A FACILE SYNTHESIS OF 4,4-BIS(TRIFLUOROMETHYL)-IMIDAZOLINES VIA A NOVEL OXIDATIVE IMIDAZOLE REARRANGEMENT

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Abstract - Oxidation of imidazole (1) with singlet oxygen or m-chloroperbenzoic acid affords novel 4,4-bis(trifluoromethyl)imidazolines in high yield via a unique oxidative ring opening and subsequent acid catalyzed dehydrocyclization.

Trifluoromethyl-substituted heterocyclic compounds have a wide range of biological activities4,5 yet these compounds remain synthetically challenging. Several 4,4-bis(trifluoromethyl)imidazolines are potent CNS agents6, antiinflammatory agents7 and angiotensin II receptor antagonists8. Recently, they were also identified as potent ACAT inhibitors and cholesterol biosynthesis inhibitors and have potential for treatment of atherosclerosis and hypocholesterolemia9. We report here a unique oxidative imidazole ring opening by singlet oxygen or m-chloroperbenzoic acid (mCPBA) and then a facile acid catalyzed dehydrocyclization process to convert readily available imidazoles to 4,4-bis(trifluoromethyl)imidazolines.

Imidazole (4) was prepared according to literature procedure10 from DL-difluorobenzoin.11 Alkylation of 4 with NaH/MeI gave 5 in 80% yield. Lithiation of 5 with n-BuLi followed by addition of \((\text{CF}_3)_2\text{C}=\text{NTMS}\)12 gave 1 in 69% yield. Treatment of 1 with singlet oxygen, generated from a 400 watt tungsten lamp with methylene blue as a sensitizer, gave rise to 6 within 1 h in CHCl3 and methanol (1:1). Treatment of the solution of 6 obtained above with a 1N HCl ether solution afforded the cyclized product (2), which was obtained in 69% along with about 6% of 3 after flash column chromatography. Intermediate (6) was not very stable. It cyclizes to 2 spontaneously on silica gel on attempts to purify and
characterize it. The singlet oxygen ring opening took as long as 8 h when 150 watt tungsten lamp was used. Alternatively, 1 could be oxidized with mCPBA in refluxing chloroform to give the same intermediate (6), which spontaneously cyclized to 2 in 76% yield (Scheme 1).

**Scheme 1**

![Scheme 1](image)

Singlet oxygen oxidation of imidazole has low selectivity in general. The singlet oxygen can add to the imidazole ring in 1,2 addition fashion to form a dioxetane (A), or 1,4 addition fashion to form an endoperoxide (C), presumably via a common zwitterion (B) (Scheme 2).13 The photooxidation of imidazole has been studied extensively and low chemoselectivity and chemical yield were observed in most cases.14 N-1 substituted imidazole should form dioxetane (A) rather than endoperoxide (C) due to the steric effect of N-substitution. On the other hand, N-1 non-substituted imidazole (R=H) should give endoperoxide (C) or both (A) and (C). Indeed, photooxidation of 7 gave 8 as a major product in 42% yield and no ring opened dibenzoylamidine or cyclized imidazoline product was observed (Scheme 3).

**Scheme 2**

![Scheme 2](image)
We were very surprised that oxidation of imidazole 1 with mCPBA gave the same product as photooxidation's. There have been few reports on oxidative cleavage of heterocycles, such as benzofurans, tetrahydrobenzofurans, and pyridone by mCPBA. This is the first oxidative cleavage of imidazole by mCPBA to our knowledge. It presumably goes through an epoxide intermediate followed by further rearrangement as shown in Scheme 4. The acidic reaction medium cyclizes 6 as soon as it is formed.

The structure of 2 and 3 was determined by analyzing all spectra data (1H-nmr, 13C-nmr, 19F-nmr, ir, uv, and ms). 2 was also confirmed by X-ray (Figure 1). p-F substitution is particularly attractive to us because fluorine can be displaced by a variety of nucleophiles, thus providing a quick access to a series of new analogs for biological testing. 2 has an IC50 20μM as an ACAT inhibitor and an IC50 2.5μM as a HMG-CoA reductase inhibitor.
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REFERENCES AND NOTES

1. Partial results were presented at 203th ACS Meeting, San Francisco, CA. and XII International Symposium on Medicinal Chemistry, Basel, Switzerland.


11. DL-4,4'-Difluorobenzoin is commercially available from Riedel-de Haen.

12. Commercially available from Sigma-Aldrich Rare Chemical Library in small quantity. Large quantities were prepared from hexafluoroacetone imine and trimethylsilylchloride with methylolithium.


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