# *S*-(1-Oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium Hexafluorophosphate. A New Reagent for Preparing Hindered Barton Esters

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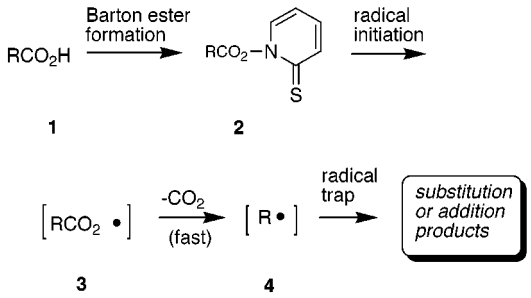
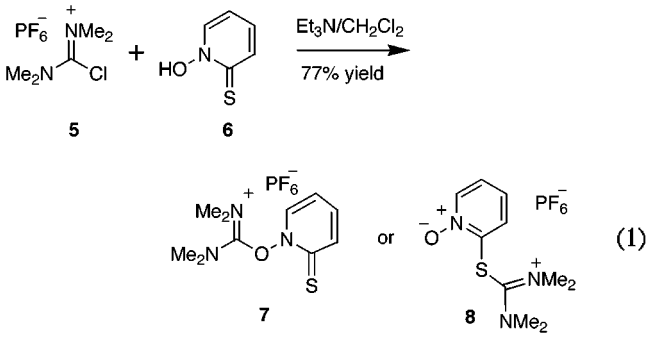
*Received May 8, 1998*

During the course of our studies on chiral acetaloxyalkyl radicals[1] generated from Barton ester precursors,[2] we noticed markedly lower overall yields with the more hindered carboxylic acid substrates. In some cases, the starting acid was detected in and/or isolated from the crude reaction mixtures after radical trapping.[3] Two explanations can account for the presence of starting acid **1** after the radical trapping reaction (Scheme 1). The first simply involves incomplete formation (or possibly inadvertent hydrolysis) of the Barton ester **2**, whereas the second requires competitive hydrogen abstraction by the intermediate carboxyl radical [$RCO_2^{\bullet}$] (**3**) instead of its decarboxylation to give the carbon-centered alkyl radical [$R^{\bullet}$] (**4**). Since the latter explanation is inconsistent with the known facility of this decarboxylation when R is alkyl,[4] we decided to focus our efforts on improving the efficiency of the esterification step.[5] We now report a new reagent for preparing Barton esters from hindered carboxylic acid precursors.

Mindful of the beneficial effect that uronium salts such as HATU[6] and TPTU[7] can have on difficult (i.e., hindered) peptide couplings, we hypothesized that an analogous uronium salt derived from 1-hydroxy-2-pyridinethione might accelerate the formation of hindered Barton esters as well. By adapting the general procedure used to make HATU,[8] equimolar amounts of **5** and **6** were combined in the presence of $Et_3N$ to produce a new compound whose combustion analysis was consistent with the molecular formula $C_{10}H_{10}N_3OSPF_6$ (eq 1). That our product possesses the thiouronium structure **8** rather than the isomeric uronium structure **7** in solution is supported by both $^{13}C$ (C-2 at $\delta$ 146.8, not >170 as expected for thiocarbonyl) and NOE (irradiation of Me enhances H-3, not H-6) data. X-ray crystallography unambiguously confirmed that this new compound exists as a thiouronium salt in the solid state as well.[9,10] In keeping with the established system of nomenclature for uronium-based reagents,[6] we suggest the abbreviation "HOTT" for this new reagent (*S*-(1-oxido-2-pyridinyl) 1,1,3,3-tetramethylthiouronium hexafluorophosphate).[11] HOTT is a stable white crystalline solid with an indefinite shelf life (no decomposition has been observed after storage in an amber bottle for 5 months in a desiccator) and can be handled without any special precautions. Barton esterifications are effected simply by combining HOTT with the carboxylic acid **1**, a tertiary amine, and a catalytic amount of DMAP in THF.[12] In most cases, the reaction is conveniently monitored via IR spectroscopy by following the disappearance of the carboxylic acid C=O stretch and concurrent appearance of the Barton ester C=O stretch (1800−1820 $cm^{-1}$).

**Scheme 1**




(1)

To illustrate the general utility of HOTT for Barton ester synthesis, we have tabulated the results of our experiments with four representative substrates **9**, **11**, **13**, and **16**. The ulosonic acid derivative **9** was chosen because it is commercially available and had been examined by Crich et al. in the context of their radical anomerization studies.[13] These workers prepared the Barton ester in situ from the corresponding acid chloride and reported a 42% yield of

† To whom inquiries concerning the X-ray structure determination of **8** should be addressed.

(1) (a) Garner, P. P.; Cox, P. B.; Klippenstein, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 4183−4184. (b) Garner, P.; Leslie, R.; Anderson, J. T. *J. Org. Chem.* **1996**, *61*, 6754−6755. (c) Garner, P.; Anderson, J. T. *Tetrahedron Lett.* **1997**, *38*, 6647−6650.

(2) Review: Crich, D. *Aldrichim. Acta* **1987**, *20*, 35−42.

(3) Others have made similar observations when preparing Barton esters. Cf. (a) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901−3924. (b) Baldwin, J. E.; Molony, M. G.; North, M. *Ibid.* **1989**, *45*, 6309−6318. (c) Ziegler, F. E.; Belema, M. *J. Org. Chem.* **1994**, *59*, 7962−7967.

(4) Bohne, C.; Boch, R.; Scaiano, J. C. *J. Org. Chem.* **1990**, *55*, 5414−5418.

(5) For a review of available methods for Barton esterification, see: Barton, D. H. R.; Samadi, M. *Tetrahedron* **1992**, *48*, 7083−7090 and references therein.

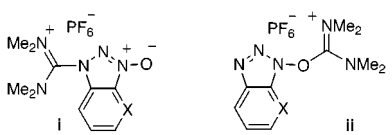
(6) HATU = *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate. Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397−4398.

(7) TPTU = 2-(2-oxo-1(2*H*)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate. Knorr, R.; Trzeciak, A.; Bannwarth, W.; Gillessen, D. *Tetrahedron Lett.* **1989**, *30*, 1927−1930.

(8) Dourtoglou, V.; Gross, B.; Lambropoulou, V.; Zioudrou, C. *Synthesis* **1984**, 572−574.

(9) The authors have deposited the atomic coordinates and thermal parameters for compound **8** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(10) Both HATU (X = N) and the structurally related *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU, X = CH) have been shown to crystallize in the guanidinium form **i** rather than the commonly depicted uronium form **ii**. See: Abdelmoty, I.; Albericio, F.; Carpino, L. A.; Foxman, B. M.; Kates, S. A. *Lett. Pept. Sci.* **1994**, *1*, 57−67.



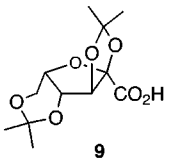
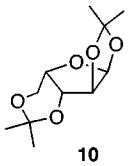
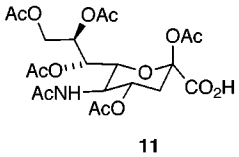
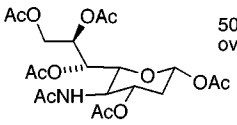
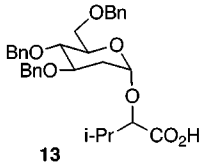
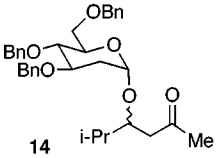
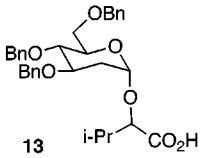
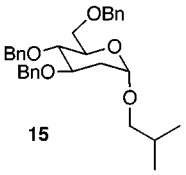
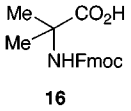
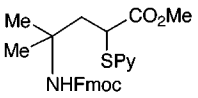
(11) The "parent" *S*-(pyridine-1-oxide-2-yl)thiouronium salt is known: Shaw, E.; Bernstein, J.; Losee, K.; Lott, W. A. *J. Am. Chem. Soc.* **1950**, *72*, 4362−4364.

(12) A detailed experimental may be found in the Supporting Information.

(13) Crich, D.; Ritchie, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 945−954.

S0022-3263(98)00870-6 CCC: $15.00 
Published on Web 07/30/1998

**Table 1. Radical Trapping Experiments Using HOTT for Barton Esterification**

| entry | substrate | esterification conditions | trapping conditions | product | isolated yield |
|---|---|---|---|---|---|
| 1. |  **9** | HOTT (1.5 equiv)<br>$Et_3N$ (4 equiv)<br>DMAP (10 mol%)<br>THF (0.1 M), RT<br>45 min | t-dodecanethiol (2 equiv)<br>and reflux (45 min) |  **10** | 78% yield<br>over 2 steps |
| 2. |  **11** | HOTT (1.5 equiv)<br>i-$Pr_2$EtN (4 equiv)<br>DMAP (10 mol%)<br>THF (0.1 M), RT<br>13 h | t-dodecanethiol (2 equiv)<br>and hν at 0 °C (3 h) |  **12** | 50% yield<br>over 2 steps |
| 3. |  **13** | HOTT (1.5 equiv)<br>i-$Pr_2$EtN (3 equiv)<br>DMAP (10 mol%)<br>THF (0.1 M), RT<br>7 h | 1) CSA (2.1 equiv)<br>$CH_2$=C($NO_2$)Me<br>(3 equiv), hν at 0 °C<br>2) 15% aq $TiCl_3$<br>$NH_4OAc$, THF<br>pH 5-6, 48 °C |  **14**<br>(ds = 4/1) | 60% yield<br>over 3 steps |
| 4. |  **13** | 1) HOTT (1.5 equiv)<br>$Et_3N$ (3 equiv)<br>DMAP (10 mol%)<br>THF (0.1 M), RT 40 min<br>2) t-dodecanethiol (2 equiv)<br>reflux (40 min) | |  **15** | 76% yield<br>over 2 steps |
| 5. |  **16** | HOTT (1.5 equiv)<br>i-$Pr_2$EtN (3 equiv)<br>DMAP (10 mol%)<br>THF (0.1 M), RT<br>2 h | $CH_2$=$CHCO_2$Me<br>(3 equiv), hν at RT |  **17** | 77% yield<br>over 2 steps |

reductive decarboxylation product **10**. Use of the HOTT reagent for this Barton esterification raised the yield of **10** to 78% (Table 1, entry 1). In a similar vein, Wong's group had reported that Barton decarboxylation of the peracetylayed *N*-acetylneuraminic acid **11** was difficult due to the sterically hindered nature of the carboxylic acid function.[14] Their optimal reaction conditions utilizing a water-soluble diimide condensing agent produced the aldose derivative **12** in only 27% yield. HOTT-mediated esterification of **11** followed by photolytic reductive decarboxylation resulted in a 50% yield of **12** (Table 1, entry 2). We had investigated the Barton esterification of substrate **13** during the early stages of our "radical aldol" project.[1b] Standard DCC-mediated esterification followed by radical aldol processing afforded only a 47% yield of **14** as a mixture of diastereomers. With HOTT, however, the overall yield of **14** was raised to 60%, which represents an average yield of 85% for each step. The hindered nature of **13** was evident from the fact that, even with HOTT, it took a full 7 h to complete this esterification. In this case, the remaining Hünig's base was neutralized with camphorsulfonic acid to inhibit base-catalyzed polymerization of the 2-nitropropene trap.[15] When an (incomplete) HOTT reaction mixture was refluxed in the presence of excess *tert*-dodecanethiol for 40 min, a 76% yield of reduced product **15** was obtained and no starting acid observed (Table 1, entry 4). This experiment indicated that the esterification could be driven to completion thermally. Finally, our standard HOTT esterification procedure was applied to *N*-Fmoc-2-aminoisobutyric acid (**16**). HOTT-mediated Barton esterification followed by radical addition to methyl acrylate proceeded cleanly to give a 77% yield of the γ-aminobutyric acid (GABA) analogue **17** (Table 1, entry 5). This result was only slightly better than that observed using Barton's mixed anhydride activation method[16] but shows that our procedure is compatible with the base-sensitive Fmoc protecting group. As these preliminary results suggest, the use of HOTT for Barton esterification may be indicated in many instances.

**Acknowledgment.** This work was supported by the National Science Foundation under Grant No. CHE-9616632. We wish to thank Professor David Crich (University of Illinois at Chicago) for helpful discussions.

**Note Added in Proof:** We have recently found that the use of 3/1 THF−MeCN as solvent is even more efficacious for Barton esterification with HOTT (esterification of **13** complete in 20 min).

**Supporting Information Available:** Experimental procedures for the preparation of HOTT, Barton esterifications, and trapping experiments, along with characterization data for all new compounds and X-ray crystallographic data for **8** (16 pages).

JO980870N

(14) Sugai, T.; Shen, G.-J.; Ichikawa, Y.; Wong, C.-H. *J. Am. Chem. Soc.* **1993**, *115*, 413−421.

(15) Barton, D. H. R.; Togo, H.; Zard, S. Z. *Tetrahedron* **1985**, *41*, 5507−5516.

(16) Barton, D. H. R.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1987**, *43*, 4297−4308.