

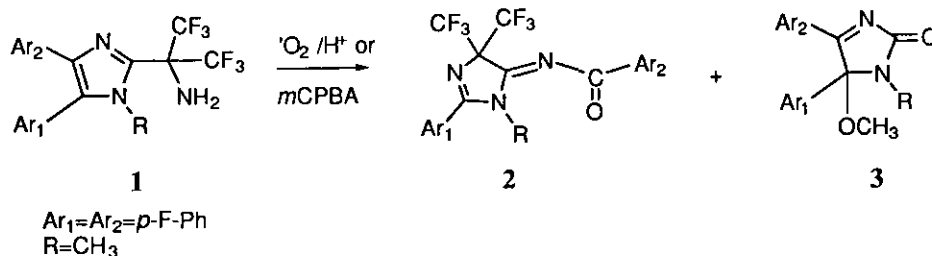
A FACILE SYNTHESIS OF 4,4-BIS(TRIFLUOROMETHYL)-IMIDAZOLINES VIA A NOVEL OXIDATIVE IMIDAZOLE REARRANGEMENT¹

Hui-Yin Li*², Indawati Delucca, Spence Drummond, and George A. Boswell*³

The DuPont Merck Pharmaceutical Company, Chemical Sciences Division
Experimental Station, Wilmington, DE 19880-0353, USA

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.

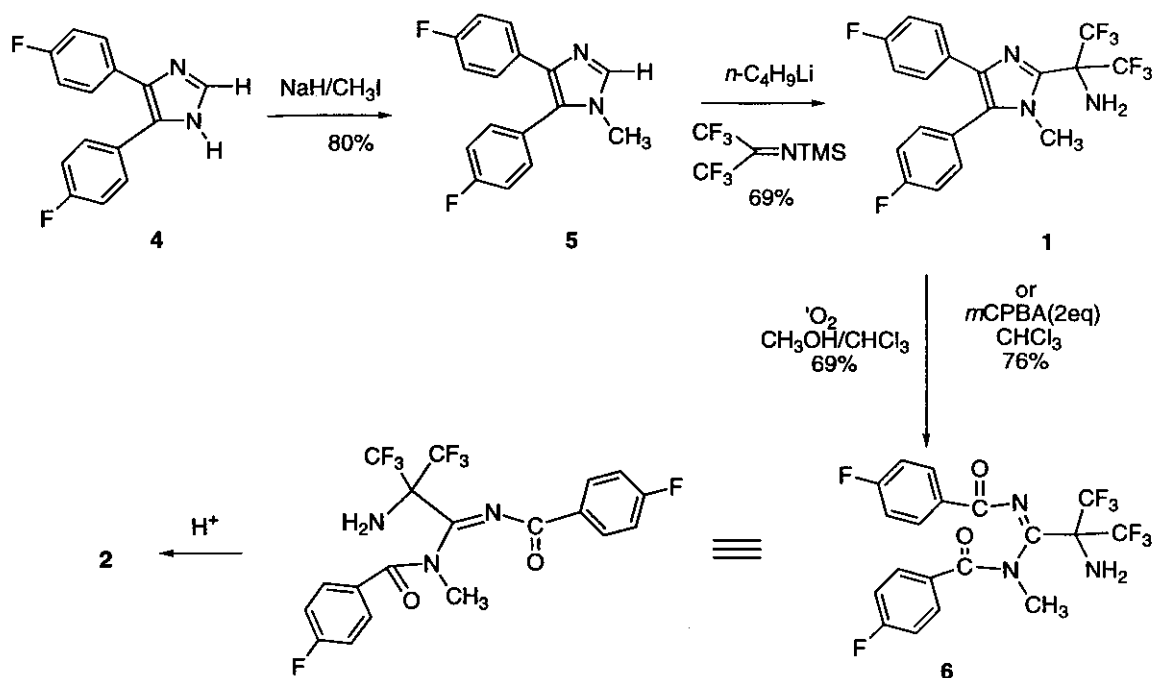
Trifluoromethyl-substituted heterocyclic compounds have a wide range of biological activities,^{4,5} yet these compounds remain synthetically challenging. Several 4,4-bis(trifluoromethyl)imidazolines are potent CNS agents,⁶ antiinflammatory agents⁷ and angiotensin II receptor antagonists.⁸ Recently, they were also identified as potent ACAT inhibitors and cholesterol biosynthesis inhibitors and have potential for treatment of atherosclerosis and hypocholesterolemia.⁹ We report here a unique oxidative imidazole ring opening by singlet oxygen or *m*-chloroperbenzoic acid (*m*CPBA) 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 (CF₃)₂C=NTMS¹² 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

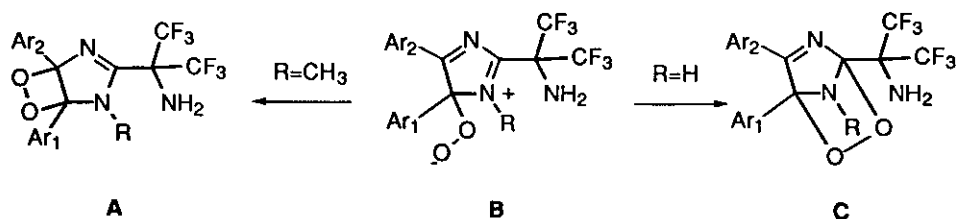
characterize it. The singlet oxygen ring opening took as long as 8 h when 150 watt tungsten lamp was used. Alternatively, **1** could be oxidized with *m*CPBA in refluxing chloroform to give the same intermediate (**6**), which spontaneously cyclized to **2** in 76% yield (Scheme 1).

Scheme 1

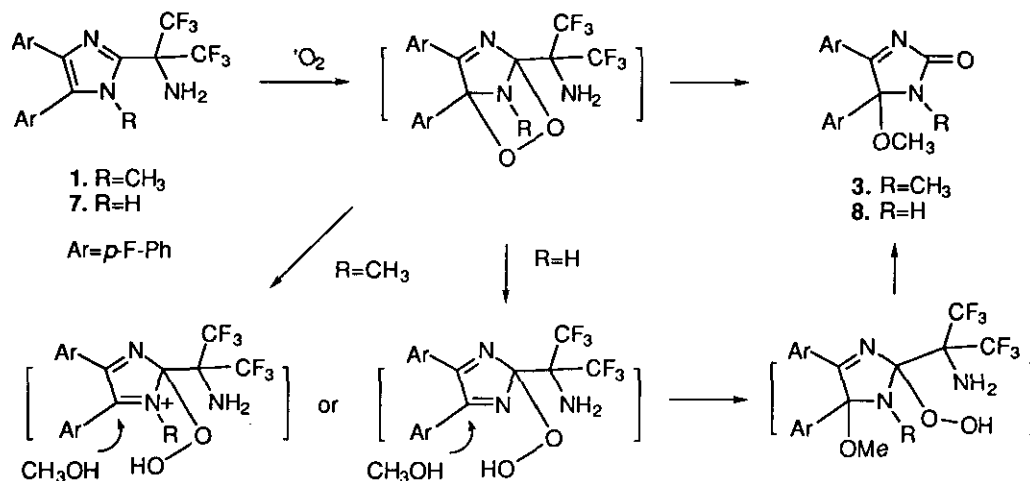


Singlet oxygen oxidation of imidazole has low selectivity in general. The singlet oxygen can add to the imidazole ring in 1,2 addition fashion to form a dioxetane (**A**), or 1,4 addition fashion to form an endoperoxide (**C**), presumably *via* a common zwitterion (**B**) (Scheme 2).¹³ The photooxidation 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

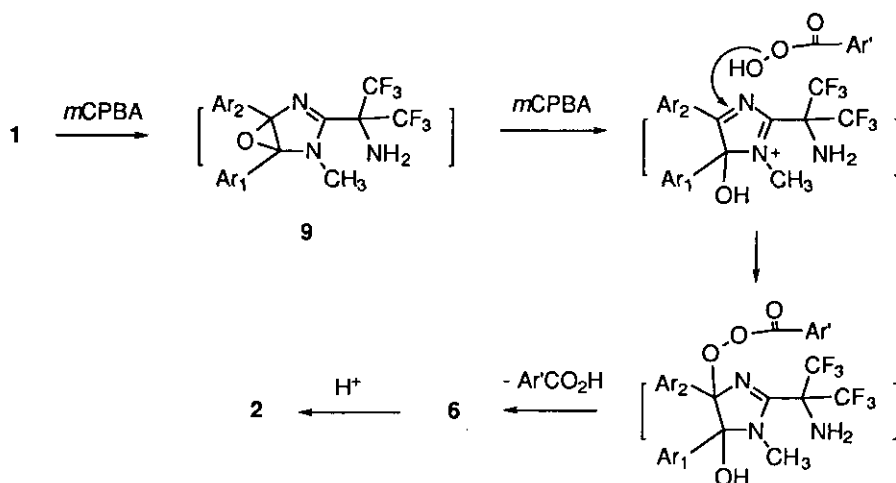


Scheme 3



We were very surprised that oxidation of imidazole **1** with *m*CPBA gave the same product as photooxidation's. There have been few reports on oxidative cleavage of heterocycles, such as benzofurans, tetrahydrobenzofurans^{15,16}, and pyridone¹⁷ by *m*CPBA. This is the first oxidative cleavage of imidazole by *m*CPBA to our knowledge. It presumably goes through an epoxide intermediate **9** followed by further rearrangement as shown in Scheme 4. The acidic reaction medium cyclizes **6** as soon as it is formed.

Scheme 4



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 20 μM as an ACAT inhibitor and an IC₅₀ 2.5 μM as a HMG-CoA reductase inhibitor.

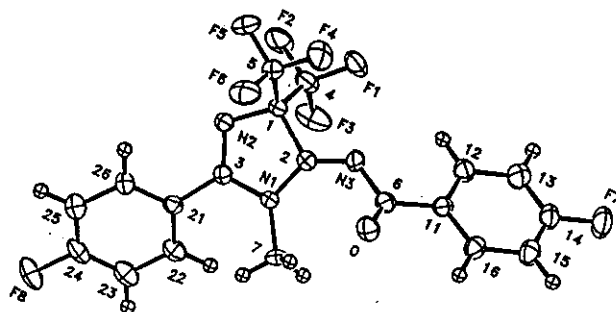


Figure 1

ACKNOWLEDGMENT

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