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Synthesis of Mixed Acyclic Imides Using Pentafluorophenyl Esters

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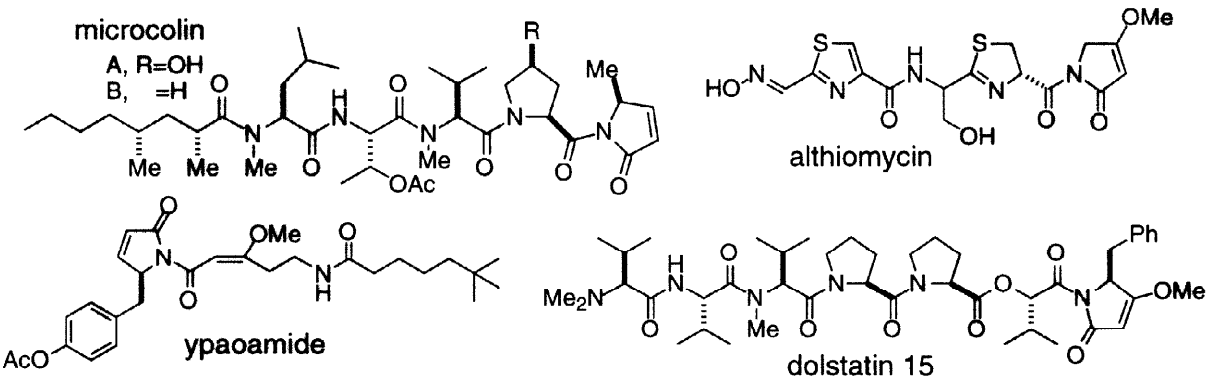
Abstract Mixed acyclic imides are assembled using amide anions and pentafluorophenyl esters reacted in THF at low temperature. Sodium hexamethyldisilazide deprotonates lactam **4** followed by addition of pentafluorophenyl (PFP) esters to give imides in high yield (85-90%). Acyclic TMS-protected primary amides were also reacted under basic conditions with PFP esters to give mixed imides. © 1998 Elsevier Science Ltd. All rights reserved.

Mixed acyclic imide functionality is shared by a growing class of natural products with diverse activity including the immunosuppressants microcolin A and B,[1] dolstatin 15,[2] a cytotoxic anticancer agent, althiomycin,[3] a potent antibiotic, and ypaoamide,[4] an antifeedant. Unlike cyclic imides, where much is known about the synthesis and reactivity,[5] only a few methods have been reported for the construction of acyclic imides.



Routes to mixed imides have most commonly involved the use of sensitive acid chlorides reacted with amides under basic conditions.[6] Anhydrides and esters, requiring strong acid conditions and high temperature, have also been used.[7] In addition, trimethylsilylamides have been reacted with acid chlorides at 0 °C to give imides in good yield.[8] Alternative routes to mixed imides include dimethylaminoalkylidenes formed at high temperature followed by hydrolysis,[9] azlacactones reacted with oxygen and palladium,[10] and amide oxidation using ruthenium tetroxide.[11] In an effort to develop a mild, general route to acyclic imides that would be tolerant of sensitive functionality for the synthesis of microcolin we developed a procedure using pentafluorophenyl (PFP) esters reacted with deprotonated amides (fig. 1).[12] Stable pentafluorophenyl esters are readily available

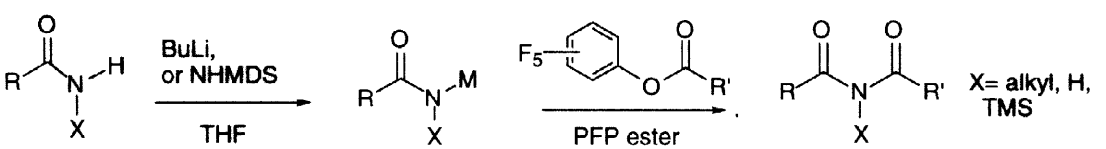


Figure 1. Metallated amides react with pentafluorophenyl (PFP) esters to give imides.

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and have previously found use for problematic amide formation.[13] We now report the PFP-based imide formation reaction can be applied to acid and base sensitive substrates and to simple non-cyclic primary amides.

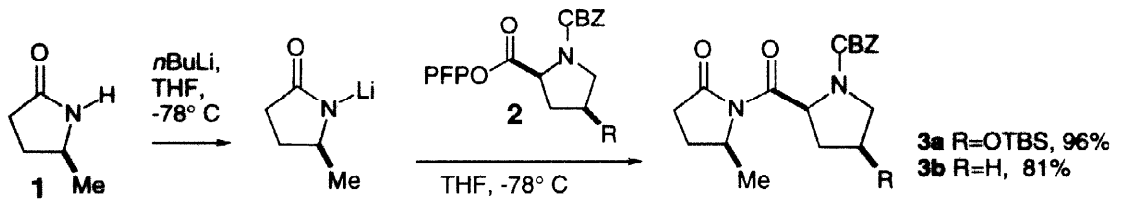
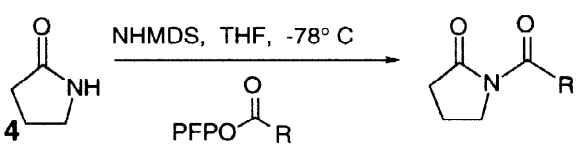


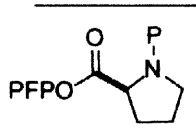
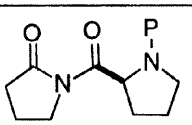
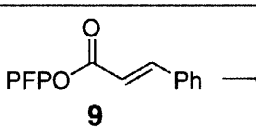
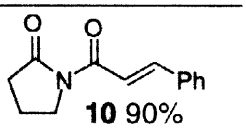
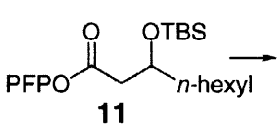
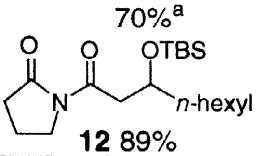
Figure 2. Microcolin precursors made from lactam **1** and PFP ester **2**.

Imides **3a** and **3b**, intermediates for the synthesis of microcolin A and B, were produced by deprotonating lactam **1** with *n*-butyllithium (2.5M in hexanes) at low temperature in THF (0.2M) followed by addition of 1 equivalent of PFP ester **2** (fig. 2). After 4 h the products were obtained in high yield following chromatography with no sign of epimerization.[12] Attempts to prepare the corresponding acid chloride of **2** using oxalyl or thionyl chloride resulted in protecting group removal and epimerization with no desired product formed.

With lactam **4**, the non-nucleophilic base sodium hexamethyl disilazide (NHMDS, 1.0M) resulted in higher yields, 85 and 88%, of the desired imides using both the CBZ and BOC-protected proline PFP esters (table 1).[14] With *n*-butyllithium as base the yields were lowered considerably to 58 and 72%. In this case a significant amount of butyl ketone by-product was also obtained resulting from butyl addition to the lactam carbonyl.[15] PFP esters **9** and **11** were made in high yield again using the established route from pentafluorophenol, dicyclohexylcarbodiimide and the corresponding acid.[12] Reactions with metallated **4** using NHMDS resulted in high yields giving imides **10** and **12**. Lower yields were again found with *n*-butyllithium and cinnamyl ester **9**. The mildness of these conditions can be seen with the sensitive β-*tert*-butyldimethylsilyl (TBS) ether PFP ester **11** which reacted with **4** and NHMDS giving **12** without elimination in 89% yield.

Table 1. Imide formation using lactam **4**.

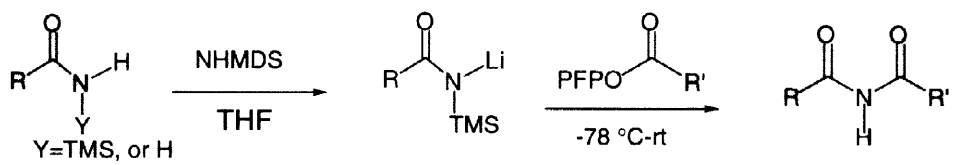


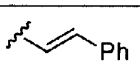
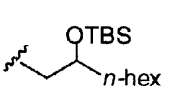
sm	product, yield	sm	product, yield
			
5 P= CBZ	**6** 85% 58%[a]	**9**	**10** 90% 70%[a]
7 P= BOC	**8** 88% 72%[a]		
		11	**12** 89%

[a] *n*BuLi was used to deprotonate **4**.

With a general route to mixed imides from secondary amides established, attention was then focused on direct imide formation from primary amides. Initially trimethylsilyl (Y=TMS) protected primary, acyclic amides (Aldrich) were reacted under various conditions with PFP esters **9** and **11** (table 2). At 1:1 amide to ester stoichiometry the reactions were slow and the imide products were obtained in low yield, 30-40% following aqueous extraction and chromatography (entries 1, 4, 7). Use of two equivalents of amide and base greatly increased the yields to the 70-80% range (entries 2, 5, 8). Under these conditions TBS protected **11** reacted to give the imide product in reasonable 59% isolated yield when reacted with TMS-pivalamide anion (entry 11). The improvement using two equivalents indicates that an equivalent of metallated TMS-amide is being consumed by TMS transfer either from the TMS-imide product or alternatively NHMDS is removing the TMS group from the TMS-amide starting material to give the free amide anion.[16] Upon acylation with the PFP ester, the acidic product imide can then transfer a proton to the amide anion. The corresponding unprotected primary amides (Y=H) were then investigated using 2.5 equivalents of lithium *tert*-butoxide at 0 °C reacted with the PFP esters (entries 3, 6, 9, 10). The N-proton of the product imide in this case is removed by the extra equivalent of *tert*-butoxide. Good yields of imide product were obtained only when α-protons were absent (entries 9 and 10).

Table 2. Mixed imide synthesis with acyclic TMS-amides.



entry	R	R'	Y	ratio[a]	time	yield
1	Me		TMS	1:1	16h	38%
2	"	"	"	2:1	3h	71%
3	"	"	H	1:1	15 min	26%[b]
4	*i*-Pr	"	TMS	1:1	16h	39%
5	"	"	"	2:1	3h	81%
6	"	"	H	1:1	15 min	42%[b]
7	*t*-Bu	"	TMS	1:1	16h	42%
8	"	"	"	2:1	3h	75%
9	"	"	H	1:1	15 min	65%[b]
10	"	"	"	1:2	"	78%[b]
11	"		TMS	2:1	15 min	59%

[a]Amide:ester ratio employed. [b]2.5 equivalent of *t*-BuOK used as base at 0 °C.

In summary, acyclic mixed imides are formed in high yields from stable PFP esters and amide anions generated at low temperature with NHMDS. Acid and base sensitive functionality are tolerated. In addition, TMS-protected primary amides allow for imide formation in high yield.

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References and Notes

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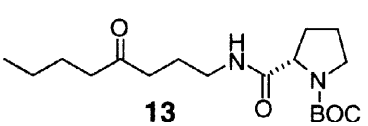
14. All intermediates and product were isolated by chromatography and adequate ^{1}H and ^{13}C NMR, IR, MS, and optical rotation data were obtained.
15. Ketones **13** and **14** were obtained in 7% and 15% yields from lactam **4** with PFP esters **5** and **9** reacted using *n*-butyllithium as base.



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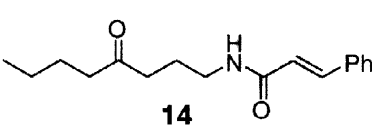

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16. Penner, G. G. H.; Polson, J. M. *J. Chem. Soc. Dalton Trans.* **1993**, 803.