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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 2757–2759

Synthesis of β-peroxy-lactones using 30% H_2O_2 ☆

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Received 13 October 2004; revised 15 January 2005; accepted 25 February 2005

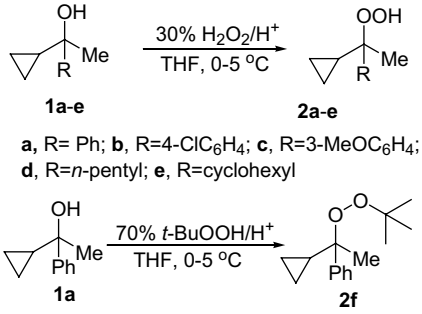
Abstract—Cyclopropyl carbinols **1a–e** react with H_2O_2 in the presence of concd H_2SO_4 at 0–5 °C to furnish the corresponding hydroperoxides **2a–e** in 45–82% yields. This efficient trapping of cyclopropylmethyl cations by the hydroperoxy group has been exploited to prepare compounds **14–23**, a new series of cyclopropyl substituted β-peroxy-lactones.

The cyclopropylmethyl cation and its rearrangement have been extensively studied in the context of cyclopropane chemistry. Cyclopropylmethyl substrates solvolyze with abnormally high rates forming the cyclopropylmethyl cation as a key intermediate, that either rearranges to the corresponding cyclobutyl cation or a homoallylic cation. Thus the products of solvolysis often include compounds not only derived from unrearranged cyclopropylmethyl cations but also from cyclobutyl and homoallylic cations.[1] On the basis of solvolysis experiments the order of stability of these cations follows the order:[2] cyclopropylmethyl cation > cyclobutyl cation ≫ homoallylic cation.

The greater stability of the cyclopropylmethyl cation is due to the presence of the cyclopropyl group. The bonds in cyclopropane cannot be pure σ bonds and have considerable sp^2 character and therefore provide a π cloud, which stabilizes the positive charge on the adjacent carbon atom.[3] The rearrangement of the cyclopropylmethyl cation to a homoallylic cation has been exploited synthetically to convert cyclopropyl carbinols into homoallylic alcohols, homoallylic acetates and homoallylic halides.[4] In the course of work designed to prepare homoallylic hydroperoxides we discovered that cyclopropyl substituted carbinols react efficiently with 30% H_2O_2 in the presence of concd H_2SO_4 to furnish cyclopropyl substituted hydroperoxides in good yields.

Thus cyclopropyl carbinols **1a–e**, easily accessible from cyclopropyl methyl ketone by reaction with an appropriate Grignard reagent, reacted with 30% H_2O_2 in the presence of concd H_2SO_4 at 0–5 °C to furnish hydroperoxides **2a–e** in 45–82% yields. A similar reaction of **1a** with *t*-BuOOH furnished the corresponding *tert*-butyl peroxide **2f** in 57% yield (Scheme 1).[5,6] Thus, H_2O_2 acts as an efficient trap for the cyclopropylmethyl cation before it rearranges to cyclobutyl or homoallylic cations.

We have extended this observation to the preparation of β-peroxy-lactones. Thus, β-hydroxy esters **4–13** prepared by reaction of cyclopropyl ketones **3** with α-halo esters/zinc were treated with 30% H_2O_2 in the presence of concd H_2SO_4 in THF at 0–5 °C to furnish β-peroxy-lactones **14–23** in 30–80% yields (Scheme 2, Table 1).[7] Peroxy-lactones **15** and **21** were isolated as an inseparable mixture of diastereomers.[8]



Scheme 1.

☆ CDRI communication no. 6666.

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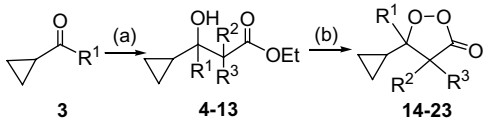
doi:10.1016/j.tetlet.2005.02.158



Scheme 2. Reagents and conditions: (a) α-bromo ester, Zn, benzene, reflux, 2–7 h; (b) 30% H_2O_2, concd H_2SO_4, THF, 0–5 °C, 4–6 h.

Table 1. Yields of β-peroxy-lactones **14**–**23**

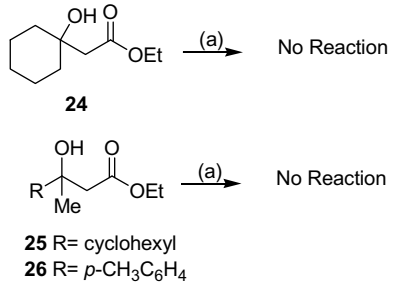
Compound	R^1	R^2	R^3	Yield (%)
14	Me	H	H	80
15	Me	H	Me	38
16	Cyclopropyl	H	H	69
17	Cyclopropyl	H	Me	39
18	Cyclopropyl	H	Et	35
19	Phenyl	H	H	42
20	4-Chlorophenyl	H	H	55
21	Me	H	Et	52
22	Me	Me	Me	33
23	Cyclopropyl	Me	Me	30

β-Peroxy-lactones have earlier been prepared from β-hydroxy acids using 90% H_2O_2.[9] Since the preparation of 90% H_2O_2 is hazardous, the present method is advantageous since commercially available 30% H_2O_2 is used. However, the presence of the cyclopropyl group is essential for this reaction as β-hydroxy esters **24**, **25** and **26** failed to react with 30% H_2O_2 under the same conditions (Scheme 3).

Since there was no report on the antimalarial activity of β-peroxy-lactones we also tested these easily accessible β-peroxy-lactones against *P. falciparum* (NF-54) in vitro[10] (Table 2).

Compounds **14** and **15** which showed activity at 10 μg/mL were also tested in vivo[11] against multi-drug resistant *P. yoelii* in mice by the intramuscular (i.m.) route (Table 3). Both these compounds showed significant suppression of parasitaemia. However, considering the high order of activity shown by artemisinin and its derivatives, the activity shown by these compounds is weak.

While various classes of peroxides such as 1,2,4-trioxanes,[12] 1,2,4,5-tetraoxanes,[13] endoperoxides,[14] H_2O_2,[15] alkyl hydroperoxides,[16] peroxyamines,[17] peroxyketals,[18]



Scheme 3. Reagents and conditions: (a) 30% H_2O_2, concd H_2SO_4, THF, 0–5 °C, 7–9 h.

Table 2. In vitro antimalarial activity of β-peroxy-lactones **14**–**23** against *P. falciparum* (NF-54)

Compound	MIC[a,b] (μg/mL)
14	10.00
15	10.00
16	>50.00
17	50.00
18	50.00
19	50.00
20	>50.00
21	>50.00
22	>50.00
23	>50.00
Artemisinin	0.03
Chloroquine	0.04

[a] MIC = Minimum concentration inhibiting development of ring stage parasites into the schizonts.
[b] 50.00 μg/mL was the highest concentration used in this study.

Table 3. In vivo antimalarial activity of compounds **14** and **15** against *P. yoelii* in Swiss mice by the i.m. route

Compound	Dose (mg/kg/day)	% Suppression on day 4[a]	No. of surviving mice on day 28
14	192	76.60	0/5
15	192	Toxic	0/5
	96	77.52	0/5

[a] Percent suppression = $[(C - T)/C] \times 100$; where C = parasitaemia in the control group, and T = parasitaemia in the treated group.

etc. have been tested for antimalarial activity, to our knowledge this is the first report on antimalarial activity of β-peroxy-lactones.

In conclusion, we have discovered that hydrogen peroxide is an efficient trap for cyclopropylmethyl cations and have exploited this observation to develop a convenient route for the preparation of β-cyclopropyl substituted β-peroxy-lactones using 30% H_2O_2. Work related to trapping of cyclopropylmethyl cations by other soft nucleophiles such as thiols is currently in progress and will be reported in our subsequent publications.

Acknowledgements

N.C.S. is grateful to the Council of Scientific and Industrial Research (CSIR), New Delhi for the award of a Senior Research Fellowship. Technical help from Mr. Akhilesh Kumar Srivastava is gratefully acknowledged.

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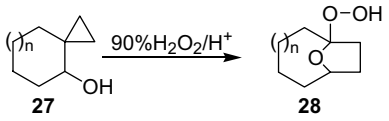
5. In sharp contrast to the reaction reported here, spirocyclopropylcarbinols **27** have been reported to react with 90% H_2O_2 under acid catalysis to give exclusively bicyclic hemiacetal peroxides **28**. [Lillie, T. S.; Ronald, R. C. *J. Org. Chem*. **1985**, *50*, 5084–5088.]



For other related studies see: (a) Ronald, R. C.; Lillie, T. S. *J. Am. Chem. Soc.* **1983**, *105*, 5709–5710; (b) Ronald, R. C.; Lillie, T. S. *Tetrahedron Lett.* **1986**, *27*, 5787–5790; (c) Ronald, R. C.; Ruder, S. M.; Lillie, T. S. *Tetrahedron Lett.* **1987**, *28*, 131–134.

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7. Typical procedure for the synthesis of β-peroxy-lactones: To an ice-cooled (0–5 °C) solution of **4** (0.5 g, 2.90 mmol) in THF (15 mL) was added 30% H_2O_2 (2 mL) followed by dropwise addition of concd H_2SO_4 (2 mL) with constant stirring and then at 0–5 °C for 5 h. The reaction mixture was diluted with cold water (50 mL) and the aq layer extracted with ether (3 × 50 mL). The combined organic layers were washed with saturated aq $NaHCO_3$ solution (50 mL) and water (2 × 25 mL). The combined organic layers were dried over anhyd Na_2SO_4 and the solvent was evaporated under vacuum to give the crude product, which on column chromatography over silica gel using benzene–hexane (1:1) as eluant furnished **14** (0.33 g, 80%).
8. Selected spectral data: Compound **2a**: oil; IR (neat, cm^{-1}): 3399; ^1H NMR (200 MHz, $CDCl_3$) δ 0.35–0.40 (m, 2H), 0.50–0.58 (m, 2H), 1.28–1.41 (m, 1H), 1.45 (s, 3H), 7.24–7.51 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 1.60, 2.79, 19.09, 21.99, 87.19, 126.55, 127.82, 128.75, 143.87; FABMS (*m/z*) 179 $(M+H)^+$. Compound **2f**: oil; IR (neat, cm^{-1}): 762, 878, 1365, 1449; ^1H NMR (200 MHz, $CDCl_3$) δ 0.31–0.51 (m, 4H), 1.23 (s, 9H), 1.27–1.35 (m, 1H), 1.45 (s, 3H), 7.21–7.50 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 0.00, 0.88, 18.57, 20.99, 25.34, 77.33, 81.78, 125.00, 125.21, 126.13, 143.63; FABMS (*m/z*) 235 $(M+H)^+$. Peroxy-lactone **14**: oil; IR (neat, cm^{-1}) 1796; ^1H NMR (200 MHz, $CDCl_3$) δ 0.47–0.64 (m, 4H), 1.02–1.20 (m, 1H), 1.43 (s, 3H), 2.85 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 0.00, 0.43, 16.05, 20.91, 41.19, 87.32, 173.89; EIMS (*m/z*) 142 (M^+). Peroxy-lactone **15** (mixture of diastereomers): oil; IR (neat, cm^{-1}) 1791; ^1H NMR (200 MHz, $CDCl_3$) δ 0.49–0.63 (m, 4H), 0.95–1.11 (m, 1H), 1.19 and 1.35 (2 × s, 3H), 1.22 and 1.34 (2 × d, 3H, J = 7.4 Hz each), 3.01 and 3.05 (2 × q, 1H, J = 7.4 Hz each); ^{13}C NMR (50 MHz, $CDCl_3$) δ 0.00, 0.19, 0.35, 0.99, 8.52, 9.03, 12.94, 15.88, 16.21, 20.77, 46.23, 47.14, 89.40, 90.08, 177.07, 177.35; FABMS (*m/z*) 157 $(M+H)^+$. Peroxy-lactone **16**: oil; IR (neat, cm^{-1}) 1798; ^1H NMR (200 MHz, $CDCl_3$) δ 0.55–0.61 (m, 8H), 1.02–1.13 (m, 2H), 2.78 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 0.00, 0.23, 15.32, 39.20, 88.77, 173.95; FABMS (*m/z*) 169 $(M+H)^+$. Peroxy-lactone **21** (mixture of diastereomers): oil; IR (neat, cm^{-1}) 1789; ^1H NMR (200 MHz, $CDCl_3$) δ 0.50–0.65 (m, 4H), 0.87–1.04 (m, 1H), 1.09–1.20 (m, 6H), 1.50–2.04 (m, 2H), 2.79–2.88 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 1.41, 1.66, 2.27, 2.36, 12.14, 12.22, 14.24, 16.72, 17.98, 19.36, 19.59, 22.79, 54.27, 54.58, 90.57, 91.27, 177.94, 178.22; FABMS (*m/z*) 171 $(M+H)^+$.
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10. The compounds **14**–**23** were evaluated against *P. falciparum* (NF-54) using a minor modification of the technique of Rieckmann et al.[19] The asynchronous parasites obtained from cultures of *P. falciparum* were synchronized after 5% sorbitol treatment so as to contain only ring stage parasites.[20] A parasite suspension in medium RPMI 1640 at 1–2% parasitaemia and 3% hematocrit was dispensed into the wells of sterile 96-well plates. Test compounds were serially diluted in duplicate wells to obtain the final test concentrations. The culture plates were incubated in a candle jar at 37 °C for 36–40 h. Thin blood smears from each well prepared at the end of incubation period were microscopically examined and the concentration, which inhibited the maturation of rings into the schizont stage, was recorded as the MIC.
11. The in vivo efficacy of compounds **14** and **15** was evaluated against *Plasmodium yoelii* (MDR) in the Swiss mice model. The colony bred Swiss mice (25 ± 1 g) were inoculated with 1×10^6 parasitized RBC on day zero and treatment was administered to a group of five mice at each dose, from days 0 to 3, in two divided doses daily. The drug dilutions were prepared in groundnut oil, so as to contain the required amount of the drug in 0.1 mL and administered intramuscularly for each dose. Parasitaemia levels were recorded from thin blood smears between days 4–28.[21]
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