Chemistry of 1,2,4-Trioxanes: Base-Mediated Formation of Highly Reactive Electrophiles and Their Entrapment with Amines and Thiols[1]

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Abstract: 6-(1-Arylvinyl)-substituted 1,2,4-trioxanes undergo a highly facile fragmentation under mild basic conditions to furnish 3-aryl-1-hydroxybut-3-en-2-ones, which react very efficiently with various amines and thiols to give Michael adducts. Both the formation of the reactive 3-aryl-1-hydroxybut-3-en-2-ones and their subsequent reaction with amines and thiols can be achieved in one pot.

Key words: 1,2,4-trioxanes, hydroxy enones, Michael additions, thiols, amines

Artemisinin (**1**), a naturally occurring 1,2,4-trioxane from *Artemisia annua*, and its semisynthetic derivatives artemether (**2**), arteether (**3**), and artesunic acid (**4**) (Figure 1) are highly effective against both chloroquine-sensitive and -resistant malaria.[2] The essentiality of a peroxy linkage in the form of the 1,2,4-trioxane ring system as the antimalarial pharmacophore of artemisinin has led to the current interest in the synthesis[3] and bioevaluation[4] of structurally simple 1,2,4-trioxanes.

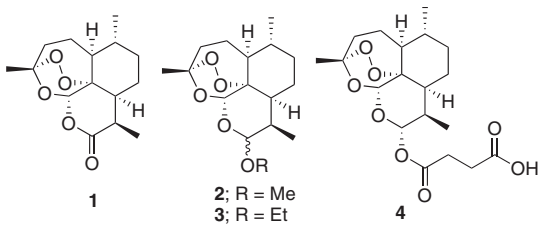
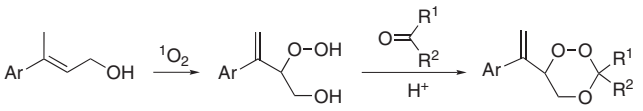


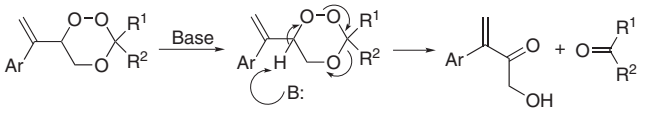
Figure 1 Artemisinin and semisynthetic derivatives thereof

We earlier reported a novel photooxygenation route for the synthesis of 1,2,4-trioxanes. Preparation of β-hydroxy hydroperoxides by photooxygenation of allylic alcohols and the acid-catalyzed reaction of these hydroperoxides with aldehydes or ketones are the key steps of this method (Scheme 1).[5]



Scheme 1 Synthesis of 1,2,4-trioxanes by a photooxygenation route

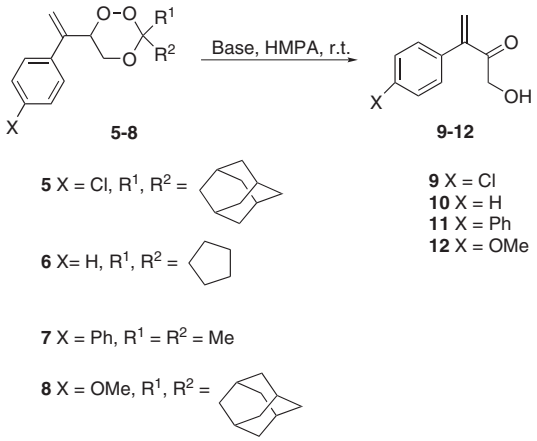
Several 1,2,4-trioxanes prepared by this method have shown promising antimalarial activity.[6] A unique feature of these trioxanes is the presence of a 1-aryl-substituted vinyl group at C-6 of the trioxane, which together with the peroxy group makes H-6 quite acidic. In fact, these trioxanes undergo a facile cleavage under mild basic conditions to regenerate the carbonyl compounds and give 3-aryl-1-hydroxybut-3-en-2-ones (Scheme 2).



Scheme 2 Cleavage of trioxanes to regenerate carbonyl compounds and give 3-aryl-1-hydroxybut-3-en-2-ones

Building on this reaction, we earlier developed 1,2,4-trioxane as a new base-cleavable protecting group for the carbonyl group.[7] Our further investigations in this area have shown that these 3-aryl-1-hydroxybut-3-en-2-ones react very efficiently with various amines and thiols to furnish the corresponding Michael adducts.

Thus the reaction of trioxane **5** with sodium bicarbonate, *n*-butylamine, and diisopropylamine in hexamethylphosphoramide at room temperature furnished 3-aryl-1-hydroxybut-3-en-2-one **9** and adamantan-2-one (**13**) in 34% and 66% yields, respectively. Similarly, trioxanes **6**–**8**, on reaction with *n*-butylamine in hexamethylphosphoramide at room temperature, furnished 3-aryl-1-hydroxybut-3-en-2-ones **10**–**12** in 36–38% yields (Scheme 3, Table 1).[8]



Scheme 3 Synthesis of 3-aryl-1-hydroxybut-3-en-2-ones from trioxanes

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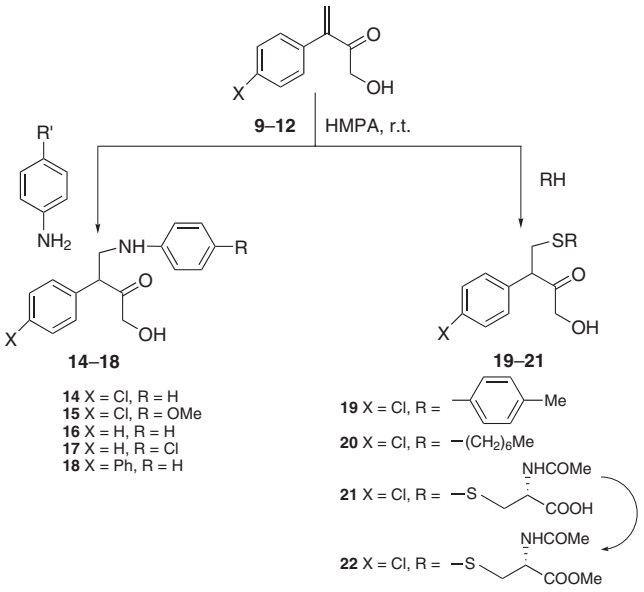
Table 1 Conditions and Yields of Base-Mediated Synthesis of 3-Aryl-1-hydroxybut-3-en-2-ones from 1,2,4-Trioxanes[a]

Entry	Trioxane	Base	Time (h)	Product	Yield (%)
1	**5**	$NaHCO_3$	8 h	**9**	34
2	**5**	*n*-$BuNH_2$	7 h	**9**	40
3	**5**	*i*-Pr_2NH	7 h	**9**	39
4	**6**	*n*-$BuNH_2$	7 h	**10**	38
5	**7**	*n*-$BuNH_2$	7 h	**11**	36
6	**8**	*n*-$BuNH_2$	7 h	**12**	37

[a] Reagents and conditions: trioxane, base, HMPA, r.t.

3-Aryl-1-hydroxybut-3-en-2-ones **9**–**12** undergo facile reactions with aniline, *p*-chloroaniline, and *p*-methoxyaniline in hexamethylphosphoramide at room temperature to give amino derivatives **14**–**18** in 80–86% yields, while similar reactions with *p*-thiocresol, heptane-1-thiol, and *N*-acetyl-L-cysteine furnish thiol derivatives **19**–**21** in 81–84% yields (Scheme 4, Table 2). Treatment of *N*-acetyl-L-cysteine adduct **21** with diazomethane in diethyl ether gave the corresponding methyl ester **22** (Scheme 4), whose purification by column chromatography gave a diastereomeric mixture (1:1, by ^1H NMR), which was fully characterized by ^1H and ^{13}C NMR spectroscopy.



Scheme 4 Synthesis of 4-sulfanyl- and 4-amino-substituted 3-aryl-1-hydroxybutan-2-ones from 3-aryl-1-hydroxybut-3-en-2-ones

Table 2 Conditions and Yields of Conjugate Additions of Amines and Thiols to 3-Aryl-1-hydroxybut-3-en-2-ones[a]

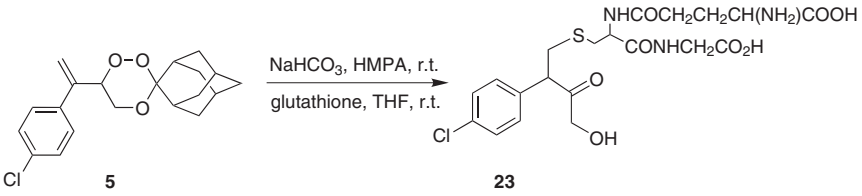
Entry	Keto alcohol	Nucleophile (equiv)	Time (h)	Product	Yield (%)
1	**9**	$PhNH_2$ (1.5)	4 h	**14**	81
2	**9**	$PMPNH_2$ (1.5)	3 h	**15**	84
3	**10**	$PhNH_2$ (1.5)	4 h	**16**	83
4	**10**	*p*-$ClC_6H_4NH_2$ (1.5)	4 h	**17**	80
5	**11**	$PhNH_2$ (1.5)	4 h	**18**	86
6	**9**	TolSH (1.5)	2 h	**19**	84
7	**9**	$Me(CH_2)_6SH$ (1.5)	2.5 h	**20**	82
8	**9**	*N*-acetyl-L-cysteine (1.5)	1 h	**21**	81

[a] Reagents and conditions: keto alcohol, nucleophile, HMPA, r.t.

When keto alcohol **5** was treated with glutathione (reduced) in tetrahydrofuran, the Michael addition product 1-hydroxy-4-sulfanylbutan-2-one **23** formed as a diastereomeric mixture (Scheme 5). The two isomers were separated by high-performance liquid chromatography and characterized by high-resolution electron-impact mass spectrometry.

To achieve the formation of the 3-aryl-1-hydroxybut-3-en-2-ones and their subsequent reactions with amines and thiols in one pot, we examined the reaction of trioxane **5** with aniline and various thiols in the presence of *n*-butylamine in hexamethylphosphoramide at room temperature (Table 3). Thus, reaction of trioxane **5** with aniline in the presence of *n*-butylamine at room temperature for eight hours furnished 4-amino-1-hydroxybutan-2-one **14** in 42% yield (Table 3, entry 1). Similar reactions of trioxane **5** with *p*-thiocresol (Table 3, entry 2), 1-heptanethiol (entry 3), and *N*-acetyl-L-cysteine (entry 4) furnished 1-hydroxy-4-sulfanylbutan-2-ones **19**, **20**, and **21**, respectively, in 60–63% yields. In these experiments, the 3-aryl-1-hydroxybut-3-en-2-one **9** generated by reaction of trioxane **5** with *n*-butylamine reacts in situ with aniline and the various thiols to give Michael adducts **14**, **19**, **20**, and **21** (Table 3).[9] Compound **21** was obtained as an inseparable mixture of diastereomers (ratio 1:1) and was converted into its methyl ester **22** by reaction with diazomethane.

In conclusion, we have investigated the reactions of several 1,2,4-trioxanes with various amines and thiols under mild basic conditions. These trioxanes undergo a very facile base-catalyzed fragmentation to generate highly reac-



Scheme 5 Synthesis of a 3-aryl-1-hydroxy-4-sulfanylbutan-2-one amino acid derivative from a trioxane and glutathione

tive 3-aryl-1-hydroxybut-3-en-2-ones,[10] which react very efficiently with various nucleophiles. The chemistry discussed here allows easy access to highly functionalized molecules such as 4-sulfanyl- and 4-amino-substituted 3-aryl-1-hydroxybutan-2-ones **14**–**21** from easily available 1,2,4-trioxanes.

Table 3 Tandem Fragmentation and Conjugate Addition of Trioxane **5** to Amines and Thiols[a]

Entry	Nucleophile (equiv)	Time (h)	Product	Yield (%)
1	$PhNH_2$ (1.5)	8 h	**14**	42
2	TolSH (1.5)	7 h	**19**	61
3	$Me(CH_2)_6SH$ (2.0)	8 h	**20**	60
4	*N*-acetyl-L-cysteine (1.5)	7 h	**21**	63

[a] Reagents and conditions: trioxane **5**, *n*-$BuNH_2$ (cat.), nucleophile, HMPA, r.t.

All glassware were oven-dried prior to use. Melting points were determined on a COMPLAB melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR RXI spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX-200 (operating at 200 MHz for ^{1}H and at 50 MHz for ^{13}C) or DRX-300 (operating at 300 MHz for ^{1}H and at 75 MHz for ^{13}C) spectrometer, with $CDCl_3$ used as solvent. TMS (0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (77.0 ppm) in ^{13}C NMR spectra. A JEOL SX 102 spectrometer was used for FAB-MS, for which argon/xenon (6 kV, 10 mA) was used as the FAB gas. Glycerol or *m*-nitrobenzyl alcohol was used as matrix. Elemental analyses were carried out on a Vario EL-III CHNS analyzer (Germany). HRMS (EI) was performed on a JEOL MS route 600H instrument. Reactions were monitored by TLC (TLC-grade silica gel, Merck). Detecting agents used for TLC were: I_2 vapour and/or spraying with an aq. soln of vanillin in 10% H_2SO_4 followed by heating at 150 °C. Silica gel (60–120 mesh, Qualigens, India) and freshly distilled solvents were used for column chromatography. All chemicals and reagents were obtained from Aldrich (USA), Lancaster (England), or Spectrochem (India) and were used without further purification.

3-(4-Chlorophenyl)-1-hydroxybut-3-en-2-one (9); Typical Procedures

Method A (Sodium Bicarbonate as Base)

$NaHCO_3$ (0.04 g, 0.57 mmol) was added to a soln of trioxane **5** (0.20 g, 0.58 mmol) in HMPA (4 mL), and the mixture was stirred at r.t. for 8 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with Et_2O (2 × 15 mL). The combined organic layer was washed successively with H_2O (2 × 5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. This gave **9** as a crude product which was purified by column chromatography (silica gel, EtOAc–hexane, 0.5:10).

Oil; yield: 0.038 g (34%).

Method B (*n*-Butylamine as Base)

n-$BuNH_2$ (0.04 g, 0.57 mmol) was added to a soln of trioxane **5** (0.20 g, 0.58 mmol) in HMPA (4 mL). The mixture was stirred at r.t. for 7 h, then diluted with H_2O (10 mL), and extracted with Et_2O (2 × 15 mL). The combined organic layer was washed successively with H_2O (2 × 5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. This gave crude product **9**, which was purified by column chromatography (silica gel, EtOAc–hexane, 0.5:10).

Oil; yield: 0.045 g (40%).

IR (neat): 1491, 1690, 3432 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.30 (t, *J* = 4.8 Hz, 1 H, OH), 4.64 (d, *J* = 4.8 Hz, 2 H), 6.09 and 6.19 (2 × s, 2 H), 7.29 (d, *J* = 8.7 Hz, 2 H), 7.65 (d, *J* = 8.7 Hz, 2 H).

FAB-MS: *m*/*z* = 197, 199 [M + H$^+$].

Anal. Calcd for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61. Found: C, 61.42; H, 4.87.

1-Hydroxy-3-phenylbut-3-en-2-one (10)

Keto alcohol **10** was prepared by the same procedure described for **9** in which *n*-$BuNH_2$ was used as base (Method B).

Oil; yield: 38%.

IR (neat): 1598, 1683, 3416 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.38 (br s, 1 H, OH), 4.66 (s, 2 H), 6.03 and 6.17 (2 × s, 2 H), 7.28–7.38 (m, 5 H).

FAB-MS: *m*/*z* = 163 [M + H$^+$].

Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 73.99; H, 6.14.

3-Biphenyl-4-yl-1-hydroxybut-3-en-2-one (11)

Keto alcohol **11** was prepared by the same procedure described for **9** in which *n*-$BuNH_2$ was used as base (Method B).

Yield: 36%; mp 115–117 °C.

IR (KBr): 1598, 1683, 3416 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.34 (br s, 1 H, OH), 4.64 (d, *J* = 2.9 Hz, 2 H), 6.09 and 6.17 (2 × s, 2 H), 7.32–7.62 (m, 9 H).

FAB-MS: *m*/*z* = 239 [M + H$^+$].

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.41; H, 5.76.

1-Hydroxy-3-(4-methoxyphenyl)but-3-en-2-one (12)

Keto alcohol **12** was prepared by the same procedure described for **9** in which *n*-$BuNH_2$ was used as base (Method B).

Oil; yield: 37%.

IR (neat): 1598, 1721, 3426 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.35 (br s, 1 H, OH), 3.82 (s, 3 H), 4.60 (d, *J* = 3.0 Hz, 2 H), 5.97 and 6.06 (2 × s, 2 H), 6.90 (d, *J* = 8.7 Hz, 2 H), 7.27 (d, *J* = 8.7 Hz, 2 H).

FAB-MS: *m*/*z* = 193 [M + H$^+$].

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.66; H, 6.18.

4-Anilino-3-(4-chlorophenyl)-1-hydroxybutan-2-one (14); Typical Procedures

Method A (from 9)

To a soln of keto alcohol **9** (0.05 g, 0.25 mmol) in HMPA (3 mL) was added aniline (0.03 g, 0.38 mmol). The mixture was stirred at r.t. for 4 h, and then diluted with H_2O (5 mL) and extracted with Et_2O (2 × 10 mL). The combined organic layer was washed successively with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. This gave crude product **14**, which was purified by column chromatography (silica gel, EtOAc–hexane, 0.5:10).

Oil; yield: 0.059 g (81%).

Method B (One-Pot Procedure from 5)

To a soln of trioxane **5** (0.1 g, 0.29 mmol) in HMPA (4 mL) was added *n*-$BuNH_2$ (0.02 g, 0.28 mmol) and aniline (0.03 g, 0.36 mmol). The mixture was stirred at r.t. for 8 h, and then diluted with H_2O (10 mL) and extracted with Et_2O (2 × 15 mL). The combined

organic layer was washed successively with H_2O (2 × 5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. This gave crude product **14**, which was purified by column chromatography (silica gel, EtOAc–hexane, 0.5:10).

Oil; yield: 0.035 g (42%).

IR (neat): 1719, 3398 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.96 (br s, 2 H, NH, OH), 3.44 (dd, *J* = 13.4, 5.6 Hz, 1 H), 3.90 (dd, *J* = 13.4, 8.1 Hz, 1 H), 4.04 (dd, *J* = 8.1, 5.6 Hz, 1 H), 4.17 (s, 2 H), 6.57 (d, *J* = 7.9 Hz, 2 H), 6.74–6.78 (m, 1 H), 7.15–7.37 (m, 6 H).

FAB-MS: *m*/*z* = 290, 292 [M + H^+].

Anal. Calcd for $C_{16}H_{16}ClNO_2$: C, 66.32; H, 5.57; N, 4.83. Found: C, 66.49; H, 5.46; N, 4.64.

3-(4-Chlorophenyl)-1-hydroxy-4-(4-methoxyanilino)butan-2-one (15)

Compound **15** was prepared by Method A used for the preparation of compound **14**.

Oil; yield: 84%.

IR (neat): 1720, 3386 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.95 (br s, 2 H, NH, OH), 3.38 (dd, *J* = 13.4, 6.0 Hz, 1 H), 3.74 (s, 3 H), 3.83 (dd, *J* = 13.4, 8.0 Hz, 1 H), 4.01 (dd, *J* = 8.0, 6.0 Hz, 1 H), 4.15 (s, 2 H), 6.54 (dd, *J* = 6.6, 2.2 Hz, 2 H), 6.77 (dd, *J* = 6.6, 2.2 Hz, 2 H), 7.16 (dd, *J* = 6.6, 1.9 Hz, 2 H), 7.33 (dd, *J* = 6.6, 1.9 Hz, 2 H).

FAB-MS: *m*/*z* = 320, 322 [M + H^+].

Anal. Calcd for $C_{17}H_{18}ClNO_3$: C, 63.85; H, 5.67; N, 4.38. Found: C, 63.49; H, 5.43; N, 4.64.

1-Hydroxy-3-phenyl-4-anilinobutan-2-one (16)

Compound **16** was prepared by Method A used for the preparation of compound **14**.

Oil; yield: 83%.

IR (neat): 1712, 3440 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.98 (br s, 1 H, OH), 3.46 (dd, *J* = 13.1, 5.3 Hz, 1 H), 3.87–4.07 (m, 2 H), 4.15 and 4.16 (2 × s, 2 H), 6.58 (d, *J* = 7.7 Hz, 2 H), 6.73 (t, *J* = 7.2 Hz, 1 H), 7.14–7.40 (m, 7 H).

FAB-MS: *m*/*z* = 256 [M + H^+].

Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.38; H, 6.43; N, 5.42.

4-(4-Chloroanilino)-1-hydroxy-3-phenylbutan-2-one (17)

Compound **17** was prepared by Method A used for the preparation of compound **14**.

Oil; yield: 80%.

IR (neat): 1716, 3445 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.98 (br s, 1 H, OH), 3.43 (dd, *J* = 13.0, 5.3 Hz, 1 H) 3.83–4.06 (m, 2 H), 4.16 (s, 2 H), 6.49 (d, *J* = 8.7 Hz, 2 H), 7.11 (d, *J* = 8.7 Hz, 2 H), 7.19–7.41 (m, 5 H).

FAB-MS: *m*/*z* = 290, 292 [M + H^+].

Anal. Calcd for $C_{16}H_{16}ClNO_2$: C, 66.32; H, 5.57; N, 4.83. Found: C, 66.54; H, 5.68; N, 4.73.

3-Biphenyl-4-yl-1-hydroxy-4-anilinobutan-2-one (18)

Compound **18** was prepared by Method A used for the preparation of compound **14**.

Yield: 86%; mp 106–108 °C.

IR (KBr): 1720, 3458 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.96 (br s, 1 H, OH), 3.52 (dd, *J* = 13.5, 5.7 Hz, 1 H), 3.97 (dd, *J* = 13.5, 8.1 Hz, 1 H), 4.11 (dd, *J* = 8.1, 5.7 Hz, 1 H), 4.22 (d, *J* = 7.8 Hz, 2 H), 6.62 (d, *J* = 7.6 Hz, 2 H), 6.76 (t, *J* = 7.6 Hz, 1 H), 7.18–7.62 (m, 11 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 45.7 (t), 53.5 (d), 67.8 (t), 113.0 (d, 2 C), 118.0 (d), 127.0 (d, 2 C), 127.5 (d), 128.0 (d, 2 C), 128.5 (d, 2 C), 128.8 (d, 2 C), 129.4 (d, 2 C), 134.4 (s), 140.1 (s), 141.1 (s), 147.0 (s), 209.2 (s).

FAB-MS: *m*/*z* = 332 [M + H^+].

HRMS (EI): *m*/*z* calcd for $C_{22}H_{21}NO_2$: 331.1572; found: 331.1569.

3-(4-Chlorophenyl)-1-hydroxy-4-(4-tolylsulfanyl)butan-2-one (19); Typical Procedures

Method A (from 9)

To a soln of keto alcohol **9** (0.09 g, 0.46 mmol) in HMPA (5 mL) was added *p*-thiocresol (0.079 g, 0.56 mmol). The mixture was stirred at r.t. for 2 h, then diluted with H_2O (5 mL), and extracted with Et_2O (2 × 10 mL). The combined organic layer was washed successively with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. This gave crude product **19**, which was purified by column chromatography (silica gel, EtOAc–hexane, 0.5:10).

Oil; yield: 0.12 g (84%).

Method B (One-Pot Procedure from 5)

To a soln of trioxane **5** (0.1 g, 0.29 mmol) in HMPA (5 mL) was added *n*-$BuNH_2$ (0.02 g, 0.28 mmol) and *p*-thiocresol (0.05 g, 0.43 mmol). The mixture was stirred at r.t. for 7 h, diluted with H_2O (10 mL), and extracted with Et_2O (2 × 15 mL). The combined organic layer was washed successively with H_2O (2 × 5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. This gave crude product **19**, which was purified by column chromatography (silica gel, EtOAc–hexane, 0.5:10).

Oil; yield: 0.056 g (61%).

IR (neat): 1720, 2363, 3508 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.34 (s, 3 H), 2.90 (t, *J* = 4.9 Hz, 1 H, OH), 3.15 (dd, *J* = 13.5, 6.3 Hz, 1 H), 3.58 (dd, *J* = 13.5, 8.7 Hz, 1 H), 3.81 (dd, *J* = 8.7, 6.3 Hz, 1 H), 4.18 (d, *J* = 4.8 Hz, 2 H), 7.09–7.12 (m, 4 H), 7.24–7.31 (m, 4 H).

FAB-MS: *m*/*z* = 321, 323 [M + H^+].

Anal. Calcd for $C_{17}H_{17}ClO_2S$: C, 63.64; H, 5.34; S, 9.99. Found: C, 63.84; H, 4.98; S, 9.79.

3-(4-Chlorophenyl)-4-(heptylsulfanyl)-1-hydroxybutan-2-one (20)

Compound **20** could be prepared as an oil by Method A (yield: 82%) or Method B (yield: 60%) described for the preparation of compound **19**.

IR (neat): 1720, 2363, 3506 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.4 Hz, 3 H), 1.26–1.61 (m, 10 H), 2.46 (t, *J* = 7.4 Hz, 2 H), 2.81 (dd, *J* = 13.0, 6.3 Hz, 1 H), 2.94 (t, *J* = 4.8 Hz, 1 H, OH), 3.22 (dd, *J* = 13.0, 8.6 Hz, 1 H), 3.85 (dd, *J* = 8.6, 6.3 Hz, 1 H), 4.26 (d, *J* = 4.8 Hz, 2 H), 7.18 (d, *J* = 8.4 Hz, 2 H), 7.32 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.46 (q), 22.99 (t), 29.13 (t), 29.24 (t), 29.96 (t), 32.09 (t), 33.56 (t), 34.64 (t), 55.02 (d), 68.55 (t), 129.75 (d, 4 C), 134.59 (s), 135.62 (s), 208.71 (s).

FAB-MS: *m*/*z* = 329, 331 [M + H^+].

Anal. Calcd for $C_{17}H_{25}ClO_2S$: C, 62.08; H, 7.66; S, 9.75. Found: C, 62.42; H, 7.32; S, 9.51.

Methyl *N*-Acetyl-*S*-[2-(4-chlorophenyl)-4-hydroxy-3-oxobutyl]cysteinate (22)

Compound **21** could be prepared by Method A (yield: 81%) or Method B (yield: 63%) described for the preparation of compound **19**. Ester **22** was prepared from compound **21** by reaction with CH_2N_2 in Et_2O.

Oil; yield: quantitative.

IR (neat): 1740, 2927, 3309 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.01 and 2.03 (2 × s, 3 H), 2.77–3.05 (m, 3 H), 3.24 (dd, *J* = 12.9, 9.0 Hz, 1 H), 3.74 and 3.75 (2 × s, 3 H), 3.92 (dd, *J* = 15.6, 9.0 Hz, 1 H), 4.23 (d, *J* = 3.9 Hz, 2 H), 4.76–4.83 (m, 1 H), 6.40 and 6.48 (2 × d, *J* = 7.2 Hz, 1 H, NH), 7.14–7.18 (m, 2 H), 7.32 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.9 (q), 34.4 (t), 34.7 and 34.9 (t), 51.8 and 52.1 (d), 52.5 and 52.7 (q), 53.9 and 54.0 (d), 68.0 (t), 129.30 (d, 4 C), 134.1 (s), 134.8 (s), 170.1 (s), 171.1 (s), 208.2 and 208.3 (s).

FAB-MS: *m*/*z* = 375, 377 [M + H^+].

HRMS (EI): *m*/*z* calcd for $C_{16}H_{20}ClNO_5S$: 374.0829; found: 374.0830.

2-Amino-4-{1-[(carboxymethyl)carbamoyl]-2-[2-(4-chlorophenyl)-4-hydroxy-3-oxobutylsulfanyl]ethylcarbamoyl}butyric Acid (23)

To a soln of trioxane **5** (0.5 g, 1.44 mmol) in HMPA (7 mL) was added $NaHCO_3$ (0.12 g, 1.44 mmol). The mixture was allowed to stir at r.t. for 8 h, then diluted with H_2O (15 mL) and extracted with Et_2O (2 × 25 mL). The combined organic layer was washed successively with H_2O (2 × 7 mL) and brine (7 mL), dried (Na_2SO_4), and concentrated. This furnished **9**, which was dissolved in THF (10 mL). Glutathione (reduced, 0.15 g, 0.51 mmol) was added, and the reaction mixture was stirred at r.t. overnight. THF was evaporated, and the residue was dissolved in H_2O (10 mL) and washed with Et_2O (2 × 5 mL). The aqueous layer was concentrated; this provided **23** as a mixture of diastereomers; yield: 0.24 g (97% based on glutathione). A part of the product was separated by HPLC (RP-18, MeOH–H_2O, 80:20) to give two pure isomers, both of which gave correct ES-MS spectra.

ES-MS (ES+): *m*/*z* = 504, 506.

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(8) The stability of 3-aryl-1-hydroxybut-3-en-2-ones **9**–**12** is low, and this could be one of the reasons why they are obtained in such poor yields.

(9) We suggest that this facile formation of 3-aryl-1-hydroxybut-3-en-2-one systems from the trioxanes on reaction with weak bases such as *n*-butylamine and the equal facile entrapment of these reactive species with amines and thiols may have relevance to the mechanism of the antimalarial action of these trioxanes. *n*-Butylamine is similar to the lysine side chain of lysine-containing proteins and an appropriate protein can generate the reactive species which could alkylate thiol residues of the same or a nearby protein, vital for the survival of the malarial parasite.

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