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Synthesis of benzene-fused 1,7,8-trioxa-spiro[5.6]dodecanes

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Abstract—Two novel organic peroxides with one or two benzene rings fused to a 1,7,8-trioxaspiro[5.6]dodecan framework were synthesized, which provided the first examples of employing Kobayashi's methodology in the synthesis of seven-membered peroxy rings. CSA was found to be a potent catalyst for introduction of the hydroperoxyl group, making a useful complement to Kobayashi's methodology in constructing spiroperoxides.

Design and synthesis of novel organic peroxides is a rapid-developing area in organic chemistry in recent years, mainly because of the great potential of this type of compounds in malaria chemotherapy.[1] A key issue in the synthesis of organic peroxides is construction of the peroxy bond. Although theoretically an organic peroxy bond could form from two alkoxyl radicals (which has also been actually demonstrated by Porter et al.[2]), the peroxy bonds of essentially all synthetic organic peroxides are derived from some species where two oxygen atoms are already bonded together. Apart from $^1O_2$, which can be obtained either by the classic photosensitization[3] or disproportion[4] of H_2O_2, ozone[5] and H_2O_2[6] are also among the most frequently employed sources of O–O bonds. In 2001, Kobayshi and co-workers[7] reported a very convenient protocol utilizing UHP (H_2O_2–urea complex) as the reagent. The methodology, however, was only demonstrated on some six-membered molecules up to now. In this letter, we wish to describe the synthesis of two seven-membered peroxides with one or two benzene rings fused to a novel peroxy spirododecane framework.

The synthesis of the first molecule is depicted in Scheme 1. The epoxide **1** reacted with the lithium species **2** (generated in situ from the bromide[8] by reaction with *n*-BuLi using the procedure[9] of Parhem) at −78 °C in the presence of $F_3B{\cdot}OEt_2$ to give **3**. The MOM protecting group was removed with conc. HCl in MeOH. The resulting **4** was oxidized to yield an intermediate aldehyde-ketone, which was treated with $Ph_3P{=}CHCO_2Et$ to afford the α,β-unsaturated ester **5** predominantly as *E*-isomer ($J = 15.7$ Hz for the $-CH{=}CHCO_2Et$).

Removal of the allyl protecting group was attempted under several sets of conditions, including $PdCl_2$/MeOH,[10a] $PdCl_2$/CuCl/DMF–H_2O/air,[10b] Pd–C/MeOH,[10c] and $Pd(PPh_3)_4$/*p*-TsOH/CH_2Cl_2.[10d] In all cases, we obtained a mixture of many components, from which we managed to isolate and identify three of them, that is, compounds **6**, **7**, and **8**. Then, we found that all these compounds could be transformed eventually into the desired hydroperoxide **9** ($J = 15.7$ Hz for the $-CH{=}CHCO_2Et$) and thus the mixture of the deallylation products was used directly in the next step without the painstaking chromatographic separation.

The subsequent hydroperoxidation was performed using Kobayashi's[7] protocol, but the expensive catalyst $Sc(OTf)_3$ and the solvent MeOH were replaced with *p*-TsOH (monohydrate) and DME (1,2-dimethoxyethane), respectively, as we have done before in the synthesis[11] of some 1,6,7-trioxa-spiro[4.5]decanes. The resulting hydroperoxy species was treated with $HNEt_2$ in F_3CCH_2OH gave the end product[12] **10**.

The second molecule was synthesized using epichlorohydrin as the central fragment (Scheme 2). Concatenation of the building blocks was realized through two epoxy ring-opening reactions by the lithium reagents derived

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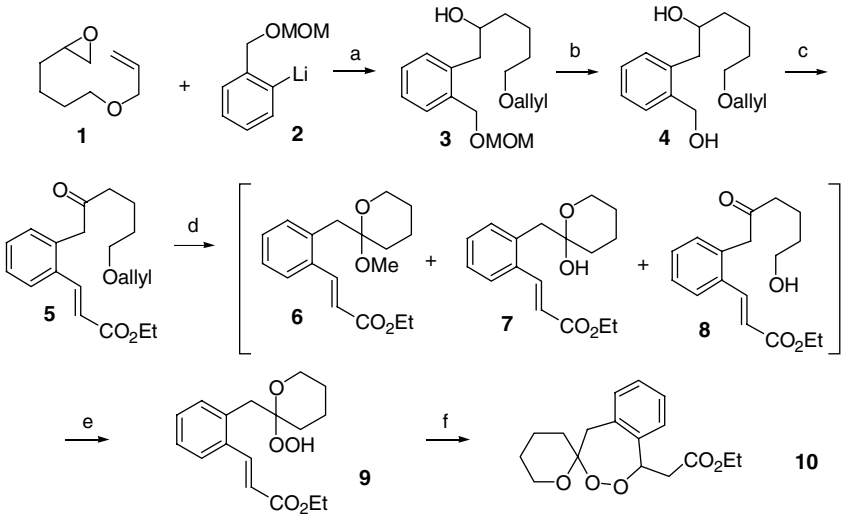
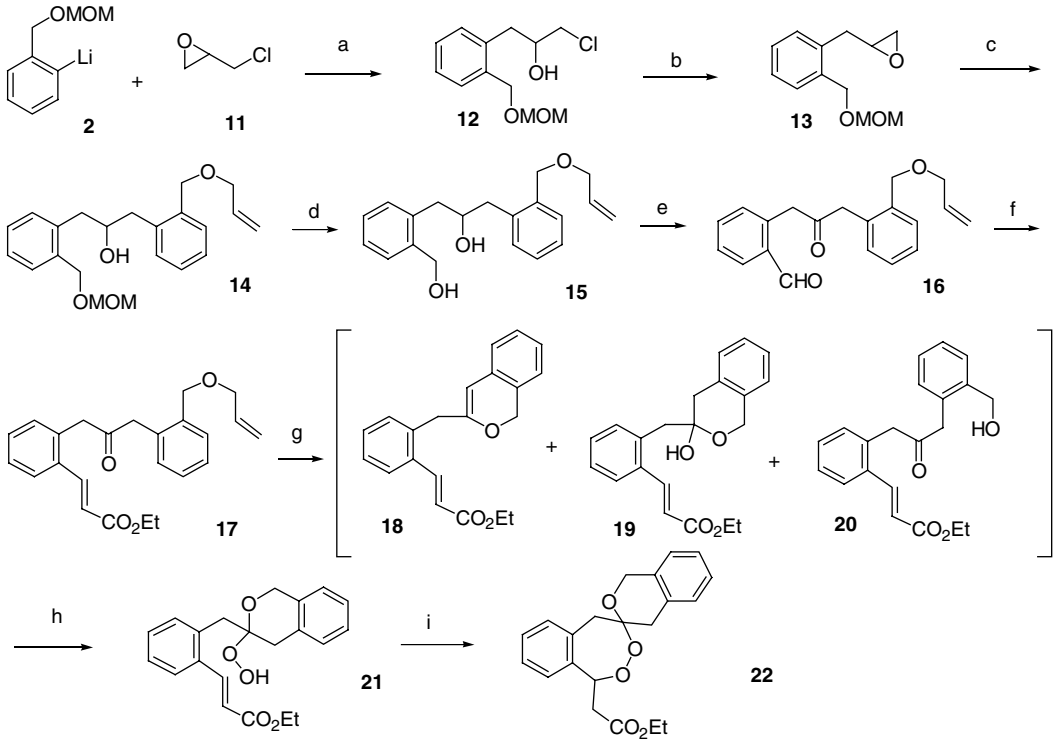


Scheme 1. Reagents and conditions: (a) $F_3B{\cdot}OEt_2/-78$ °C/1 h, 80%; (b) conc. HCl/MeOH/rt/4 d, 93%; (c) (i) $(COCl)_2$/DMSO/Et_3N; (ii) $Ph_3P{=}CHCO_2Et$/rt/12 h, 85% (from **4**); (d) $PdCl_2$/MeOH/rt/24 h, then 60 °C/4 h; (e) UHP (ca. 7 equiv)/*p*-TsOH (0.9 equiv)/DME/rt/22 h, 71% (from **5**); (f) $HNEt_2/CF_3CH_2OH$/rt/19 h, 59%.



Scheme 2. Reagents and conditions: (a) $F_3B{\cdot}OEt_2/-78$ °C; (b) NaH/THF, 67% from **2**; (c) *n*-BuLi/$BrC_6H_4CH_2OCH_2CH{=}CH_2/-78$ °C/1 h, then **13**/$BF_3OEt_2/-78$ °C/1 h, 76%, (d) conc. HCl/MeOH/rt/3 d, 99%; (e) $(COCl)_2$/DMSO/Et_3N; (f) $Ph_3P{=}CHCO_2Et$/rt/12 h, 77% from **15**; (g) $PdCl_2$/CuCl/DMF–H_2O/air/rt/12 h; (h) UHP (ca. 13 equiv)/CSA (ca. 5 equiv)/DME–EtOH (4:1)/rt/7 d, 33% from **17** (together with ca. 67% of recovered **18** and **20**); (i) $HNEt_2/CF_3CH_2OH$/rt/21 h, 24%.

from protected *o*-bromophenylmethanol. Thus, in the presence of $F_3B{\cdot}OEt_2$ epichlorohydrin reacted with **2** to yield **12**. Although this reaction could also give epoxide **13** directly, the yield of **13** was significantly higher if **12** was worked up before treating with NaH. The second epoxy ring-opening was achieved using an allyl-protected lithium species but still under similar conditions. The MOM protecting group was then removed by hydrolysis. The resulting **15** was oxidized and treated directly with $Ph_3P{=}CHCO_2Et$ to afford **17** predominantly as *E*-isomer ($J = 15.9$ Hz for the –CH=CHCO$_2$Et).

The subsequent deallylation was first carried out with $PdCl_2$/MeOH at 60 °C. The product was very compli-

cated and direct treatment with UHP/*p*-TsOH/DME as done in the synthesis of **9** led to no peroxy products at all after one day's stirring, giving the first sign that the situation was different in this system. Using $PdCl_2$/CuCl/DMF–H_2O/air/rt[10b] gave a simpler product mixture, which allowed for separation and identification of three main components (**18**, **19**, and **20**).

Treatment of **19** with 7 equiv of UHP and 0.9 equiv of *p*-TsOH/DME for three days, however, failed to yield any expected product. Addition[13] of 3 equiv of CSA (10-camphorsulfonic acid) facilitated the reaction significantly. After only 12 h at rt, the desired **21** could be clearly spotted on TLC, along with some **18** and **20** (which were much more resistant to the hydroperoxidation). In preparative runs, the mixture of **18**, **19** and **20** was treated with 13 equiv of UHP and 5 equiv of CSA[14] to afford **21** ($J = 15.9$ Hz for the –CH=CHCO$_2$Et) in 33% yield, together with the recovered **18** and **20** (ca. 67% altogether, which could be recycled).

The final ring closure was also realized with $HNEt_2$/F_3CCH_2OH. However, with an additional benzene ring in the substrate, the Michael addition became much more difficult. The highest yield of **22**[15] we could obtain was only 24%, significantly lower[16] than that for **10**. The reason for this unexpected outcome was not clear yet. Perhaps the π–π interactions between the benzene rings somehow made it more difficult for the hydroperoxyl group to approach the C–C double bond.

In summary, to develop potential antimalarial leads we have designed and synthesized two novel peroxides that carry one or two benzene rings fused to a 1,7,8-trioxaspiro[5.6]dodecan framework (which may be useful because of the presence of UV chromophore(s) stable to hydrolysis and the ability to generate benzyl radicals on cleavage by single-electron reducing species). CSA was found to be a potent catalyst for introduction of the hydroperoxyl group, making a useful complement to Kobayashi's methodology in constructing spiroperoxides.

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12. For spectroscopic data of **10** and **22** (used as starting materials there) see: Wu, Y.-K.; Jin, H.-X.; Liu, H.-H.; Zhang, Q. *J. Org. Chem.* **2005**, *70*, 4240–4247.
13. We have also tried some other acid catalysts (e.g., $F_3B{\cdot}OEt_2$, F_3CCO_2H, CH_3SO_3H), but none of them gave satisfactory results.
14. In order to dissolve the large excess of UHP and CSA required for (partially) converting **18** and **20** into **21** some EtOH must be introduced as a co-solvent.
15. Although the diastereomers of monocyclic peroxides could be separated,[7b] most of the spiroperoxides we prepared appeared as one spot on TLC. Besides, the separated[7b] diastereomers showed essentially the same antimalarial potency. Therefore, we did not make exhaustive efforts (e.g., using HPLC) to separate our diastereomers.
16. We have also examined some other bases (LiOH, Et_3N, etc.) or extending the reaction time, but none of them led to better yields.