Pergamon

Tetrahedron Letters 41 (2000) 9809–9813

TETRAHEDRON LETTERS

Efficient synthesis of primary amides using 2-mercaptopyridone-1-oxide-based uronium salts

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Received 10 July 2000; accepted 5 October 2000

Abstract

S-(1-Oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium tetrafluoroborate (TOTT) and hexafluorophosphate (HOTT) are cheap and convenient reagents for the rapid and high-yielding preparation of primary amides when reacted with carboxylic acids and ammonium chloride in the presence of diisopropylethylamine. The reaction is chemoselective and undesired ammonolysis of other sensitive functional groups is not observed. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: aminium salts; primary amides; coupling reagents.

The preparation of primary amides from the corresponding carboxylic acids is a basic and well-known transformation in organic synthesis.[1] Addition of ammonia to carboxylic acid derivatives such as acyl halides, anhydrides or esters is an easy and effective procedure when non-sensitive substrates are implied. However, when the starting carboxylic acid presents other functionalities which could react via addition or substitution reactions with the basic and nucleophilic ammonia, lower yields and undesirable by-products are obtained. This problem is especially serious when working in the preparation of amino acid-derived amides due to the common use of protecting groups, such as the Fmoc, which could be sensitive to these conditions. Pharmaceutically important peptide amides contain this type of amino acid derivatives, for example thyrotropin-releasing hormone (TRH) analogues such as taltirelin[2] and azetirelin,[3] antibiotics such as the amythiamicins[4] and berninamycin,[5] oxytocin antagonists such as atosiban,[6] gonad-stimulant principles such as ganirelix[7] or fungicides such as majusculamide A.[8] For this reason, the development of simple, mild, efficient, cheap and, therefore, easily scalable methods for achieving this carboxylic acid-to-primary amide transformation is desirable.

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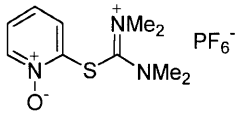
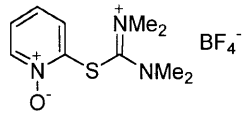
PII: S0040-4039(00)01775-5

The use of dicyclohexylcarbodiimide (DCC) in presence of 1-hydroxybenzotriazole (HOBt) for the activation of the carboxylic group and further reaction with ammonia is a known procedure.[9] Moreover, di-*tert*-butyl pyrocarbonate has also been used for activation and trapping of ammonia, generated in situ from ammonium hydrogencarbonate and pyridine in dioxane as solvent.[10] Recently, the peptide coupling reagents DCC, EDAC, PyBOP and HBTU[11] have been employed in a similar methodology affording high yields.[12] However, the best results were achieved using expensive HOBt-derived coupling reagents such as PyBOP or HBTU, the addition of an extra stoichiometric amount of HOBt and 4 equiv. of diisopropylethylamine (DIEA) being even necessary. In this communication we present the use of the uronium salts *S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethyluronium hexafluorophosphate (**1**, HOTT) and tetrafluoroborate (**2**, TOTT) as cheap and efficient reagents for the selective preparation of primary amides. HOTT (**1**) has previously been used for the preparation of hindered Barton esters, which are precursors of radicals.[13] More recently these uronium salts **1** and **2** have been employed for the synthesis of secondary amides and as adequate peptide coupling reagents, affording final peptides with yields and racemization degrees comparable to other more expensive and commonly used coupling reagents.[14]



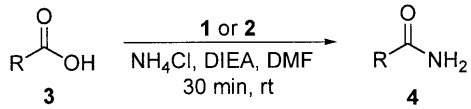
1 (HOTT)



2 (TOTT)

The uronium reagents **1** (HOTT) and **2** (TOTT) were prepared from *N*-hydroxy-2-pyridinethione and 1,1,3,3-tetramethylurea as previously described.[5] Reaction of different carboxylic acids with HOTT (**1**) or TOTT (**2**) in the presence of ammonium chloride and DIEA in DMF as solvent, afforded pure primary amides (^{1}H NMR, 300 MHz) after extractive work-up (Scheme 1). Yields were high in almost all cases (Table 1), and quite similar employing **1** or **2**, which would suggest TOTT (**2**) as the reagent of choice due to its lower cost.[5] When triethylamine was attempted as alternative base, isolated yields were lower (Table 1, entry 10).

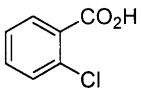
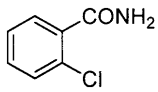
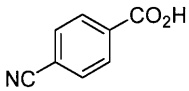
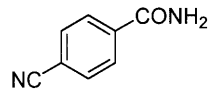
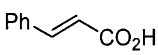
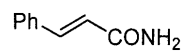
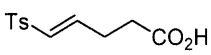
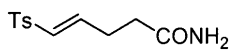
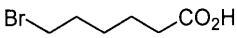
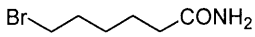
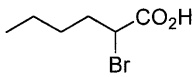
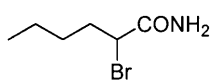
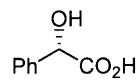
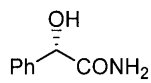
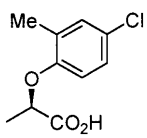
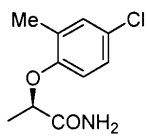
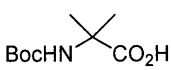
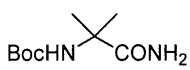
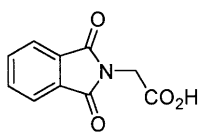
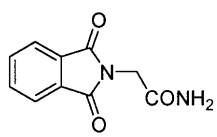
The reaction took place with aliphatic and aromatic carboxylic acids, even in hindered cases (Table 1, entries 1–4). No by-products were observed even if functional groups sensitive to ammonolysis were present. Thus, no trace of Michael addition product was detected in the reaction with an α,β-unsaturated acid such as cinnamic acid (Table 1, entry 5), only the pure amide being isolated. In addition, no competitive addition product was observed when a carboxylic acid bearing a α,β-unsaturated sulfone moiety was employed (Table 1, entry 6), the obtained amide being reported as a precursor of the indolizidine skeleton.[15] Similarly, no nucleophilic substitution reaction was observed when the reaction was performed with haloacids such as ε-bromocaproic acid (Table 1, entry 7) or even with the more sensitive α-bromocaproic acid although in this case the isolated yield was lower (Table 1, entry 8). When the amidation reaction was carried out with (*S*)-mandelic acid, the corresponding enantiomerically pure



3 **4**

Scheme 1.

Table 1
Preparation of amides employing HOTT (**1**) and/or TOTT (**2**)

Entry	Acid	Coupling reagent	Amide[a]	Yield[b] (%)	Mp[c] (°C)	Lit. mp (°C)
1	t-$BuCO_2H$	**1**	t-$BuCONH_2$	70	154–155	154–157[17]
		2		64		
2	$PhCO_2H$	**1**	$PhCONH_2$	83	128–129	130[18]
		2		83		
3		**1**		84	142–143	142[18]
		2		85		
4		**2**		77	223	223[18]
5		**2**		93	146–148	147[18]
6		**2**		85	121–123	122–123[15]
7		**1**		93	94–95[d]	105–106[19]
		2		92		
8		**1**		55	52–54	57–58[20]
9		**1**		46[e]	120–121	123–124[18]
10		**1**		96	105–107	–
		2		95[f,g,h]		
11	Fmoc–Leu–OH	**1**	Fmoc–Leu–NH_2	99[i]	181–183	138–139[10]
		2		99		
12	Cbz–Tyr(Bn)–OH	**1**	Cbz–Tyr(Bn)–NH_2	99[j,k]	184–186	–
		2		98		
13		**1**		64	167–169	175[21]
14		**2**		54	270–271	260–262[22]

[a] All compounds gave satisfactory spectroscopic data (^1H and ^{13}C NMR, IR and MS).
[b] Isolated pure compounds (^1H NMR, 300 MHz).
[c] Isolated crude products.
[d] Mp 105–107°C after recrystallization (hexane/AcOEt).
[e] $[\alpha]_D^{25}$ +84 (*c* 1.6, acetone); lit.[18] $[\alpha]_D^{20}$ +73 (*c* 1.6, acetone).
[f] 85% yield when triethylamine was used as base.
[g] $[\alpha]_D^{29}$ −18.3 (*c* 1, acetone).
[h] Anal. calcd for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56. Found: C, 56.29; H, 5.66; N, 6.68.
[i] $[\alpha]_D^{25}$ −13.5 (*c* 1, EtOH); lit.[10] $[\alpha]_D^{20}$ −17.6 (*c* 1, EtOH).
[j] $[\alpha]_D^{28}$ −7.1 (*c* 1, acetone).
[k] Anal. calcd for $C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.93. Found: C, 71.46; H, 5.75; N, 6.97.

primary amide was isolated (Table 1, entry 9). This direct transformation of a α-hydroxyacid into a α-hydroxyamide is not very easy, usually requiring harsh conditions, Lewis acid catalysis or protection/deprotection sequences.[16] Protecting groups such as benzyl esters remained intact as in the case of the reaction of Cbz–Tyr(Bn)–OH (Table 1, entry 12), and the reaction was quantitative when Cbz- or base-sensitive Fmoc-protected amino acids were used (Table 1, entries 11 and 12). Even a hindered amino acid such as Boc-protected α-aminoisobutyric acid (Aib) afforded a good yield of the corresponding pure amide (Table 1, entry 13).

In conclusion, the uronium salts HOTT (**1**) and TOTT (**2**) are convenient reagents for the rapid preparation of primary amides under mild and simple reaction conditions. The possibility of performing the reaction in a selective way, independently of the presence of other sensitive functionalities, the usual high yields and the low cost of these coupling reagents make them competitive compared to more expensive HOBt-based reagents. Further studies on other applications of these peptide coupling reagents are underway.

In a *typical procedure*, DIEA (340 μL, 2 mmol) and NH_4Cl (183 mg, 2 mmol) were added to a solution of **1** or **2** (1.5 mmol) and of the corresponding acid (1 mmol) in DMF (4 mL) and the mixture was stirred for 30 min at room temperature. Saturated aqueous NaCl (50 mL) was added and the mixture was extracted with AcOEt (3×20 mL). The organics were washed with 2N HCl (2×10 mL), water (2×10 mL), saturated $NaHCO_3$ (2×10 mL) and water (4×10 mL), dried (Na_2SO_4), filtered and evaporated (15 torr) affording pure amides.

Acknowledgements

We thank the Dirección General de Enseñanza Superior e Investigación Científica (project no. 1FD97-0721) of the Ministerio de Educación y Cultura (MEC) for financial support.

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