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# *O*-Succinimidyl-1,3-dimethyl-1,3-trimethyleneuronium salts as efficient reagents in active ester synthesis

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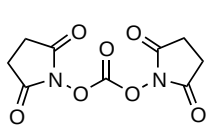
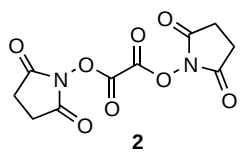
**Abstract**—The new uronium salts *O*-succinimidyl-1,3-dimethyl-1,3-trimethyleneuronium hexafluorophosphate (HSDU) and tetrafluoroborate (TSDU) have been prepared from 1,3-dimethylpropyleneurea (DMPU) and employed in the synthesis of *N*-hydroxysuccinimide-derived active esters. High yields were obtained at room temperature in short reaction times and no racemization was observed. 

The generation of *N*-hydroxysuccinimide (HOSu)-derived active esters is an important step in the activation of the carboxylic acid function, and has been employed profusely for the generation of the amide bond in peptide synthesis,[1] and also for reduction of acids to alcohols[2] or for the synthesis of tetramic acids.[3] These esters are generally isolable and easy to purify, an important point when final highly pure peptides are required. Moreover, HOSu esters are fairly stable in aqueous solutions,[1a] allowing their generation from water-soluble or rather insoluble carboxylic acids. Typically, DCC has been used as the initial coupling reagent, in spite of problems related to removing the urea by-product, formation of acylisoureas and Lossen rearrangements.[4] Moreover, the use of this DCC–HOSu methodology frequently produces unacceptable levels of racemization in peptide synthesis.[1h] In order to avoid the use of DCC, a number of activated derivatives of HOSu have been developed, such as the carbonate **1**,[5] prepared from HOSu and trichloromethyl chloroformate, or by reaction of *O*-trimethylsilyloxysuccinimide and phosgene. In addition, the oxalate **2**,[6] prepared from HOSu and oxalyl chloride, and the phosphate **3**,[7] derived from HOSu and diphenylphosphochlorhydrate can be used for the generation of hydroxysuccinimido esters as well as the combination chlorophosphate/HOSu/base.[8] They have also been isolated via transesterification reactions mediated by polystyrene-supported 1-hydroxybenzotriazole-derived esters.[9] Furthermore, a 1,1,3,3-tetramethylurea (TMU)-derived uronium salt such as *O*-succinimidyl-1,1,3,3-tetramethyluronium tetrafluoroborate (**4**, TSTU) has been employed for the in situ preparation of these type of esters.[10]



**1**



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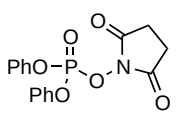

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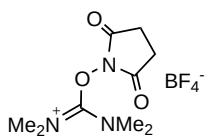

**4**

Recently, we have studied the synthetic applications of thiouronium salts derived from 2-mercaptopyridone-1-oxide and ureas as peptide coupling reagents[11] and for the synthesis of primary amides[12] and hydroxamates.[13] In these studies we have also been searching for an alternative to the use of TMU which, in spite of its reported toxicity,[14] is probably the most frequently employed urea in peptide coupling reagent synthesis.[1h] In this way, we have found that the common solvent 1,3-dimethylpropyleneurea (DMPU, **5**) can be employed as a safer and economical alternative for the preparation of these thiouronium salts.[11b,c,13] Therefore, it was assumed that DMPU could be suitable for the synthesis of new *N*-hydroxysuccinimide-derived uronium salts related to TSTU (**4**), useful in the preparation of active esters. In this paper we report the

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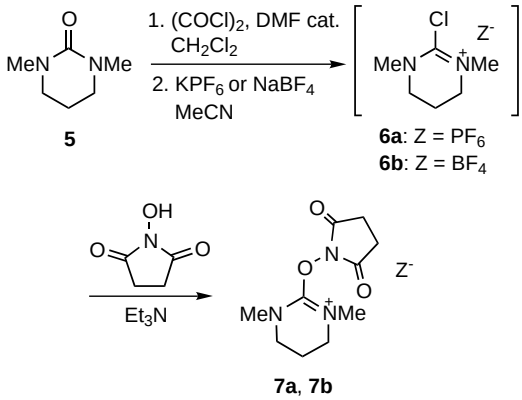
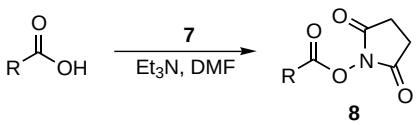
synthesis of new uronium salts derived from *N*-hydroxysuccinimide and DMPU[11c] and their use as efficient active ester-forming reagents.

The uronium salts *O*-succinimidyl-1,3-dimethyl-1,3-trimethyleneuronium hexafluorophosphate (**7a**, HSDU) and the corresponding tetrafluoroborate (**7b**, TSDU) were prepared following a one-pot procedure, which implied reaction of DMPU (**5**) with oxalyl chloride and a catalytic amount of DMF (Scheme 1). The corresponding chlorouronium salts were treated with potassium hexafluorophosphate or sodium tetrafluoroborate to afford crude salts **6a** and **6b**,[11b,c] and subsequently with *N*-hydroxysuccinimide in the presence of triethylamine. The uronium salts HSDU (**7a**) and TSDU (**7b**) were obtained in 54 and 64% overall yield, respectively, as white crystalline solids which could be stored at ambient temperature for months without appreciable decomposition.



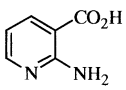
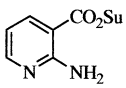
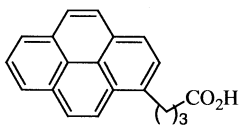
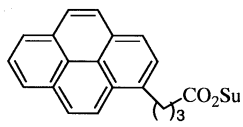

**Scheme 1.**

These new uronium salts were employed for the synthesis of *N*-succinimidyl active esters **8** (Scheme 2). Thus, reaction of **7a** or **7b** with a carboxylic acid function in the presence of triethylamine as base, in DMF as solvent and at room temperature afforded pure crude esters **8** ($^1$H and $^{13}$C NMR) after aqueous work-up (Table 1).




**Scheme 2.**

**Table 1.** Preparation of succinimide-derived active esters employing HSTU (**7a**) or TSTU (**7b**)

| Entry | Acid | Reagent | Active ester | Time (h) | Yield[a,b] (%) | Mp[c] (°C) | $[\alpha]_D^{25c}$ (*c* 2.0, dioxane) |
|---|---|---|---|---|---|---|---|
| 1 | $PhCO_2H$ | **7a** | $PhCO_2Su$ | 0.5 | 80 (88) | 134–136 | |
| 2 | $PhCO_2H$ | **7b** | $PhCO_2Su$ | 0.5 | 89 (88) | 134–136 | |
| 3 | (*E*)-PhCH=$CHCO_2H$ | **7b** | (*E*)-PhCH=$CHCO_2Su$ | 0.5 | 86 (86) | 180–183 | |
| 4[d] |  | **7b** |  | 0.5 | 51 (47) | 170–172 | |
| 5 |  | **7b** |  | 1 | 73 | 131–133 | |
| 6 | CbzGlyOH | **7a** | CbzGlyOSu | 0.5 | 85 (86) | 114–115 (113–114) | |
| 7 | CbzGlyOH | **7b** | CbzGlyOSu | 0.5 | 87 (86) | 114–115 (113–114) | |
| 8 | BocGlyOH | **7a** | BocGlyOSu | 0.5 | 88 (62) | 165–166 (168–170) | |
| 9 | BocGlyOH | **7b** | BocGlyOSu | 0.5 | 88 (62) | 164–165 (168–170) | |
| 10 | CbzAlaOH | **7b** | CbzAlaOSu | 0.5 | 84 (65) [97] | 120–121 (123–123.5) | −37 (−37.2) |
| 11 | BocAlaOH | **7b** | BocAlaOSu | 0.5 | 87 (71) [81] | 143–144 (143–144) | −49 (−49) |
| 12 | CbzValOH | **7b** | CbzValOSu | 0.5 | 84 (53) [100] | 114–115 (117–117) | −25 (−25.1) |
| 13 | BocValOH | **7b** | BocValOSu | 0.5 | 86 (74) [89] | 126–127 (128–129) | −36 (−37) |
| 14 | FmocValOH | **7b** | FmocValOSu | 0.5 | 85 | –[e] | −25 |
| 15 | BocLeuOH | **7b** | BocLeuOSu | 0.5 | 80 (48) [83] | 113–114 (116) | −42 (−41.8) |
| 16 | BocAibOH | **7b** | BocAibOSu | 1 | 73 | 166–167 | |

[a] Isolated pure crude compounds ($^1$H, $^{13}$C NMR) after work-up.
[b] In parenthesis, yields obtained using DCC overnight (Ref. 17). In brackets, yields obtained using carbonate **1** (Ref. 5).
[c] For crude products. In parenthesis, reported values (Ref. 17).
[d] A mixture of THF/water (2/1 v/v) was used as solvent.
[e] White foam (Ref. 18).

Typically, the reactions were completed in 30 min, the final isolated yields being high in most of the studied cases. In general, the use of reagent **7b** afforded similar or higher yields than when **7a** was employed, therefore the use of the former was preferred. For example, benzoic acid gave 89% yield using **7b** and 80% using **7a** (Table 1, entries 1 and 2), whereas a similar 88% yield was reported in 4 h reaction time when DCC in the presence of a polymeric 1-hydroxybenzotriazole (P-HOBt) was used.[8] Using the later DCC–P-HOBt combination, an 86% yield of the active ester from cinnamic acid was obtained in 7 h,[8] whereas an identical yield was obtained in just 0.5 h using **7b** (Table 1, entry 3). A problematic starting material, such as 2-aminonicotinic acid afforded a 51% yield using **7b**, but only a 47% in 24 h reaction time when DCC was used[15] (Table 1, entry 4). In this case, a mixture of THF/water was used as solvent due to the solubility of the starting acid in water, thus proving the effectivity of reagent **7b** in aqueous conditions. In addition, 1-pyrenebutanoic acid gave a 73% yield of the corresponding active ester, which has recently been used for protein immobilization via π-stacking[16] (Table 1, entry 5). Also, different *N*-Cbz-, *N*-Boc- and *N*-Fmoc-protected amino acids were transformed into their corresponding active esters (Table 1, entries 6–16). In most cases, yields were considerably higher in 0.5 h reaction time using **7** than when using DCC overnight,[17] and generally comparable to the use of carbonate **1**,[5] no appreciable racemization being detected after comparison of their optical rotation values (see Table 1, entries 10–15). Even a hindered amino acid such as *N*-Boc-aminoisobutyric acid (Aib) afforded a good yield of the corresponding active ester in 1 h reaction time (Table 1, entry 16).

We also explored the utility of these reagents in the formation of amide bonds. For example, the reaction of benzoic acid with *n*-butylamine in the presence of TSDU (**7b**) for 4 h in DMF at room temperature afforded 89% yield of the amide after extractive work-up when all the reaction components were mixed at once. A similar 86% yield was isolated when the acid was allowed to form the active ester in situ by reaction with TSDU (**7b**) for 0.5 h before addition of the amine and reaction for 4 h.

We conclude that uronium salts derived from *N*-hydroxysuccinimide and non-toxic DMPU are efficient reagents for the preparation of succinimidyl-derived active esters in a rapid, high-yielding and racemization-free fashion.

## Procedure for synthesis of 7

To a solution of 1,3-dimethylpropyleneurea (DMPU, 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 24 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 **7a**, 8.8 g, 48 mmol) or $NaBF_4$ (for **7b**, 5.27 g, 48 mmol) were added. The mixture was stirred at room temperature for 24 h and to the resulting suspension was added *N*-hydroxysuccinimide (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 **7a** and **7b** were obtained after crystallization with MeOH/isopropanol (**7a**: 8.0 g, 75%; **7b**, 8.0 g, 57%).

HSDU (**7a**): mp 171–172°C (EtOH). $\nu$ ($cm^{-1}$): 1755, 1697, 849. $\delta_H$ (DMSO-$d_6$): 2.02–2.06 (m, 2H), 2.86 (s, 4H), 3.20 (s, 6H), 3.57 (t, $J=6.1$, 4H). $\delta_C$ (DMSO-$d_6$): 20.0, 25.7, 38.2, 49.0, 158.0, 171. Anal. calcd for $C_{10}H_{16}N_3OPF_6$: C, 32.34; H, 4.35; N, 11.32. Found: C, 32.32; H, 4.44; N, 11.18.

TSDU (**7b**): mp 105–106°C (MeOH/*i*-Pr-OH). $\nu$ ($cm^{-1}$) 1739, 1693, 1040. $\delta_H$ (DMSO-$d_6$): 2.00–2.08 (m, 2H), 2.86 (s, 4H), 3.19 (s, 6H), 3.56 (t, $J=6.1$, 4H). $\delta_C$ (DMSO-$d_6$): 20.0, 25.7, 38.2, 49.0, 158.0, 171.0. Anal. calcd for $C_{10}H_{16}N_3O_3BF_4$: C, 38.32; H, 5.15; N, 13.42. Found: C, 38.16; H, 5.14; N, 12.94.

## A typical procedure for synthesis of 8

To a solution of the carboxylic acid (1 mmol) in DMF (5 mL) was added triethylamine (0.14 ml, 1 mmol) and reagent **7a** or **7b** (1 mmol). The resulting mixture was stirred at room temperature for 0.5 or 1 h. Saturated NaCl was added (50 mL) and the solution was extracted with AcOEt (3×25 mL). The organics were washed with 2N HCl (2×10 mL) (except for entry 4, Table 1), saturated $NaHCO_3$ (2×10 mL) and water (6×10 mL). The organic layer was dried ($Na_2SO_4$), filtered off and the solvent was evaporated (15 Torr) affording esters **8**, after trituration of the residue in water followed by filtration.

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