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Direct synthesis of hydroxamates from carboxylic acids using 2-mercaptopyridone-1-oxide-based thiouronium salts

Miguel A. Bailén, Rafael Chinchilla, David J. Dodsworth and Carmen Nájera*

Departamento de Química Orgánica, Universidad de Alicante, Apartado 99, 03080 Alicante, Spain

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Abstract—Tetrafluoroborate and hexafluorophosphate thiouronium salts derived from 2-mercaptopyridone-1-oxide and tetramethylurea (TOTT and HOTT) or *N*,*N*′-dimethylpropyleneurea (TODT and HODT) convert carboxylic acids to Weinreb amides and *N*-methoxy or *N*-benzoxyamides in high yields by reaction with *N*,*O*-dimethylhydroxylamine and *O*-methyl- or *O*-benzylhydroxylamine hydrochlorides, respectively, in the presence of triethylamine or DIEA. © 2001 Elsevier Science Ltd. All rights reserved.

N-Methoxyamides derived from *N*,*O*-dimethylhydroxylamine (Weinreb amides) and *O*-methyl- or *O*-benzylhydroxylamines have enjoyed wide importance in organic synthesis. Weinreb amides are extensively used as acyl cation equivalents for the preparation of carbonyl compounds,[1] whereas *N*-methoxyamides are good precursors of *N*-methoxy-*N*-acylnitrenium ions in electrophilic aromatic substitutions[2] and for the synthesis of β-lactams.[3] In addition, *N*-benzoxyamides are precursors of hydroxamic acids by hydrogenolysis which present a wide variety of biological properties, such as anti-inflammatory, antiasthmatic, antimetastatic, antibiotic, psychotropic, insecticidal, acaricidal and nematocidal activities.[4] They can act also as metal chelators, specially iron, in microbial siderophores such as alcaligin,[5a] bisucaberin,[5b] desferrioxamines,[5c] nannochelin A[5d] and danoxamine,[5e] whereas others have been used as enzyme inhibitors of metalloproteases.[6] A general method for the synthesis of Weinreb amides[1,7a] and *O*-benzylhydroxamates[7b] is the heating of esters with aluminium derivatives of *O*-methyl-*N*-methyl and *O*-benzyl-hydroxylamine, respectively. Acyl chlorides, mixed anhydrides and carboxylic acids have been used for the synthesis of substituted hydroxamates.[1b,c] Several peptide coupling reagents[8] such as BOP,[9a–d] PyBOP,[9e] DCC,[10] EDC,[11a,b] CDI,[11c] PPAA,[12a,b] TBTU,[12c] DEPC,[10b,13a,b] and 2-chloro- and 2-bromo-1-methylpyridinium iodides[13c] have been used for the coupling of carboxylic acids with *N*-alkoxyamines, mainly for the synthesis of Weinreb amides. Other reagents such as carbon tetrabromide and triphenylphosphine[14a] and [bis(2-methoxyethyl)aminosulfur trifluoride (deoxo-fluor reagent)[14b] are also very effective for the synthesis of Weinreb amides and involve in situ formation of acyl bromides and fluorides, respectively. Recently, we have studied the synthetic applications of economical thiouronium salts derived from 2-mercaptopyridone-1-oxide and tetramethylurea *S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (**1**, TOTT) and hexafluorophosphate (**2**, HOTT)[15] as peptide coupling reagents[16a] and for the synthesis of primary amides.[16b] In this communication we propose that reagents **1** and **2** together with the related new thiouronium salts derived from *N*,*N*′-dimethylpropyleneurea (DMPU), **3** (TODT), and **4** (HODT), are efficient reagents for the direct coupling of carboxylic acids and *N*-protected amino acids with alkyl hydroxylamine hydrochlorides. The new compounds *S*-(1-oxido-2-pyridinyl)-1,3-dimethylpropyleneuronium tetrafluoroborate (**3**, TODT) and the corresponding hexafluorophosphate (**4**, HODT) could be promising reagents, since they are prepared from a common organic solvent which does not present the reported toxicity of tetramethylurea.[17]

Abbreviations: BOP, benzotriazol-1-yl-*N*-oxy-tris(dimethylamino)-phosphonium hexafluorophosphate; CDI, 1,1′-carbonyldiimidazole; DEPC, diethylphosphoryl cyanide; EDC, 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride; PPAA, 2-propanephosphonic acid anhydride; PyBOP, benzotriazol-1-yl-*N*-oxy-tris-(pyrrolidino)phosphonium hexafluorophosphate; TBTU, *N*-[(1*H*-benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide.

Keywords: coupling reagents; amino acids; carboxylic acids; hydroxamates; Weinreb amides.

* Corresponding author. Fax: +34 96 5903549; URL: www.ua.es/dept.quimorg; e-mail: cnajera@ua.es

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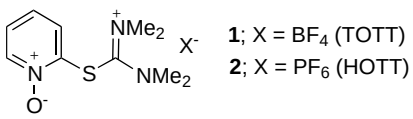
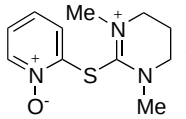


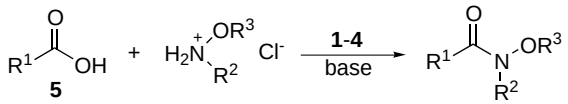
1; X = BF_4 (TOTT)
2; X = PF_6 (HOTT)



3; X = BF_4 (TODT)
4; X = PF_6 (HODT)

The thiouronium salts **1**–**4** were prepared by reaction of tetramethylurea or DMPU with oxalyl chloride and a catalytic amount of DMF. The corresponding chlorouronium salts were treated with sodium tetrafluoroborate or potassium hexafluorophosphate and subsequently with *N*-hydroxy-2-pyridinethione.[16a] The new uronium salts TODT (**3**) and HODT (**4**) were obtained in 60 and 81% yield, respectively.[18] The coupling of different carboxylic acids and *N*-protected α-amino acids **5** with *N*,*O*-dimethyl- or *O*-benzylhydroxylamine hydrochlorides was carried out in acetonitrile at room temperature with 2 equiv. of triethylamine in the case of TOTT (**1**) and HOTT (**2**), and in DMF with diisopropylethylamine (DIEA) as base when **3** and **4** were used (Scheme 1 and Table 1).

Weinreb amides **6** were obtained as highly pure crude products for all the coupling reagents after 3 h at rt in good yields (Table 1, entries 1–14). The hexafluorophosphates **2** and **4** afforded slightly higher yields than the corresponding tetrafluoroborates **1** and **3** in the case of undecanoic acid (Table 1, entries 1–4), and therefore they were used for the rest of the couplings. The reaction took place in shorter reaction times



6; $R^2 = R^3 = Me$
7; $R^2 = H$, $R^3 = Me$
8; $R^2 = H$, $R^3 = PhCH_2$

Scheme 1.

Table 1. Synthesis of Weinreb amides and *O*-alkylhydroxamates from carboxylic acids using thiouronium salts

Entry	Acid (**5**)	Reagent[a]	Time (h)	Product[b]			
				No.	Yield (%)[c]	Mp (°C)[c] (Lit. mp)	$[\alpha]_D^{25}$[d] (Lit. $[\alpha]_D$)
1	$CH_3(CH_2)_9CO_2H$	**1**	3	**6a**	80	Oil	
2		**2**	3	**6a**	95		
3		**3**	3	**6a**	90		
4		**4**	3	**6a**	95		
5	$PhCO_2H$	**2**	3	**6b**	86	Oil	
6		**4**	3	**6b**	70		
7	(*E*)-PhCH=CHCO$_2$H	**2**	3	**6c**	91	Oil	
8		**4**	3	**6c**	80		
9	Boc-Ala-OH	**2**	3	**6d**	82	152–154 (150)[9a]	−25.5 (−26)[19a]
10		**4**	3	**6d**	80	152–154	−26.0
11	Cbz-Ala-OH	**2**	3	**6e**	76	81–83 (78–80)[19b]	−16.0
12		**4**	3	**6e**	74	82–84	−15.7
13	Fmoc-Ala-OH	**2**	3	**6f**	80	121–123	−10.2
14		**4**	3	**6f**	78	122–124	−10.3
15	$CH_3(CH_2)_9CO_2H$	**2**	2	**7a**	94	35–37	
16		**4**	2	**7a**	90	35–37	
17	$PhCO_2H$	**2**	2	**7b**	82	61–62 (62–64)[19c]	
18	(*E*)-PhCH=CHCO$_2$H	**2**	2	**7c**	90	88–90	
19		**3**	2	**7c**	74	88–90	
20		**4**	2	**7c**	76	88–90	
21	Cbz-Ala-OH	**2**	2	**7e**	80	123–125 (112–113)[19d]	−23.0
22		**4**	2	**7e**	60	122–124	−18.8
23	$PhCO_2H$	**2**	3	**8b**	85	103–104 (103–104)[19e]	
24		**4**	3	**8b**	75	103–104	
25	(*E*)-PhCH=CHCO$_2$H	**2**	3	**8c**	90	100–101 (100–101)[5d]	
26		**4**	3	**8c**	80	100–101	
27	Fmoc-Ala-OH	**2**	3	**8f**	67	146–148	−22.0
28		**4**	3	**8f**	71	146–148	−19.8
29	Cbz-Gly-OH	**2**	3	**8g**	76	124–126 (115–116)[7b]	
30		**4**	3	**8g**	67	124–126	
31	Boc-Phe-OH	**2**	3	**8h**	70	129–131	−9.5
32		**4**	3	**8h**	66	129–131	−9.2

[a] The reaction was carried out in MeCN/Et_3N in the case or reagents **1** and **2**, and in DMF/DIEA when **3** and **4** were used.
[b] All compounds gave satisfactory spectroscopic data (^1H and ^{13}C NMR, IR and MS).
[c] Isolated crude pure compounds.
[d] (*c* 1.0, MeOH).

and with similar yields compared to other recently used coupling agents, such as the deoxo-fluor reagent.[14b] Moreover, no racemization was observed during the coupling process according to the optical rotation value shown in the final hydroxamate for Boc-Ala-OH (Table 1, entries 9 and 10). In addition, the use of these reagents allows for the preparation of *O*-methyl hydroxamates (Table 1, entries 15–22) with comparable yields and in a more direct and easy manner than when using, for instance, acyl chlorides.[19] In the case of *O*-benzyl hydroxamates (Table 1, entries 23–32) yields were similar or even higher than when using other less direct methodologies. For instance, *O*-benzyl-*N*-cinnamoyl hydroxylamine was obtained in 90 and 80% yield using **2** and **4**, respectively (Table 1, entries 25 and 26), whereas it was obtained in only 49% yield when using a mixed anhydride methodology.[5d] In all cases, the Boc, Cbz and Fmoc *N*-protecting groups of α-amino acids were found to be stable under the reaction conditions employed.

We conclude that thiouronium salts **1**–**4** are convenient reagents for the easy, clean and direct preparation of different hydroxamates in high yields. Further studies on the application of these compounds are now underway.[20]

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18. TODT (**3**): mp 111–112°C (EtOH). HODT (**4**): mp 123–124°C (MeOH/*i*PrOH).

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20. In a typical reaction, to a mixture of the carboxylic acid (1 mmol), the corresponding hydroxylamine hydrochloride (1 mmol) and the organic base (2 mmol) in the appropriate solvent (5 mL) [Et_3N in MeCN for **1** and **2**, and DIEA in DMF for **3** and **4**] was added reagent **1**–**4** (1 mmol) at rt. The solution was stirred at rt until completion (GC or TLC) and saturated NaCl (50 mL) was added. The mixture was extracted with AcOEt (2×20 mL), washed with 2 M HCl (2×10 mL), saturated $NaHCO_3$ (2×10 mL) and water (6×10 mL), and dried (Na_2SO_4). Evaporation (15 torr) afforded pure crude hydroxamates.