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S-(2-Pyridinyl)-1,1,3,3-Tetramethylthiouronium Hexafluorophosphate. A New Reagent for the Synthesis of 2-Pyridinethiol Esters

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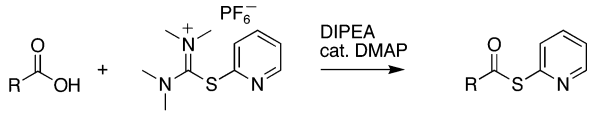
ABSTRACT

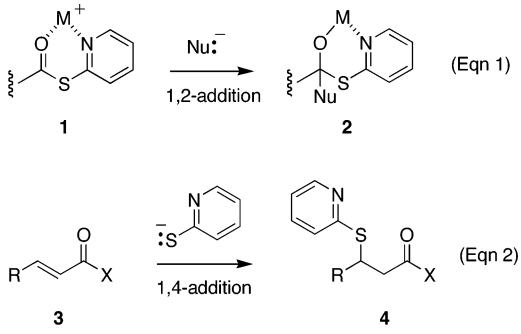


(R = alkyl, aryl, and alkenyl)

A new thiouronium-based reagent for the synthesis of 2-pyridinethiol esters under non-nucleophilic conditions from the corresponding carboxylic acids was developed. The resulting procedure enables the preparation of previously unavailable α,β-unsaturated 2-pyridinethiol esters as well as their aliphatic and aromatic counterparts.

2-Pyridinethiol esters are synthetically useful carboxylic acid derivatives. They can be used to activate the carbonyl group toward nucleophilic attack via chelation, as shown in eq 1 (M = metal or proton).[1] Chelation is also responsible for the enhanced stability of tetrahedral intermediate **2**, which forms the basis for Mukaiyama's synthesis of unsymmetrical ketones by organometallic addition to 2-pyridinethiol esters (Nu = alkyl or aryl).[2]

While a variety of methods are available for the synthesis of aliphatic and aromatic 2-pyridinethiol esters (see below), the preparation of α,β-unsaturated 2-pyridinethiol esters presents a significant challenge. The problem with the existing methodology arises from the presence of at least 1 equiv of the soft 2-pyridinethiolate nucleophile, which undergoes conjugate addition to the α,β-unsaturated acid chloride, active ester, or product as shown in eq 2. For this reason, α,β-unsaturated 2-pyridienethiol esters have only been reported for systems that either contain a hindered β-carbon (**3**, R = sterically encumbered alkyl group, X = 2-thiopyridine) or favor elimination to regenerate the double bond (R = conjugated aromatic ring or polyene).[3] Our attempts to convert simple α,β-unsaturated carboxylic acids into their corresponding 2-pyridinethiol esters via reaction of the carboxylic acid with either thiopyridyl chloroformate[3a]



(1) For recent examples, see: (a) Yu, L.; Lindsey, J. S. *J. Org. Chem.* **2001**, *66*, 7402 and references therein. (b) Grisenti, P.; Magni, A.; Olgiati, V.; Manzocchi, A.; Ferraboschi, P.; Villan, V.; Pucciarello, R.; Celotti, F. *Steroids* **2001**, *66*, 803. (c) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. *Chem. —Eur. J.* **2000**, *6*, 133 and references therein.

(2) Mukaiyama, T.; Araki, M.; Takey, H. *J. Am. Chem. Soc.* **1973**, *95*, 4763.

(3) (a) Corey, E. J.; Clark, D. A. *Tetrahedron. Lett.* **1979**, *31*, 2875. (b) Di Fabio, R.; Alvaro, G.; Bertani, B.; Giacobbe, S. *Can. J. Chem.* **2000**, *78*, 809. (c) Willard, D. M.; Levinger, N. E. *J. Phys. Chem. B* **2000**, *104*, 11075. (d) Waterhouse, R. N.; Sultana, A.; Guo, N.; Lee, B.; Simpson, N.; Collier, L.; Laruelle, M. *J. Labelled Compd. Radiopharm.* **2002**, *45*, 91.

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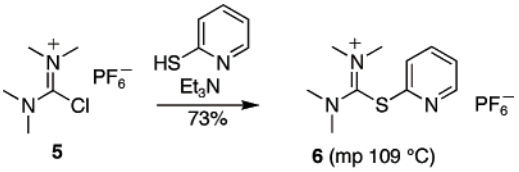
or 2,2′-dipyridyl disulfide and triphenylphosphine,[4] as well as through the standard reaction of acid chloride with 2-mercaptopyridine,[4] all met with failure due to conjugate addition of 2-pyridinethiolate to the activated α,β-unsaturated carbonyl system.[5] An alternative route based on quenching a vinyl organometallic species with 2-thiopyridylchloroformate was also tried, but it led instead to 2-pyridyl(vinyl)-thioether.[6] We now report a general solution to the problem that provides access to a variety of α,β-unsaturated 2-pyridinethiol esters as well as their aliphatic and aromatic counterparts.

Our attention was drawn to the possible use of a thiouronium-based reagent corresponding to $XC(NR_2)NR_2^+$ (where X = 2-thiopyridine).[7] Analogous uronium salts are known to activate carboxylic acids under mild conditions for subsequent peptide couplings (X = 1-oxybenzotriazole, etc.).[8] We also had some experience developing a thiouronium-based reagent for the synthesis of hindered Barton esters (X = 1-oxido-2-pyridinethiyl).[9] Most important for the problem at hand, however, was the expectation that the proposed reagent would only generate the nucleophilic 2-pyridinethiolate during the activation of the carbonyl, thus minimizing unwanted conjugate addition. (*S*)-(2-Pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate (HPTT, **6**) was prepared in good yield by the condensation of 2-mercaptopyridine with known[10] chloroformamidinium salt **5** (Scheme 1).[11] The thiouronium salt **6** was obtained as a stable white crystalline solid, and its molecular structure was confirmed by X-ray crystallography.[12]

In combination with diisopropylethylamine (DIPEA) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP), this new reagent effects the conversion of a variety of carboxylic acids **7a**−**f** to their corresponding 2-pyridinethiol esters **8a**−**f** (Table 1). The hydrolytically sensitive products may be isolated by rapid extractive workup followed by filtration through silica gel and characterized by ^{1}H and ^{13}C NMR spectroscopy.[13]

Both aliphatic and aromatic 2-pyridinethiol esters can be obtained in this manner in yields that are comparable to those reported for other procedures (entries 1 and 2). Similarly, cinnamic acid was converted to its 2-pyridinethiol ester in high yield (entry 3).[14] Most notably, 2-pyridinethiol esters

Scheme 1. Synthesis of *S*-(2-Pyridinyl)-1,1,3,3-tetramethylthiouronium Hexafluorophosphate (**6**) and Crystal Structure of its Cation



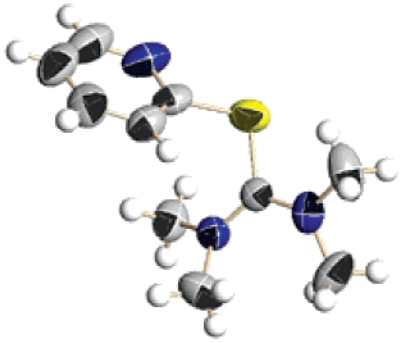
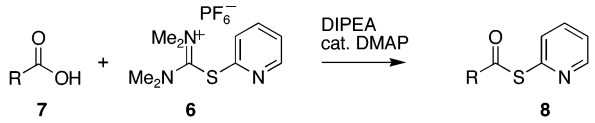
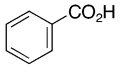
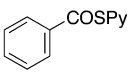
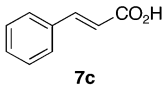
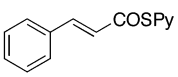
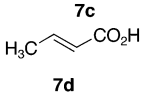
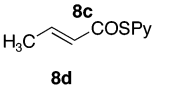
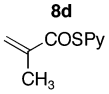
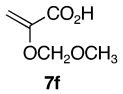
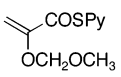


Table 1. Synthesis of 2-Pyridinethiol Esters



Entry	Substrate	Product	Yield (%)
1	 **7a**	 **8a**	94
2	$CH_3CH_2CH_2CO_2H$ **7b**	$CH_3CH_2CH_2COSPy$ **8b**	83
3	 **7c**	 **8c**	85
4	 **7d**	 **8d**	62
5	 **7e**	 **8e**	50
6	 **7f**	 **8f**	57

(4) Rao, P. D.; Littler, B. J.; Geier, G. R., III; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 1084.

(5) For example, from crotonic acid was isolated 3-(pyridyl-2-ylsulfanyl)-butyric acid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 (d, 3H, *J* = 7.0 Hz), 2.65 (dd, 1H, *J* = 8.0, 15.8 Hz), 2.95 (dd, 1H, *J* = 5.1, 15.8 Hz), 4.19 (ddq, 1H, *J* = 7.0, 8.0, 5.1 Hz), 7.02 (ddd, 1H, *J* = 1.1, 5.0, 7.4 Hz), 7.18 (ddd, 1H, *J* = 0.9, 1.1, 8.0 Hz), 7.52 (ddd, 1H, *J* = 1.9, 7.4, 8.0 Hz), 8.44 (ddd, 1H, *J* = 0.9, 1.9, 5.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.82, 35.97, 42.49, 120.00, 123.39, 136.54, 149.25, 158.21, 175.52.

(6) Apparently, the organometallic species transfers an electron to PySCOCl to give the corresponding radical anion, which fragments into $PySCO^{\bullet} + Cl^-$. The former can decarbonylate to give $PyS^{\bullet}$, which then reacts with the organometallic radical cation to give $CH_2{=}CHSPy$. See: Nagasaki, I.; Matsumoto, M.; Yamashita, M.; Miyashita, A. *Heterocycles* **1999**, *51*, 1015.

(7) The *S*-phenyl thiouronium species is known: Kessler, H.; Kalinowsky, H. O.; Von Chamier, C. *Liebigs Ann. Chem.* **1969**, 228.

(8) (a) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397. (b) Knorr, R.; Trzeciak, A.; Bannwarth, W.; Gillessen, D. *Tetrahedron Lett.* **1989**, *30*, 1927.

(9) Garner, P. P.; Anderson, J. T.; Dey, S. *J. Org. Chem.* **1998**, *63*, 5732.

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

(11) ***S*-(2-Pyridinyl)-1,1,3,3-tetramethylthiouronium Hexafluorophosphate (HPTT, 6).** To a stirred solution of tetramethylchloroformamidinium hexafluorophosphate (**5**) (4.488 g, 16.00 mmol) and 2-mercaptopyridine (1.779 g, 17.58 mmol) in dry dichloromethane was added triethylamine (2.23 mL, 16.0 mmol) dropwise under argon. After 10 min the reaction mixture was concentrated under reduced pressure. The resulting crude orange oil was crystallized from a mixture methanol/2-propanol (ca. 3:1) to give **6** as a white solid (4.150 g, 73% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.28 (s, 12H), 7.32 (ddd, 1H, *J* = 0.9, 4.8, 7.5 Hz), 7.51 (ddd, 1H, *J* = 0.9, 0.9, 7.9 Hz), 7.81 (ddd, 1H, *J* = 1.9, 7.5, 7.9 Hz), 8.52 (ddd, 1H, *J* = 0.9, 1.9, 4.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 44.06, 123.70, 125.42, 138.82, 151.07, 151.26, 172.07.

of crotonic acid, methacrylic acid and 2-methoxymethoxyacrylic acid can be prepared (entries 4−6) using the described procedure. The resulting α,β-unsaturated 2-pyridinethiol esters were found to be reasonably stable if kept at −30 °C, but they slowly rearranged to give 3-(2-pyridinethiyl)-propionic acid derivatives at room temperature.[15] Even under our optimized conditions, the 2-pyridinethiol ester of acrylic acid could not be obtained.

In conclusion, a new reagent has been developed for the conversion of aliphatic, aromatic, and α,β-unsaturated carboxylic acids into their corresponding 2-pyridinethiol ester derivatives. This reagent, termed HPTT, enables the preparation of previously inaccessible α,β-unsaturated 2-pyridinethiol esters. In view of its ease of preparation and use, we expect HPTT to find widespread application for the synthesis of 2-pyridinethiol esters.

Acknowledgment. This work was supported by the National Science Foundation under Grant CHE-0111831.

Supporting Information Available: Complete experimental procedures and characterization data for compounds **5**, **6**, **7f**, and **8a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Atomic coordinates and thermal parameters for compound **6** have been deposited 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.

(13) **General Procedure for the Preparation of 2-Pyridinethiol Esters (8a−f).** To an ice-cold stirred solution of carboxylic acid (**7**) in dry methylene chloride (0.1 M) were added *S*-(2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate (**6**, 1.2 equiv), dry diisopropylethylamine (1.2 equiv), and 4-(dimethylamino)pyridine (0.12 equiv) under argon. The reaction mixture was stirred overnight during which time the temperature was allowed to reach room temperature. The mixture was then concentrated under reduced pressure to give an oil, which was partitioned between diethyl ether and 10% aqueous sodium carbonate solution. The aqueous layer was extracted three times with diethyl ether, and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a yellow oil. The crude product was filtered through a plug of silica gel ca. 4 cm in length eluting with 4:1 diethyl ether/pentane to yield the 2-pyridinethiol esters **8**. In the case of particularly hydrolytically sensitive systems, the silica gel was first washed with 1:1 diethyl ether/pentane containing 3% triethylamine followed by 1:1 diethyl ether/pentane. Diagnostic NMR data for 2-pyridinethiol esters: ^{1}H δ 8.5−8.7 (pyridine H-6); ^{13}C δ 151−152 (pyridine C-1) and δ 186−196 (C═O).

(14) Products **8a**−**c** are known. For **8a**, see, for example: Amos, R. A.; Fawcett, S. M. *J. Org. Chem.* **1984**, *49*, 2637. For **8b**, see ref 1c. For **8c**, see: Balsamini, C.; Bedini, A.; Diamantini, G.; Spadoni, G.; Tarzia, G.; Tontini, A.; Di Fabio, R.; Donati, D. *Farmaco* **1999**, *54*, 101.

(15) Purification by flash chromatography was attempted for compound **8d**, but only 3-(pyridyl-2-ylsulfanyl)-butyric acid was isolated.