A new and efficient protocol for preparation of thiol esters from carboxylic acids and thiols in the presence of 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU)

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Abstract
A novel and convenient method has been developed for the synthesis of thiol esters from the corresponding carboxylic acids and thiols at room temperature using 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) as the coupling reagent.

Keywords: Thiol esters, TBTU, coupling reagent, carboxylic acids, thiols

Introduction
Thiol esters show higher reactivity and selectivity toward nucleophiles than their oxygen analogues. They play important roles in biological systems such as acyl coenzyme A, and S-acetyl dihydrolipolic acid.1 Thiol esters are used as mild acyl transfer reagents,2 as intermediates in the synthesis of ketones3, for asymmetric aldol reactions4 and in the preparation of macrocyclic lactones.5 The growing importance of thiol esters in organic synthesis has stimulated recent extensive research towards improved methods for their preparation.6 Thiol esters are generally prepared from compounds having an active carbonyl group such as acid chlorides6j,6l-n or carboxylic acid anhydrides.6k We have recently reported the synthesis of thiol esters from N-acylphthalimides and thiols in the presence of KF/Al2O3.7 Recently, Katritzky and coworkers introduced a procedure for preparation of thiol esters by reactions of N-acylbenzotriazoles with thiols.8

Coupling of carboxylic acids with a variety of nucleophiles to prepare amides, esters, thiol esters, etc. continues to be one of the most commonly used transformations in organic chemistry.1 Modern coupling reagents utilize an equimolar amount of acid and nucleophile.
Besides being effective and easily handled, it is crucial that the conditions employed are mild and compatible with a wide variety of functional groups including the most commonly protecting groups.\textsuperscript{9,10}

Coupling reactions of carboxylic acids with thiols using carbodiimides such as DCC and EDC\{1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride\} are common methods for synthesis of thiol esters.\textsuperscript{11} Although the procedure gives the products in good yields,\textsuperscript{11} equimolar amounts of highly insoluble ureas are formed which can cause difficulties in purification of the main product. A recent method\textsuperscript{12} using tetramethylfluoroformamidinium hexafluorophosphosphate (TFFH) as the coupling reagent for the reaction of carboxylic acids with thiols gave the corresponding thiol esters in 60-94\% yields.

The coupling reagent field has clearly evolved in the last decade from carbodiimides to onium (phosphonium and uronium) salts. One of such onium salts is 2-(1-\textit{H}-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) which has been used as an activating agent of carboxylic acids for preparation of 1,2,4, oxadiazoles,\textsuperscript{13} amides and phenylhydrazides,\textsuperscript{14} and esters.\textsuperscript{15}

\textbf{Results and Discussion}

Here we wish to report our results demonstrating the use of TBTU as a coupling reagent in the reaction of carboxylic acids with thiols for the synthesis of thiol esters (Scheme 1).

\[
\begin{align*}
\text{R}^1\text{CO}_2\text{H} & \xrightarrow{\text{TBTU, DIPEA, EtOAc}} \text{R}^2\text{SH} & \xrightarrow{25 \, ^\circ\text{C}} \text{R}^1\text{COSR}^2
\end{align*}
\]

\textbf{Scheme 1}

The results are summarised in Table 1. The reaction can be performed with aromatic and aliphatic carboxylic acids and thiols at room temperature. The yields of thiol esters are in the range 72-92\%. The structures of all the products were established from their analytical and spectral (IR, \textsuperscript{1}H and \textsuperscript{13}C NMR) properties. The reactions between various carboxylic acids and aromatic thiols are in general very fast and complete in 15-45 min. The results show clearly the need for much longer reaction times for aliphatic thiols (benzyl mercaptan, entries 5 and 7, Table 1). The effects of several solvents were examined and the best results were obtained with ethyl acetate (EtOAc).

The proposed mechanism for this coupling reaction is depicted (Scheme 2). X-Ray crystallographic studies have revealed that TBTU exists, at least in the solid state, as zwitterion I comprising a triazol-N-oxide and a guanidinium moiety.\textsuperscript{16} \textit{N,N'-Diisopropylethylamine} (DIPEA)
removes the acidic hydrogen from the carboxylic acid, and the carboxylate anion reacts with TBTU. The intermediate acyloxy-aminium/uronium salt 2 cannot be detected and reacts immediately with the benzotriazole derivative to give 3, which reacts with thiol to give the corresponding thiol ester 4 and 1-hydroxybenzotriazole (HOBt, 5) as a water-soluble by-product.

Conclusions

In summary, TBTU has been introduced as an efficient S-acylating reagent of thiols to give diverse thiol esters in high to excellent yields. The present method has the advantages of operational simplicity, mild reaction conditions, ready availability and use of non-toxic materials, fast reaction rates, and simple reaction work-up.

Table 1. Thiol esters from carboxylic acids and thiols using TBTU

| Entry | R¹   | R²   | Time (min) | Thiol ester Yields (%)²
|-------|------|------|------------|------------------------
| 1     | Ph   | Ph   | 30         | 86¹⁶                  |
| 2     | Ph   | 4-MeC₆H₄ | 30    | 82¹⁶                  |
| 3     | Ph   | 4-MeOC₆H₄ | 45    | 72¹⁶                  |
| 4     | Ph   | 4-ClC₆H₄ | 15    | 91⁶k                  |
| 5     | Ph   | PhCH₂ | 150     | 78¹⁷                  |
| 6     | PhCH₂ | Ph   | 30    | 74¹⁸                  |
| 7     | PhCH₂ | PhCH₂ | 360   | 92⁶f                  |
| 8     | 4-ClC₆H₄ | Ph   | 20    | 92¹⁹                  |
| 9     | n-C₁₁H₂₃ | Ph   | 15    | 77¹⁷                  |
| 10    | n-C₁₃H₃₁ | Ph   | 15    | 84⁶i                  |

¹ Yields refer to those of pure isolated products characterized by IR, ¹H and ¹³C NMR spectroscopy
² references for known compounds.
Experimental Section

General Procedures. TBTU was purchased from Zhejiang company (China). All products were characterized by comparison of their spectroscopic data with those of known samples. IR spectra were obtained using an ABB FTLA 2000 instrument. NMR spectra were recorded on a Bruker AQS 300 Avance instrument at 300 MHz for $^1$H and at 75 MHz for $^{13}$C NMR in CDCl$_3$ solutions.

Representative experimental procedure for preparation of S-(4-methylphenyl) benzenecarbothioate (entry 2, Table 1)

To a solution of benzoic acid (122 mg, 1.0 mmol) dissolved in EtOAc (35 mL) were added TBTU (353 mg, 1.1 mmol) and DIPEA (198 mg, 1.5 mmol) and the mixture was stirred at 25 °C. After 30 min, 4-methylthiophenol (124 mg, 1.0 mmol) was added and the reaction was allowed to proceed for 30 min. The solvent was evaporated in vacuo to give the crude product, which was purified by preparative thin layer chromatography (silica gel, eluent EtOAc/ n-heptane = 1 : 3) to afford the pure thiol ester (187 mg, 82%) as colorless crystals, mp 64.2-65.1 °C (lit. 17 mp 65-66 °C); IR (KBr) ν 1674 cm$^{-1}$; $^1$H NMR $\delta$ 2.43 (s, 3H), 7.30 (d, $J = 8.1$ Hz, 2H), 7.42 (d, $J = 8.1$ Hz, 2H), 7.50 (t, $J = 7.6$ Hz, 2H), 7.63 (t, $J = 7.4$ Hz, 1H), 8.05 (d, $J = 8.5$ Hz, 2H); $^{13}$C NMR $\delta$ 21.38, 123.75, 127.46, 128.71, 130.10, 133.56, 135.02, 136.70, 139.80, 190.59.
Selected physical and spectral data

**S-Benzyl phenylethanethioate (entry 7).** Oil; IR (neat) ν 1689, 1504, 1458 cm⁻¹; ¹H NMR δ 3.87 (s, 2H), 4.14 (s, 2H), 7.25-7.39 (m, 10H); ¹³C NMR δ 33.62, 50.23, 127.28, 127.46, 128.61, 128.67, 128.86, 129.62, 133.44, 137.27, 196.80.

**S-Phenyl n-dodecanethioate (entry 9).** Oil; IR (neat) ν 1702 cm⁻¹; ¹H NMR δ 0.90 (t, J = 6.9 Hz, 3H), 1.25-1.29 (m, 16H), 1.73 (quin, J = 7.5 Hz, 2H), 2.67 (t, J = 7.4 Hz, 2H), 7.43 (s, 5H); ¹³C NMR δ 14.10, 22.67, 25.59, 28.94, 29.23, 29.31, 29.40, 29.57, 31.89, 43.72, 127.95, 129.12, 129.25, 134.46, 197.59.

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**References**


