Notes

2-Mercaptopyridone 1-Oxide-Based Uronium Salts: New Peptide Coupling Reagents[1,2]

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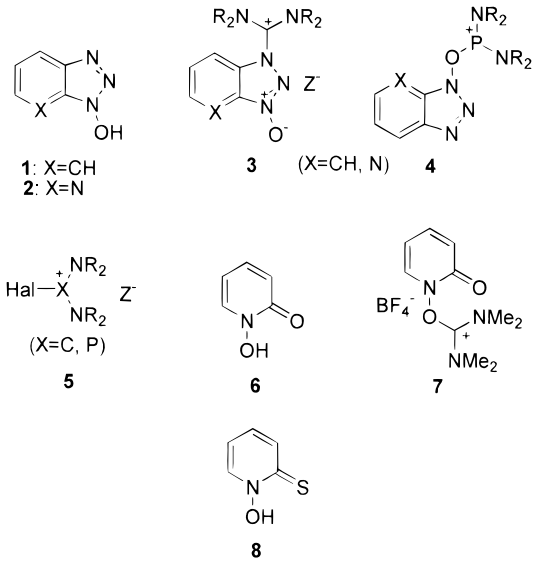
Peptide coupling reagents have been important targets in the last 20 years. The common problems encountered in the amide synthesis are extensive racemization of the amino acid components, usually through oxazolone formation, undesired side reactions such as diketopiperazine cyclization and guanidino or *N*-carboxyanhydride formation, and low coupling rates especially under solid-phase conditions.[3] Coupling reagents can be divided into the following groups: (a) carbodiimide or another coupling reagent in combination with additives such as 1-hydroxybenzotriazole (HOBt, **1**)[4] (see Chart 1) or 1-hydroxy-7-azabenzotriazole (HOAt, **2**);[5] (b) aminium salts **3** derived from HOBt (e.g. HBTU,[6] TBTU,[7] HBPyU,[8] HBPipU[9]) or HOAt[5] (e.g. HATU, HAPyTU, HAPyU, HAPipU, HAMDU, HAMTU); (c) phosphonium salts **4** derived from HOBt (e.g. BOP,[10] PyBOP[11]) or HOAt[5] (e.g. AOP, PyAOP); (d) halouronium or halophosphonium salts **5** (e.g. PyClop,[12] PyBrop,[12] PyClU,[12] BroP,[13] CIP,[14] TFFH,[15] BTFFH[15]); (e) reagents forming mixed anhydrides (e.g. $ClCO_2Bu^i$,[16] PPA,[17] BOP-Cl,[18] Dpp-Cl[19]); (f) hydroxamic acid-type reagents, in combination with a carbodiimide, such as *N*-hydroxysuccinimide (HONSu),[20] 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine (HODhbt),[22] *N*-hydroxyphthalimide (HOPht),[22] *N*-hydroxy-5-norbornene-2,3-di-

Chart 1



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(1) A preliminary account of this work was presented at the 25th European Peptide Symposium, Budapest, Hungary, August 30−September 4, 1998, P-047.

(2) Abbreviations used in this paper: AOP, (7-azabenzotriazol-1-yl)oxytris(dimethylamonino)phosphonium hexafluorophosphate; BOP, benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate; BOP-Cl, bis(2-oxo-3-oxazolidinyl)phosphinic chloride; BroP, bromotris(dimethylamino)phosphonium hexafluorophosphate; BTFFH, bis(tetramethylenefluoroformamidinium) hexafluorophosphate; CIP, 2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate; DppCl, diphenylphosphinic chloride; HAMDU, *O*-(7-azabenzotriazol-1-yl)-1,3-dimethyl-1,3-dimethyleneuronium hexafluorophosphate; HAMTU, *O*-(7-azabenzotriazol-1-yl)-1,3-dimethyl-1,3-trimethyleneuronium hexafluorophosphate; HAPipU, *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate; HAPyTU, *S*-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)thiouronium hexafluorophosphate; HAPyU, *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)-uronium hexafluorophosphate; HATU, *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HBPipU, *O*-(benzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uronium hexafluorophosphate; HBPyU, *O*-(benzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate; HBTU, *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HOTT, *S*-(1-Oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate; PyAOP, (7-azabenzotriazol-1-yl)oxytris(pyrrolidino)phosphonium hexafluorophosphate; PyBOP, benzotriazol-1-yloxy-tripyrrolidinophosphonium hexafluorophosphate; PyBrop, bromotripyrrolidinophosphonium hexafluorophosphate; PyCloP, chlorotripyrrolidinophosphonium hexafluorophosphate; PyClU, chloro-1,1,3,3-bis(tetramethylene)formamidinium hexafluorophosphate; PPA, propanephosphoric acid anhydride; TBTU, *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate; TDBTU, *O*-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate; TFFH, tetramethylfluoroformamidinium hexafluorophosphate; TOTT, *S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium tetrafluoroborate.

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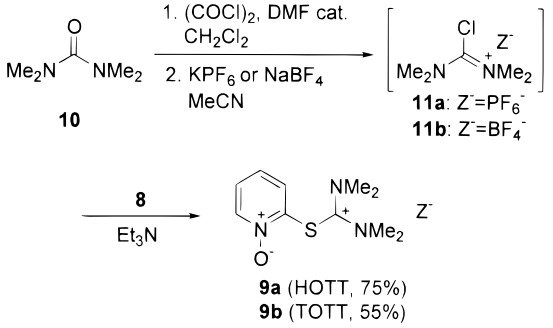
Scheme 1



carboxylic acid imide (HONB),[23] and *N*-hydroxy-1,2-dihydro-2-oxopyridine (HOPyr, **6**);[24] (g) hydroxamic acid-based uronium salts such as *O*-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU, **7**).[7] In relation with this latter reagent, we envisaged that 2-mercaptopyridine 1-oxide (**8**) could represent, from an economical point of view, an interesting alternative to HOPyr (**6**) and other *N*-hydroxy derivatives for the preparation of peptide coupling reagents. 2-Mercaptopyridine 1-oxide (**8**) has been mainly used for the preparation of Barton thiohydroxamate esters, adequate precursors of radicals by photolysis.[25] In connection with our project on the development of new cheaper reagents for large-scale peptide couplings, we have found that effectively compound **8** is an appropriate starting material for the preparation of a new class of uronium salts **9**[26] related to HOBt and HOAt as well as to hydroxamic acid-type reagents.

The uronium salts **9** were prepared by the one-pot phosgene-free procedure outlined in Scheme 1. Thus, the reaction of *N*,*N*,*N*′,*N*′-tetramethylurea (**10**) with oxalyl chloride in the presence of a catalytic amount of DMF afforded the chlorouronium salt. This crude compound was treated with potassium hexafluorophosphate or sodium tetrafluoroborate yielding the corresponding salts **11a** or **11b**, which reacted with *N*-hydroxy-2-pyridinethione (**8**) in the presence of triethylamine to give the uronium salts **9a** (HOTT) or **9b** (TOTT), in 75 and 57% isolated overall yields, respectively. The chlorouronium salts **11** could also be prepared by reaction of the urea with the more expensive triphosgene, but no difference in the final overall yields of **9** was observed. In addition, the bidentate nucleophilic character of thiopyridone **8** would allow two possible structures for the resulting final product. However, the disappearance of the typical C=S signal in the ^{13}C NMR spectra of the final uronium salts, and the presence of a deshielded signal at $\delta = 8.52$ ppm corresponding to an aromatic H6 in the ^{1}H NMR spectra,[27] ruled out the alternative thiopyridone-derived structure, confirming thus the pyridinium *N*-oxide structure for **9**.[28]

The uronium salts obtained **9** were used as new peptide coupling reagents for the preparation of a series of di- and tripeptides. Thus, different Boc-, Cbz- and Bz-*N*-protected amino acids or dipeptides reacted with ethyl or methyl ester amino acid hydrochlorides in the presence of the uronium salts **9** and triethylamine as base in acetonitrile as solvent, affording the peptides with the yields shown in Table 1. The results obtained show, in most cases, few differences in the final yield when **9a** or **9b** was used. Only a better solubility in acetonitrile was observed when **9b** was used. Furthermore, acetonitrile seems to be the solvent of choice, as other solvents such as dichloromethane or DMF lowered considerably the final yields. After workup, the corresponding crude peptides were isolated free of any impurity (^{1}H NMR, 300 MHz).

When difficult couplings using α,α-dialkyl amino acids such as α-aminoisobutyric acid (Aib) were performed (Table 1, entries 13−18), the uronium salt **9b** afforded generally higher yields than **9a** (Table 1, compare entries 15 and 16, and entries 17 and 18). The yields of these obtained Aib-containing peptides are, in general, higher than when using other previously employed coupling reagents such as CIP or PyBroP,[14] specially with *N*-Boc-protected amino acids (Table 1, entries 13−16), which are particularly prone to *N*-carboxyanhydride formation.[32] Moreover, in these difficult cases yields using **9b** were not very different than when using other known high-priced uronium salts. For example, when HATU was employed as coupling agent, the dipeptide Cbz-Val-Aib-OMe was obtained in 89% yield, whereas using **9b** the yield was 80% (Table 1, entry 18). In addition, hindered *N*-methylated amino acids, such as Cbz-MeVal-OH, which usually proves resistant in coupling reactions,[33] afforded good isolated yields of the corresponding peptides when coupled with Val-OMe using **9a** or **9b** (Table 1, entries 19 and 20).

Using Young's test[29] (the coupling of Bz-Leu-OH and Gly-OEt·HCl, Table 1, entries 9 and 10) and the Anteunis' test[30] (the coupling of Cbz-Gly-Phe-OH and Val-OMe·HCl, Table 1, entries 11 and 12), the extent of racemization with the two reagents was examined. It is interesting that, in the case of **9b**, only 3.7% racemization was observed using the Young test (Table 1, entry 10), a lower value than when using other HOBt-based uronium salts such as BOP (20%), PyBOP (15%), or HBTU (12.7%),[8,11] or even HOAt-derived salts such as HATU, which afforded a 20% racemization. In addition, when Anteunis' test was performed using the HOPyr (**6**)-derived TPTU (**7**) as coupling reagent, which is chemically related to reagents **9**, a higher yield of the corresponding tripeptide was obtained using **7** (98%) but also a higher degree of epimerization was shown (6.5:1 diastereomer ratio using **7**, 10:1 diastereomer ratio using **9**, ^{1}H NMR 500 MHz; see Table 1, entries 11 and 12).

The uronium salts **9** were also employed as amide-

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Table 1. Prepared Peptides Using Compounds 9 as Coupling Reagents

entry	reagents	*t* (h)	peptides	yields (%)[a]	mp[b] (°C)	$[\alpha]_D^{25}$ [b] (*c*, solvent)
1	**9a**	3	Boc-Gly-Gly-OMe	89	207−209	
2	**9b**			87		
3	**9a**	9	Boc-Gly-Ala-OMe	96	168−170	−16.0 (1, AcOEt)
4	**9b**			97		
5	**9a**	9	Boc-Ala-Ala-OMe	81	109−110	−50.2 (1, EtOH)
6	**9b**			78		
7	**9a**	9	Cbz-Val-Val-OMe[c]	85	110−111	−18.7 (1, EtOH)
8	**9b**			85		−22.1 (1, EtOH)
9	**9a**	9	Bz-Leu-Gly-OEt[d]	71	151−152	−29.3 (3.1, EtOH)[e]
10	**9b**			69	155−156	−31.5 (3.1, EtOH)[f]
11	**9a**	9	Cbz-Gly-Phe-Val-OMe[g]	68		
12	**9b**			71		
13	**9a**	4	Boc-Aib-Val-OMe	58	110−111	19.5 (1, EtOH)
14	**9b**			44		
15	**9a**	4	Boc-Val-Aib-OMe	35	148−149	−17.0 (1, EtOH)
16	**9b**			67		
17	**9a**	4	Cbz-Val-Aib-OMe[h]	60	88−89	−23.0 (1, EtOH)
18	**9b**			80		
19	**9a**	9	Cbz-MeVal-Val-OMe	80[i]		−78.8 (1, EtOH)[j]
20	**9b**			82[i]		

[a] Isolated yield based on the starting amino acids. [b] Measured from the crude peptide without further purification. [c] Lit.[11] 107−109 °C; $[\alpha]_D^{20}$ −21 (*c* 1, EtOH). [d] Young's test: lit.[29] mp = 156.7−157 °C; $[\alpha]_D^{20}$ −34 (*c* 3.1, EtOH). [e] 7% of epimerization. [f] 3.7% epimerization. [g] Anteunis' test[30] (underline representing the created bond): 10:1 diastereomer ratio (^{1}H NMR, 500 MHz). [h] Lit.[31] mp = 83−84 °C; $[\alpha]_D$ −24 (*c* 1, EtOH). [i] Isolated yields after flash chromatography (silica gel). [j] Lit.[32] $[\alpha]_D^{20}$ −90.0 (*c* 1, EtOH).

Table 2. Compounds 9 as Amidation Reagents

entry	acid	amine	reagent	amide yields (%)[a,b]
1	$PhCO_2H$	*n*-$BuNH_2$	**9a**	90
2	$PhCO_2H$	*n*-$BuNH_2$	**9b**	87
3	$PhCO_2H$	*i*-$PrNH_2$	**9a**	83
4	$PhCO_2H$	*t*-$BuNH_2$	**9a**	45
5	$PhCO_2H$	$C_6H_{11}NH_2$	**9a**	95
6	$PhCO_2H$	$C_6H_{11}NH_2$	**9b**	90
7	$PhCO_2H$	Piperidine	**9a**	86
8	$PhCO_2H$	Piperidine	**9b**	86
9	$C_{10}H_{21}CO_2H$	*n*-$BuNH_2$	**9a**	84
10	$C_{10}H_{21}CO_2H$	*i*-$PrNH_2$	**9a**	93
11	$C_{10}H_{21}CO_2H$	*t*-$BuNH_2$	**9a**	84
12	$C_{10}H_{21}CO_2H$	$PhNH_2$	**9a**	89

[a] Isolated yield of the pure (^{1}H NMR, 300 MHz) crude amide based on the starting acid. [b]Nonoptimized yields.

forming reagents in the reaction between carboxylic acids and amines (see Table 2). Thus, aromatic (Table 2, entries 1−8) and aliphatic (Table 2, entries 9−12) carboxylic acids were condensed with differently substituted amines in the presence of reagents **9** in DMF as solvent, generally with similar high yields in both cases. The final crude amides showed pure by ^{1}H NMR (300 MHz) analysis after the usual work up.

We conclude that the reagents **9a** (HOTT) and **9b** (TOTT), which can be easily prepared in a one-pot procedure, without using the very toxic phosgene, could be promising reagents for peptide coupling and amidation reactions. The simplicity of the synthesis and the lower price of the starting material, compared for example with HOBt, HOAt, or HOPyr, could make these thiopyridone-derived reagents very competitive with other presently being used coupling reagents. Specially TOTT (**9b**) can be recommended, not only because of its generally better performance in difficult couplings but also from an economical point of view due to the much lower price of the starting tetrafluoroborate salt.

Experimental Section

General Methods. *N*-Hydroxy-2-pyridinethione (**8**) can be obtained in a cheaper way in 85% yield from an aqueous 40% solution of sodium 2-pyridinethiol 1-oxide (Fluka) after acidification with concentrated HCl, following a reported procedure.[34] All other reagents were commercially available and used without further purification. The prepared peptides and amides were characterized by NMR (^{1}H and ^{13}C).

Synthesis of *S*-(1-Oxido-2-pyridinyl)-1,1,3,3-tetramethyluronium Hexafluorophosphate and Tetrafluoroborate (9a, 9b). To a solution of 1,1,3,3-tetramethylurea (4.8 mL, 40 mmol) and DMF (0.3 mL) in CH_2Cl_2 (40 mL) was added dropwise oxalyl chloride (4.2 mL, 48 mmol) at room temperature. The solution was stirred for 1 h at room temperature and then refluxed for 4 h. The solvent was evaporated (15 Torr), and the resulting solid was stirred with portions of CH_2Cl_2 (2 × 10 mL) followed by evaporation of the organics (15 Torr) after each treatment. The obtained crude chlorouronium salt was dissolved in MeCN (40 mL), and KPF_6 (for **9a**, 8.8 g, 48 mmol) or $NaBF_4$ (for **9b**, 5.27 g, 48 mmol) was added. The mixture was stirred at room temperature for 24 h, and to the resulting suspension was added *N*-hydroxy-2-pyridinethione (**8**) (5.1 g, 40 mmol). Triethylamine (6.7 mL, 48 mmol) was added dropwise keeping the temperature below 25 °C, and the resulting suspension was stirred at room temperature for 5 h and at 45 °C for 1 h. The solution was filtered through a plug of Celite, the solvents were evaporated (15 Torr) and the uronium salts **9a**,**b** were obtained after crystallization with MeOH/2-propanol (**9a**, 11 g, 75%; **9b**, 7.1 g, 57%).

***S*-(1-Oxido-2-pyridinyl)-1,1,3,3-tetramethyluronium Hexafluorophosphate (9a):** mp 115−117 °C; IR (KBr) 3066, 1618, 842 cm^{-1}; ^{1}H NMR (CD_3CN, 300 MHz) δ 8.52 (1 H, m), 7.87 (1 H, m), 7.58−7.50 (2 H, m), 3.22 (12 H, s); ^{13}C NMR (CD_3CN, 75 MHz) δ 171.7, 140.8, 131.2, 128.0, 127.1, 44.0. Anal. Calcd for $C_{10}H_{16}N_3OSPF_6$: C, 32.34; H, 4.35; N, 11.32. Found: C, 32.49; H, 4.74; N, 11.19.

***S*-(1-Oxido-2-pyridinyl)-1,1,3,3-tetramethyluronium Tetrafluoroborate (9b):** mp 107−108 °C; IR (KBr) 3098, 1623, 1041 cm^{-1}; ^{1}H NMR (CD_3CN, 300 MHz) δ 8.52 (1 H, m), 7.87 (1 H, m), 7.61−7.50 (2 H, m), 3.22 (12 H, s); ^{13}C NMR (CD_3CN, 75 MHz) δ 171.7, 140.8, 131.2, 128.0, 127.1, 44.0. Anal. Calcd for $C_{10}H_{16}N_3OSBF_4$: C, 38.33; H, 5.15; N, 13.42; S, 8.63. Found: C, 38.44; H, 5.14; N, 13.23.

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Peptide Coupling Reactions. General Procedure. A solution of the *N*-protected amino acid (1 mmol), the amino acid ester hydrochloride (1 mmol), triethylamine (0.28 mL, 2 mmol), and **9a** or **9b** (1 mmol) in MeCN (10 mL) was stirred at room temperature until disappearance of the free esterified amino acid (TLC, ninhydrin). Saturated NaCl was added, and the mixture was extracted with AcOEt. The organic layers were washed with 2 N HCl, saturated $NaHCO_3$, and water. The organics were dried (Na_2SO_4), filtered, and evaporated (15 Torr) affording the corresponding peptides (see Table 1).

Amidation Reactions. General Procedure. A solution of the carboxylic acid (1 mmol) and **9a** or **9b** (1 mmol) in DMF (10 mL) was stirred at room temperature for 30 min. The corresponding amine (1 mmol) was added, and the resulting mixture was stirred at room temperature for 4 h. Saturated NaCl was added, and the mixture was extracted with AcOEt. The organic layers were washed with 2 N HCl, saturated $NaHCO_3$ and water. The organics were dried (Na_2SO_4), filtered, and evaporated (15 Torr) affording the corresponding pure amides (see Table 2).

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