# $KF/Al_2O_3$ catalysed synthesis of thiol esters from *N*-acylphthalimides and thiols

**Barahman Movassagh[a,b]* and Yousef Zakinezhad[a]**

[a]*Department of Chemistry, K. N. Toosi University of Technology, P.O. Box 16315-1618, Tehran, Iran*

[b]*Kermanshah Oil Refining Company, Kermanshah, Iran*

A new method for the preparation of thiol esters from *N*-acylphthalimides and thiols in the presence of $KF/Al_2O_3$ is introduced.

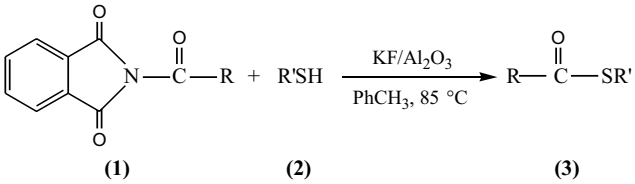
**Keywords:** thiol esters, *N*-acylphthalimides, thiols, $KF/Al_2O_3$

Thiol esters are versatile functional groups which facilitate the formation of carbon-carbon bonds and act as mild acyl transfer agents, particularly in the preparation of macrocyclic lactones,[1e,2] as intermediates in the synthesis of ketones,[3] and for asymmetric aldol reactions.[4] They show higher reactivity towards nucleophiles than their oxygen analogues and are important roles in biological system as acyl coenzyme A, and *S*-acetyl dihydrolipoic acid.[5] Methods for the synthesis of thiol esters, from carboxylic acids or their derivatives.[2a,6] involve toxic reagents, harsh conditions, or uncommon starting materials. Recently, we have reported two methods for the synthesis of thiol esters from disulfides using $Zn/AlCl_3$ system.[7]

Reagents immobilised on porous solid supports have advantages over conventional solution phase systems because of good dispersion of active reagent sites, better selectivity and easier work-up. We have examined the application of the solid supported reagent potassium fluoride on alumina ($KF/Al_2O_3$).[8] By taking advantage of the strongly basic nature of this solid supported reagents, we now describe another procedure for the preparation of thiol esters (**3**) from *N*-acylphthalimides (**1**) and various thiols (**2**) in dry toluene at 85 °C using $KF/Al_2O_3$ (Scheme 1).

As shown in Table 1, a series of thiols (both aliphatic and aromatic) were treated with *N*-acetyl-, *N*-propionyl-, and *N*-benzoylphthalimides in the presence of $KF/Al_2O_3$ reagent to afford the corresponding thiol esters. Thiol esters obtained from *N*-acetyl- and *N*-propionylphthalimides showed much greater reactivity than the *N*-benzoyl derivative due to the lower reactivity of the benzoyl carbonyl group of *N*-benzoylphthalimide towards nucleophilic thiolate anions, produced by the reaction of thiols with $KF/Al_2O_3$ reagent.

In conclusion, the procedure described above is a valuble alternative to the direct transformation of a carboxylic acid




**Scheme 1**

to the corresponding thiol ester. This method offers several advantages such as the greater availability of the starting material, simple reaction work-up, and it avoids the use of toxic reagents such as heavy metal thiolates or phenyl dichlorophosphates.

## Experimental

$KF/Al_2O_3$ catalyst was prepared according to the method reported earlier.[8b] *N*-Acetylphthalimide (m.p. 134 °C; Lit.[9,10] m.p. 133 °C) and *N*-propionylphthalimide (m.p. 142 °C; Lit.[9,10] m.p. 143–144 °C) were obtained from direct acylation of phthalimide by the corresponding carboxylic anhydrides.[9] *N*-Benzoylphthalimide was prepared as follows: Benzoic anhydride (0.226 g, 1.0 mmol) was added to a solution of phthalimide (0.15 g, 1.0 mmol) and triethylamine (0.3 g, 3.0 mmol) in tetrahydrofuran (THF, 10 ml). The mixture was heated to reflux for 9 h. The THF was evaporated and $Et_2O$ (30 ml) was added. The mixture was washed with 5 % sodium hydroxide solution (2 × 30 ml) and water (2 × 20 ml). The organic phase was dried ($Na_2SO_4$) and evaporated to give the crude product, which recrystallised from ethanol; yield: 0.2 g (80 %); m.p. 165–166 °C (Lit.[10] m.p. 166–168 °C). All starting *N*-acylphthalimides and the products were characterised by comparison of their physical and spectroscopic data with those of known samples. Boiling points and melting points were determined with a Büchi B-540 melting point/boiling point capillary apparatus. IR spectra were obtained using a Shimidazu IR-460 instrument. $^1H$ NMR and $^{13}C$ NMR were recorded with either a Bruker AQS-300 or Bruker DRX-500 spectrometer, with nominal

**Table 1** Thiol esters from *N*-acylphthalimides and thiols using $KF/Al_2O_3$

| Entry | R | R′ | Time/h | Yield/%[a] | M.p. (°C)/b.p. (°C)/Torr | |
|---|---|---|---|---|---|---|
| | | | | | Found | Reported[b] |
| 1 | $CH_3$[9,10] | Ph | 3 | 90 | Oil | Oil[11] |
| 2 | $CH_3$ | 4-$CH_3C_6H_4$ | 3.5 | 88 | Oil | Oil[11] |
| 3 | $CH_3$ | 4-$ClC_6H_4$ | 2.7 | 91 | 38–39 | 39–41[12] |
| 4 | $CH_3$ | $PhCH_2$ | 3.25 | 86 | Oil | Oil[8,13] |
| 5 | $CH_3CH_2$[9,10] | Ph | 3.5 | 88 | 145–149 | 60–70/0.01[6j] |
| 6 | $CH_3CH_2$ | 4-$CH_3C_6H_4$ | 4 | 87 | 168–171 | 90/0.01[6j] |
| 7 | $CH_3CH_2$ | 4-$ClC_6H_4$ | 3 | 90 | 162–166 | 90–100/0.05[6j] |
| 8 | $CH_3CH_2$ | $CH_3(CH_2)_7$ | 3.75 | 83 | Oil | Oil[14] |
| 9 | Ph[10] | Ph | 5.5 | 48 | 56–58 | 56–57[6j] |
| 10 | Ph | 4-$CH_3C_6H_4$ | 6.5 | 43 | 65–66 | 64–66[12] |
| 11 | Ph | 4-$ClC_6H_4$ | 6.0 | 49 | 73–74 | 72–74[15] |
| 12 | Ph | $PhCH_2$ | 6.25 | 44 | Oil | Oil[16] |

[a]Yield of isolated pure product. [b]References for physical data of products.

* Correspondent. E-mail: bmovass1178@yahoo.com

frequencies of 300 and 500 MHz for proton or 75 and 125 MHz for carbon, respectively. The $^1$H NMR spectrum of compound 11 was recorded on Jeol JNM-EX90A (90 MHz) spectrometer.

*General experimental procedure*

The *N*-acylphthalimide (1.0 mmol) was added to a stirred mixture of thiol (1.0 mmol) and $KF/Al_2O_3$ (0.72 g, 40 % by weight) in toluene (10 ml). The resulting reaction mixture was heated to 85 °C for the appropriate time (Table 1). The progress of the reaction was monitored by TLC. After completion of the reaction, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The pure products were obtained by preparative TLC (silica gel, eluent, *n*-hexane/EtOAc = 4: 1) to afford the desired thiol esters.

Selected spectroscopic data of some thiol esters:

*S-4-Tolyl thioacetate* **2:** IR (neat) $\nu_{max}$/cm$^{-1}$ 1706, 1598, 1494, 808; $^1$H NMR ($CDCl_3$) $\delta_H$ 7.31 (d, 2H, $J$ = 8.5 Hz), 7.24 (d, 2H, $J$ = 8.5 Hz), 2.43 (s, 3H), 2.39 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta_C$ 194.53, 139.72, 134.44, 130.06, 124.52, 30.09, 21.34.

*S-4-Tolyl thiopropionate* **6:** IR (neat) $\nu_{max}$/cm$^{-1}$ 1698, 1588, 1481, 800; $^1$H NMR ($CDCl_3$) $\delta_H$ 7.31 (d, 2H, $J$ = 8.5 Hz), 7.24 (d, 2H, $J$ = 8.5 Hz), 2.69 (q, 2H, $J$ = 7.5 Hz), 2.39 (s, 3H), 1.24 (t, 3H, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta_C$ 198.88, 139.58, 134.56, 129.99, 124.42, 36.59, 28.80, 9.10.

*S-4-Chlorophenyl thiopropionate* **7:** IR (neat) $\nu_{max}$/cm$^{-1}$ 1700, 1561, 1464, 811; $^1$H NMR ($CDCl_3$) $\delta_H$ 7.40 (d, 2H, $J$ = 8.6 Hz), 7.35 (d, 2H, $J$ = 8.6 Hz), 2.70 (q, 2H, $J$ = 7.5 Hz), 1.25 (t, 3H, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta_C$ 198.12, 135.97, 129.65, 126.56, 36.96, 9.21.

*S-Octyl thiopropionate* **8:** IR (neat) $\nu_{max}$/cm$^{-1}$ 1736; $^1$H NMR ($CDCl_3$) $\delta_H$ 2.87 (t, 2H, $J$ = 7.3 Hz), 2.56 (q, 2H, $J$ = 7.5 Hz), 1.57 (quin., 2H), 1.39–1.23 (m, 10H), 1.18 (t, 3H, $J$ = 7.5 Hz), 0.88 (t, 3H, $J$ = 7.3 Hz); $^{13}$C NMR ($CDCl_3$) $\delta_C$ 200.44, 37.42, 31.77, 29.68, 29.58, 29.07, 28.83, 28.76, 22.61, 14.05, 9.71.

*S-4-Tolyl thiobenzoate* **10:** IR (KBr) $\nu_{max}$/cm$^{-1}$ 1661, 1575, 1473, 766, 682; $^1$H NMR ($CDCl_3$) $\delta_H$ 8.05 (d, 2H, $J$ = 8.7 Hz), 7.63 (t, 1H, $J$ = 7.5 Hz), 7.50 (t, 2H, $J$ = 7.5 Hz), 7.43 (d, 2H, $J$ = 8.5 Hz), 7.29 (d, 2H, $J$ = 8.5 Hz), 2.43 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta_C$ 190.6, 139.8, 136.7, 135.0, 133.6, 130.1, 128.7, 127.5, 123.8, 21.4.

*S-4-Chlorophenyl thiobenzoate* **11:** IR (KBr) $\nu_{max}$/cm$^{-1}$ 1681, 1570, 1475, 839, 684; $^1$H NMR (90 MHz, $CDCl_3$) $\delta_H$ 8.03(d, 2H, $J$ = 8.3 Hz), 7.52 (d, 2H, $J$ = 8.3 Hz), 7.44 (s, 5H); $^{13}$C NMR ($CDCl_3$) $\delta_C$ 189.65, 136.36, 136.33, 136.00, 133.88, 129.53, 128.84, 127.53, 125.85.

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