-*H*); ^{13}C NMR ($CDCl_3$) δ 102.8 (Ar*C*-S), 137.7 (d, J = 256 Hz, *C*F), 142.3 (d, J = 258 Hz, *C*F), 146.8 (d, J = 250 Hz, *C*F), 195.3 (S-*C*O).
8. An added advantage is that **5**, and the other PFTP esters investigated, gave exceptionally strong responses in the UV-visualisation of TLC plates.
9. To a stirred solution of **5** (0.50 g, 0.77 mmol) in anhydrous DCM (5 ml) was added a solution of cyclohexylamine (83 mg, 0.85 mmol) and Et_3N (85 mg, 0.85 mmol) in anhydrous DCM (5 ml). After stirring for 8 h at room temperature, analysis by TLC implied that all of **5** had been consumed. Evaporation of the solvent left an oil which was passed through a plug of silica, eluting with ethyl acetate-hexane (1:1). Evaporation of the eluent gave amide **4** as a white solid (0.36 g, 85%): IR (film from DCM) 3394, 3298, 1719, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.75 (s, 3 H, 18-Me), 0.95 (s, 3 H, 19-Me), 1.09 (d, 3 H, 21-Me), 3.72 (br m, 1 H, C*H*-NH), 4.71 (br m, 1 H, 3β-*H*), 5.06 (m, 1 H, 7β-*H*), 5.21 (m, 1 H, 12β-*H*), 5.48 (d, 1 H, N*H*), 8.02, 8.08, 8.18 (3 s, 3 x 1 H, O-CO-*H*).
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