Oxidation of Alkynyl Ethers with Potassium Permanganate. A New Acyl Anion Equivalent for the Preparation of α-Keto Esters

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Received May 15, 1995

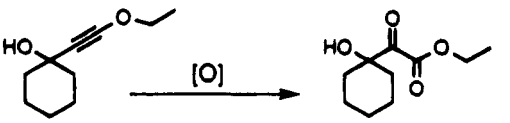
α-Keto esters and derivatives play an important role in organic synthesis[1] and are found in many biologically relevant molecules.[2] During the recent development of potential immunosupressive agents, it became of interest to investigate new synthetic methods for the preparation of such functionality.

Considering the versatility of alkynes in organic synthesis, in particular the reaction of lithioethoxyacetylene (**1**) with electrophiles,[3] it was envisaged that a clean and efficient oxidation of substituted alkynyl ethers would provide a general method for the preparation of α-keto esters and derivatives. The synthesis of α-keto esters, acids, and amides using an umpoled synthon approach has been previously reported.[4] Herein is described an alternative synthon strategy, using an equivalent of the acyl anion **2** for the preparation of α-keto esters as well as α,β-diketo esters and α-keto-β-hydroxy esters in excellent yield.

1 **2**

Potassium permanganate ($KMnO_4$) in a buffered (pH 7.0–7.5) aqueous acetone mixture is well known to oxidize alkynes to α,β-diketones[5] and was found in this investigation to rapidly oxidize alkynyl ethers to the corresponding substituted α-keto esters. For example, the oxidation of the alkynyl ether **3**, obtained by the condensation of lithioethoxyacetylene with cyclohexanone using standard conditions,[3] was complete at room temperature within 2 min, affording the α-keto-β-hydroxy ester **4** in 98% isolated yield. This result was compared to those obtained by the reaction of the same substrate using other oxidative methods (Table 1).[6] The $KMnO_4$ oxidation has clear advantages over the reported methods. Specifically, shorter reaction times and higher product yields are observed with the $KMnO_4$ procedure.

Table 1. Oxidative Transformation of Hydroxy Alkynyl Ether 3 to α-Keto-β-hydroxy Ester 4



3 **4**

oxidant	time	yield[a] (%)
$KMnO_4$	2 min	98
$PhIO / RuCl_2(PPh_3)_3$	30 min	48
OsO_4	18 h	42

[a] Isolated yields.

Having completed the initial study described above, the $KMnO_4$ oxidation was applied to a variety of alkynyl ethers (Table 2). The majority of the substrates utilized were synthesized by reaction of the corresponding ketone (entries 1–6), alkyl halide (entry 8), or aldehyde (entries 9–10) with lithioethoxyacetylene in THF at low temperatures. The substrate used for entry 7 was prepared via a palladium/copper-mediated coupling of iodobenzene with ethyl ethynyl ether.[7] The time required to effect complete oxidation was similar for each substrate, and product yields were consistently high. The lower yields obtained for entries 9 and 10 were primarily due to substrate instability. Therefore, the best results were obtained when the isolated substrates were oxidized immediately following their preparation.[8] The reaction conditions were compatible with olefin functionality (entries 5 and 6), although prolonged exposure of such substrates to the reaction mixture resulted in the formation of multiple side products. Oxidations were also performed successfully in the presence of secondary and tertiary alcohols. An attempt was made to use the addition/oxidation procedure for direct preparation of α,β-diketo esters. Ethynyl ketone precursors were successfully obtained by the addition of lithioethoxyacetylene to acid chlorides and Weinreb amides. However, these ketones were found to be unstable to the $KMnO_4$ reaction conditions. The lability of ethynyl ketones of this type has been previously reported.[9] α,β-Diketo esters were eventually obtained in high yield by oxidation of α-keto-β-hydroxy esters with manganese(IV) oxide (MnO_2) in a hexane/methylene chloride mixture (eq 1).[10] The α,β-diketo ester **6** was isolated as the corresponding monohydrate. Hydration of the central carbonyl in these systems has been rigorously established by Wasserman and co-workers using X-ray crystallographic methods.[11]

In conclusion, substituted alkynyl ethers were easily prepared from the readily available ethyl ethynyl ether. The oxidation of alkynyl ethers with $KMnO_4$ was shown, in this investigation, to be an effective method for the

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(2) (a) Read, L. J. *Acc. Chem. Res.* **1974**, *7*, 40. (b) Vezina, C.; Kudelski, A.; Sehgal, S. N. *J. Antibiot.* **1975**, *28*, 721. (c) Tanaka, H.; Kuroda, A.; Marusawa, H.; Hanataka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T. *J. Am. Chem. Soc.* **1987**, *109*, 5031. (d) Hagihara, M.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6570. (e) Ocain, T.; Rich, D. H. *J. Med. Chem.* **1992**, *35*, 451.

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(4) For examples, see: (a) Eliel, E. L.; Hartmann, A. J. *J. Org. Chem.* **1972**, *37*, 505. (b) Takahashi, T.; Okano, T.; Harada,T.; Imamura, K.; Yamada, H. *Synlett* **1994**, 121. (c) Wasserman, H.; Ho, W. B. *J. Org. Chem.* **1994**, *59*, 4364.

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(6) For examples of alkynyl ether oxidation using iodosylbenzene with a ruthenium catalyst, see: Müller, P.; Godoy, J. *Tetrahedron Lett.* **1982**, *23*, 3361. For examples of alkynyl ether oxidation using osmium tetraoxide, see: Bassignani, L.; Brandt, A.; Caciagli, V.; Re, L. *J. Org. Chem.* **1978**, *43*, 4245.

(7) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467.

(8) Storage of substrates **9** and **10** in a −20 °C freezer prevented decomposition for a period of months.

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(10) Fatiadi, A. J. *Synthesis* **1976**, 65.

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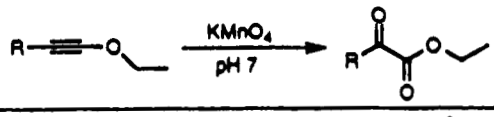
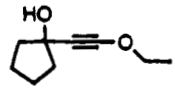
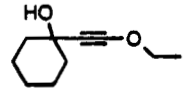
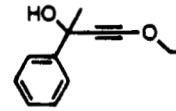
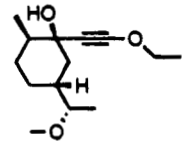
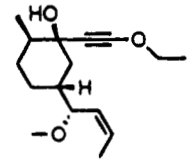
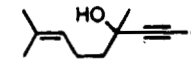
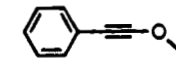
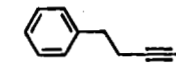
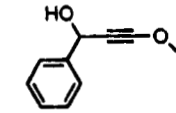
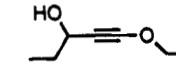
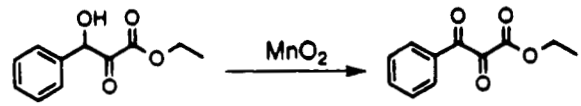
0022-3263/95/1960-6221$09.00/0

Table 2. Oxidation of Alkynyl Ethers by Potassium Permanganate in Buffered Aqueous Acetone



entry	substrate	yield[a](%)
1		97
2		98
3		95
4		97
5		91
6		80
7		97
8		93
9		78
10		76

[a]Isolated yields



(1)

5 6

preparation of α-keto esters and derivatives. The generality of the procedure was demonstrated with a variety of substrates containing different functionality and substitution patterns. This methodology should prove to be convenient and useful for organic synthesis.

Experimental Section

Alkyne additions were performed in septum-sealed flasks under a positive pressure of argon. The majority of reagents used were purchased from the Aldrich Chemical Co.[12] Ethyl ethynyl ether was purchased as a 50 wt % solution in hexane. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Flash column chromatography was performed using silica gel 60 (Merck Art. No. 9385). ^{1}H NMR spectra were recorded in $CDCl_3$ at 300 MHz, and chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane. Infrared absorption spectra were recorded using a Perkin-Elmer 1600 series FTIR. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

General Alkyne Addition Procedure. Ethyl ethynyl ether (1.0 g, 14.25 mmol, 1.4 equiv) as a 50 wt % solution in hexane was diluted with THF (10 mL) and cooled to −78 °C with stirring. n-BuLi (8.9 mL of a 1.6 M solution in hexane, 14.25 mmol, 1.4 equiv) was added dropwise over 15 min. The reaction mixture was maintained at −78 °C for 2 h and then treated dropwise with the electrophilic substrate (10.81 mmol, 1 equiv) in THF (10 mL). The reaction mixture was maintained at −78 °C until TLC analysis indicated complete addition.[13] The reaction mixture was poured into H_2O (50 mL) and extracted with EtOAc (2 × 25 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (generally, eluting with 10−20% EtOAc in hexanes) to provide the alkynyl ether product.

1-(Ethoxyethynyl)cyclopentanol (entry 1): colorless oil; IR (film) 3383 (br), 2965, 2263 cm^{-1}; ^{1}H NMR δ 1.36 (t, 3 H, J = 7.2 Hz), 1.66−1.92 (m, 9 H), 4.08 (q, 2 H, J = 7.2 Hz). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.04; H, 9.23.

1-(Ethoxyethynyl)cyclohexanol (entry 2): colorless oil; IR (film) 3374 (br), 2933, 2259 cm^{-1}; ^{1}H NMR δ 1.38 (t, 3 H, J = 7.2 Hz), 1.50−1.86 (m, 11 H), 4.06 (q, 2 H, J = 7.2 Hz). Anal. Calcd for $C_{10}H_{16}O_2$ C, 71.39; H, 9.59. Found: C, 71.45; H, 9.64.

4-Ethoxy-2-phenylbut-3-yn-2-ol (entry 3): colorless oil; IR (film) 3386 (br), 2983, 2263 cm^{-1}; ^{1}H NMR δ 1.37 (t, 3 H, J = 7.2 Hz), 1.72 (s, 3 H), 2.19 (s, 1 H), 4.12 (q, 2 H, J = 7.2 Hz), 7.23−7.35 (m, 3 H), 7.62−7.65 (m, 2 H). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.64; H, 7.48.

1(*S*)-(Ethoxyethynyl)-5(*R*)-(1(*S*)-methoxyethyl)-2(*R*)-methylcyclohexanol (entry 4): colorless oil; IR (film) 3505 (br), 2932, 2261 cm^{-1}; ^{1}H NMR δ 1.05 (d, 3 H, J = 5.3 Hz), 1.07 (d, 3 H, J = 5.6 Hz), 1.36 (t, 3 H, J = 7.2 Hz), 1.42−2.18 (m, 9 H), 3.07 (m, 1 H), 3.29 (s, 3 H), 4.07 (q, 2 H, J = 7.2 Hz). Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 70.05; H, 10.12.

1(*S*)-(Ethoxyethynyl)-5(*R*)-(1(*S*)-methoxybut-2-enyl)-2(*R*)-methylcyclohexanol (entry 5): colorless oil; IR (film) 3504 (br), 2934, 2260 cm^{-1}; ^{1}H NMR δ 1.03 (d, 3 H, J = 7.5 Hz), 1.21−1.33 (m, 3 H), 1.36 (t, 3 H, J = 7.2 Hz), 1.41−1.62 (m, 3 H), 1.66 (d, 3 H, J = 6.9 Hz), 1.72−2.21 (m, 3 H), 3.23 (s, 3 H), 3.67−3.74 (m, 1 H), 4.06 (q, 2 H, J = 7.2 Hz), 5.25 (t, 1 H, J = 9.3 Hz), 5.75 (m, 1 H). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.22; H, 9.94.

1-Ethoxy-3,7-dimethyloct-6-en-1-yn-3-ol (entry 6): colorless oil; IR (film) 3386 (br), 2976, 2261, 1091 cm^{-1}; ^{1}H NMR δ 1.37 (t, 3 H, J = 7.2 Hz), 1.46 (s, 3 H), 1.65 (s, 3 H), 1.69 (s, 3 H), 4.08 (q, 2 H, J = 7.2 Hz), 1.92 (s, 1 H), 2.10−2.37 (m, 4 H), 5.17 (t, 1 H, J = 7.2 Hz). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.12; H, 10.36.

(Ethoxyethynyl)benzene (entry 7): colorless oil; IR (film) 2978, 2258, 1321, 1063 cm^{-1}; ^{1}H NMR δ 1.46 (t, 3 H, J = 7.2 Hz), 4.21 (q, 2 H, J = 7.2 Hz), 7.19−7.37 (m, 5 H). Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 82.12; H, 6.91.

(4-Ethoxybut-3-enyl)benzene (entry 8): colorless oil; IR (film) 2954, 2260 cm^{-1}; ^{1}H NMR δ 1.38 (t, 3 H, J = 7.2 Hz), 2.52 (t, 2 H, J = 7.5 Hz), 2.94 (t, 2 H, J = 7.5 Hz), 4.22 (q, 2 H, J = 7.2 Hz), 7.13−7.25 (m, 5 H). Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.58; H, 8.17.

3-Ethoxy-1-phenylprop-2-yn-1-ol (entry 9). colorless oil; IR (film) 3374, 2263, 1232 cm^{-1}; ^{1}H NMR δ 1.39 (t, 3 H, J = 7.2 Hz), 2.05 (d, 1 H, J = 5.9 Hz), 4.14 (q, 2 H, J = 7.2 Hz), 5.50 (d, 1 H, J = 5.9 Hz), 7.25−7.40 (m, 3 H), 7.52−7.56 (m, 2 H); HRMS ($C_{11}H_{12}O_2$, M^+) calcd 176.0837, found 176.0841.

1-Ethoxypent-1-yn-3-ol (entry 10): colorless oil; IR (film) 3358, 2968, 2263 cm^{-1}; ^{1}H NMR δ 0.98 (t, 3 H, J = 7.2 Hz), 1.37 (t, 3 H, J = 6.9 Hz), 1.58−1.73 (m, 3 H), 4.09 (q, 2 H, J = 7.2

(12) Experimental details for the preparation of the substrates utilized in entries 4 and 5 will be reported elsewhere. Tatlock, J. *Bioorg. Med. Chem. Lett.* Manuscript submitted.

(13) The preparation of the alkyne utilized in entry 8 included 3 equiv of HMPA, added prior to *n*-BuLi. The final reaction mixture was warmed to −30 °C and maintained for 3 hours before quenching.

Hz), 4.34 (q, 1 H, J = 5.9 Hz); HRMS ($C_7H_{12}O_2$, M^+) calcd 128.0837, found 128.0843.

General Oxidation Procedure. The alkynyl ether (**3**) (0.5 g, 3.0 mmol, 1.0 equiv) was dissolved in acetone (50 mL). To this was added a solution of $NaHCO_3$ (0.15 g, 1.8 mmol, 0.6 equiv) and $MgSO_4$ (0.72 g, 6.0 mmol, 2.0 equiv) in water (50 mL). The mixture was stirred vigorously at 23 °C and treated with $KMnO_4$ (1.41 g, 9.0 mmol, 3.0 equiv).[14,15] The reaction mixture was stirred at 23 °C for 2–5 min, then poured into water and extracted with EtOAc (4 ×). The combined organics were washed with water and brine until colorless.[16] The organics were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (eluting with 10% EtOAc in hexanes) to provide keto ester **4**. The keto ester products were generally eluted with 10–25% EtOAc in hexanes.

(1-Hydroxycyclopentyl)oxoacetic acid ethyl ester (entry 1): colorless oil; IR (film) 3513 (br), 2964, 1723 (br) cm^{-1}; ^1H NMR δ 1.34 (t, 3 H, J = 7.2 Hz), 1.66–1.95 (m, 9 H), 4.28 (q, 2 H, J = 7.2 Hz). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.94; H, 7.66.

(1-Hydroxycyclohexyl)oxoacetic acid ethyl ester (enrty 2): colorless oil; IR (film) 3510 (br), 2964, 1725 (br) cm^{-1}; ^1H NMR δ 1.36 (t, 3 H, J = 7.2 Hz), 1.50–2.05 (m, 11 H), 4.24 (q, 2 H, J = 7.2 Hz). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.04; H, 8.08.

3-Hydroxy-2-oxo-3-phenylbutyric acid ethyl ester (entry 3): colorless oil; IR (film) 3515 (br), 2986, 1744, 1692, 1236 cm^{-1}; ^1H NMR δ 1.09 (t, 3 H, J = 7.2 Hz), 1.65 (s, 3 H), 4.22 (q, 2 H, J = 7.2 Hz), 7.41–7.68 (m, 3 H), 8.09 (m, 2 H). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.65; H, 6.46.

[1(*S*)-Hydroxy-5(*R*)-1(*S*)-methoxyethyl)-2(*R*)-methylcyclohexyl]oxoacetic acid ethyl ester (entry 4): colorless oil; IR (film) 3523, 2934, 1738, 1718 cm^{-1}; ^1H NMR δ 0.80 (d, 3 H, J = 6.9 Hz), 1.09 (d, 3 H, J = 6.2 Hz), 1.37 (t, 3 H, J = 7.2 Hz), 1.39–2.09 (m, 9 H), 3.08 (m, 1 H), 3.31 (s, 3 H), 4.35 (q, 2 H, J = 7.2 Hz). Anal. Calcd for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88. Found: C, 61.56; H, 8.94.

[1(*S*)-hydroxy-5(*R*)-1(*S*)-methoxybut-2-enyl)-2(*R*)-methylcyclohexyl]oxoacetic acid ethyl ester (entry 5): colorless oil; IR (film) 3517, 2931, 1738, 1721 cm^{-1}; ^1H NMR δ 0.79 (d, 3 H, J = 6.5 Hz), 0.92–1.20 (m, 3 H), 1.37 (t, 3 H, J = 7.2 Hz), 1.41–1.61 (m, 2 H), 1.65 (d, 3 H, J = 6.9 Hz), 1.71–2.11 (m, 4 H), 3.21 (s, 3 H), 3.65–3.71 (m, 1 H), 4.35 (q, 2 H, J = 7.2 Hz), 5.22 (t, 1 H, J = 9.3 Hz), 5.76 (m, 1 H). Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found: C, 64.23; H, 8.81.

3-Hydroxy-3,7-dimethyl-2-oxooct-6-enoic acid ethyl ester (entry 6): colorless oil; IR (film) 3446, 2981, 1731, 1717 cm^{-1}; ^1H NMR δ 1.39 (t, 3 H, J = 7.2 Hz), 1.65 (s, 3 H), 1.67 (s, 3 H), 1.69 (s, 3 H), 1.97–2.32 (m, 5 H), 4.01 (q, 2 H, J = 7.2 Hz), 5.11 (t, 1 H, J = 7.2 Hz). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 62.85; H, 8.96.

Oxophenylacetic acid ethyl ester (entry 7): colorless oil; IR (film) 1736, 1689, 1201 cm^{-1}; ^1H NMR δ 1.43 (t, 3 H, J = 7.2 Hz), 4.45 (q, 2 H, J = 7.2 Hz), 7.52 (m, 2 H), 7.64 (t, 1 H, J = 7.5 Hz), 8.01 (d, 2 H, J = 7.2 Hz). Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.25; H, 5.68.

2-Oxo-4-phenylbutyric acid ethyl ester (entry 8): colorless oil; IR (film) 1730, 1690 cm^{-1}; ^1H NMR δ 1.35 (t, 3 H, J = 7.2 Hz), 2.76 (t, 2 H, J = 7.5 Hz), 2.94 (t, 2 H, J = 7.5 Hz), 4.46 (q, 2 H, J = 7.2 Hz), 7.15–7.31 (m, 5 H). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.75; H, 6.79.

3-Hydroxy-2-oxo-3-phenylpropionic acid ethyl ester (entry 9): colorless oil; IR (film) 3425, 1744, 1692, 1236 cm^{-1}; ^1H NMR δ 1.09 (t, 3 H, J = 7.2 Hz), 4.22 (q, 2 H, J = 7.2 Hz), 5.27 (s, 1 H), 7.41–7.68 (m, 3 H), 8.07 (d, 2 H, J = 8.4 Hz). Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.27; H, 5.92.

3-Hydroxy-2-oxopentanoic acid ethyl ester (entry 10): colorless oil; IR (film) 3456, 2979, 1732 (br) cm^{-1}; ^1H NMR δ 0.89 (t, 3 H, J =7.2 Hz), 1.31 (t, 3 H, J = 6.9 Hz), 1.42–1.78 (m, 2 H), 4.21 (t, 3 H, J = 7.2 Hz), 4.31 (q, 1 H, J = 5.9 Hz). Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.27; H, 7.58.

2,3-Dioxo-3-phenylpropionic Acid Ethyl Ester (6). Manganese(IV) oxide (0.084 g, 0.96 mmol, 2.0 equiv) was added in one portion to a stirring solution of α-keto-β-hydroxy ester **5** (0.1 g, 0.48 mmol, 1.0 equiv) in a 1:1 mixture of dichloromethane and hexanes (2 mL) at 23 °C and maintained for 1 h. The mixture was applied directly to a column of silica gel and eluted with 10% ethyl acetate in hexanes to provide α,β-diketo ester **6** (0.089 g, 90%) as a white crystaline solid: mp 116–118 °C; IR ($CHCl_3$) 3455, 1745, 1720, 1687cm^{-1}; ^1H NMR δ 1.08 (t, 3 H, J = 7.2 Hz), 4.22 (q, 2 H, J = 7.2 Hz), 5.32 (br s, 2 H), 7.41–7.63 (m, 3 H), 8.12 (d, 2 H, J = 8.4 Hz). Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 58.74; H, 5.47.

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(14) It was not necessary to use powdered $KMnO_4$.
(15) Oxidation of the alkyne utilized in entry 6 was performed at 0 °C for 0.5–1 min.
(16) Generally, three to four wash cycles was sufficient.