Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 3443–3448

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

# ANTIINFLAMMATORY 4,5-DIARYLIMIDAZOLES AS SELECTIVE CYCLOOXYGENASE INHIBITORS

Thomas E. Barta,* Michael A. Stealey, Paul W. Collins, and Richard M. Weier

*G.D. Searle and Co., 4901 Searle Parkway, Skokie, IL 60077, U.S.A.*

Received 2 July 1998; accepted 12 October 1998

**Abstract:** The synthesis and activity of a series of 4,5-diarylimidazole analogs are described. One analog had an $IC_{50}$ of 80 nM, was 6750-selective against COX-1, and demonstrated in vivo potency in the mouse air pouch model. 

## Chemistry

It has been recently discovered that the body contains at least two isoforms of cyclooxygenase: COX-1 and COX-2.[1] COX-1 is thought to be involved in normal metabolic housekeeping, for example, cytoprotection of the stomach lining. COX-2 is present in inflamed tissues. Unselective cyclooxygenase inhibitors which disrupt the action of COX-1, such as aspirin and ibuprofen, can lead to stomach ulcers. This effect can be dose limiting in patients with chronic inflammatory conditions, such as osteoarthritis. Clinical studies support the hypothesis that the newer, COX-2 selective inhibitors show an improved safety profile vs. traditional non-steroidal antiinflammatory drugs.[1]

We embarked on a discovery project to identify COX-2 selective 4,5-diarylimidazoles. 4,5-Diarylimidazoles had been proposed as possible antiinflammatory agents previously,[2] and, thus, seemed like a logical starting point for our research. Studies suggested that COX-2 selectivity could be easily conferred by incorporation of a suitably disposed methyl sulfone or sulfonamide pharmacophore.

Our first imidazole synthesis (Scheme 1) adopted a general synthetic approach similar to one described by Lombardino,[2] proceeding from a benzoin condensation.[3] The benzoin condensations were facilitated by converting either of the aldehyde components into *O*-trimethylsilyl cyanohydrins. Oxidation of the resulting benzoins **1** to benzils **2a** using either copper sulfate in pyridine conditions or Rigby's method involving bismuth (III) oxide in acetic acid[4] proved successful, but unsatisfactory due to difficulty in product isolation and generally poor yields. In contrast, the Swern oxidation[5] proved reliable and effective. The benzils thus obtained were condensed with ammonium acetate/triflouroacetaldehyde ethyl hemiacetal. *S*-methyl substituted intermediates **3** were easily oxidized to the crystalline sulfones **4** with hydrogen peroxide in acetic acid. This route addressed early compound needs, but presented a few difficulties. The benzoin condensation step was capricious and difficult to scale, and toxic HCN was produced in the hydrolysis. With these limitations in mind we developed a shorter, more modern sequence, eliminating the condensation step and employing Wittig methodology to form the key carbon–carbon bonds (Scheme 2). Benzylic phosphonium salts **5**, often available off-the-shelf, were deprotonated to make the corresponding ylids and condensed with 4-(mercaptomethyl)benzaldehyde.

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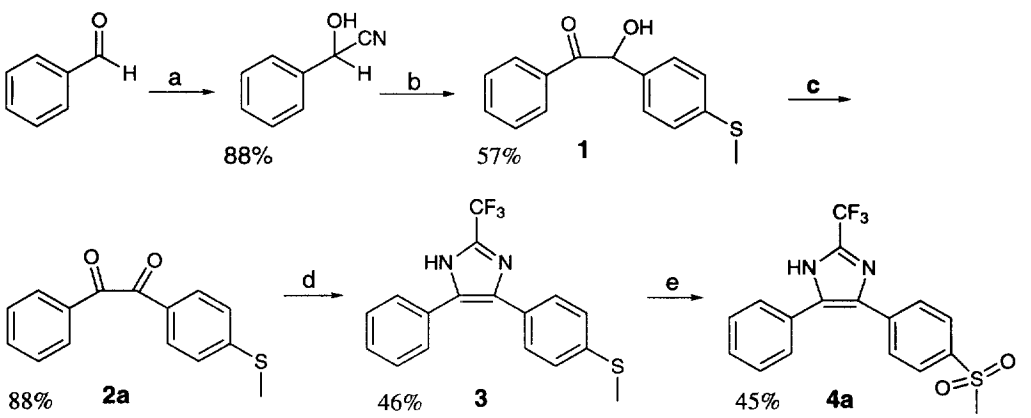
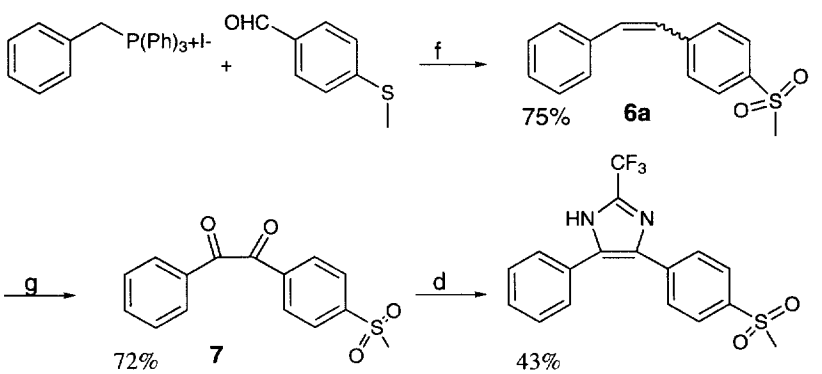
*PII:* S0960-894X(98)00627-1



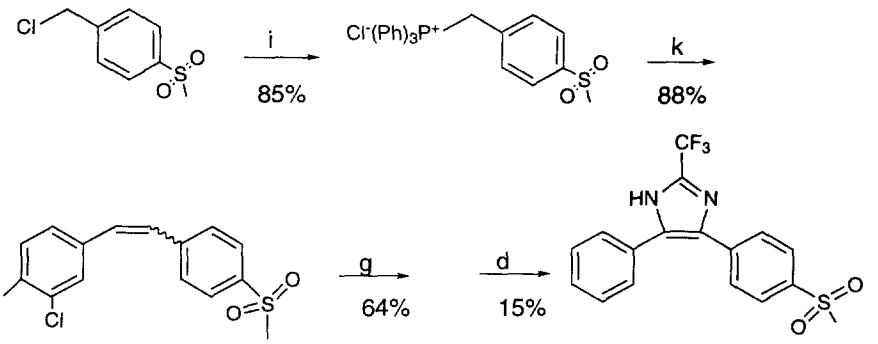

**Scheme 1**. *Reagents and Conditions*: (a) TMS-CN, $ZnI_2$; (b) LiHMDS/THF/-78 °C, then 4-(MeS)-benzaldehyde, then hydrolysis; (c) DMSO/$TFA_2O$/$CH_2Cl_2$/-55 °C; (d) $NH_4OAc$/$CF_3CH(OEt)(OH)$/AcOH/reflux; (e) $H_2O_2$/AcOH/100 °C.

The resulting stilbenes **6**, which were *cis–trans* mixtures, were chemoselectively oxidized to sulfones[6] using Oxone™. It was necessary at this point to expediently transform the stilbenes into benzils **7a**. This was cleanly and easily accomplished using $KMnO_4$ in acetic anhydride.[7] These conditions converted both double bond isomers, and we did not observe C–C bond cleavage, a known complication of some metal mediated oxidations of α heteroatom substituted carbonyl compounds. The benzils obtained could be carried forward as in Scheme 1.




**Scheme 2**. *Reagents and Conditions*: (f) LiOEt/EtOH/ambient, then Oxone™/MeOH (aq) /0 °C to ambient; (g) $KMnO_4$/$Ac_2O$/0 °C; (d) $NH_4OAc$/$CF_3CH(OEt)(OH)$/AcOH/reflux.

In Scheme 3, 4-(methanesulfonyl)-benzyl chloride[8] was used to further streamline the sequence. In this case, the ylid was somewhat less reactive due the electron-withdrawing sulfone, so heating was required to effect stilbene formation. The stilbene was oxidized to the benzil and carried on as in the previous schemes.




**Scheme 3.** *Reagents and Conditions*: (i) triphenylphosphine/toluene/reflux; (k) aldehyde/LiOEt/EtOH/reflux; (g) $KMnO_4/Ac_2O/0$ °C; (d) $NH_4OAc$ /$CF_3CH(OEt)(OH)$/AcOH/reflux.

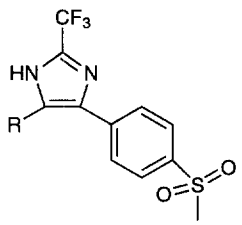
## Discussion

Table 1 shows the biological data for in vitro COX-2 and COX-1 enzyme inhibition, and the results of in vivo testing in the mouse air-pouch assay.[9] It is clear that some very potent analogs that exhibit significant selectivity were identified, notably the analogs with mid-sized substituents (e.g., chloro) in the 3-position of the aryl group. Analog **4f**, for example, shows 6750-fold selectivity and good activity in the air pouch (98% inhibition @ 2 MPK). These results differ somewhat from the known art exemplified by compounds such as Celecoxib, where 4-substitution was preferred,[10] but as with that series, subtle changes on the aryl rings, such as changing from H- to F- may have significant impact on the in vitro activity.

Experiences with Celecoxib and other diarylheterocycles showed that, although sulfonamides typically have poorer in vitro COX-2/COX-1 selectivity than the corresponding sulfones; sulfonamides sometimes have superior in vivo potency.[10] We wished to assess whether sulfonamides offered any advantages in the present case. Several analogs were transformed from sulfones into sulfonamides. The imidazole N-H was protected using SEM-Cl/NaH/THF. Using Huang's[11] methodology, the methyl of the methylsulfone was cleaved with triethylborane, and the resulting sulfinate anion was reacted with hydroxylamine-*O*-sulfonic acid. The SEM protecting group was subsequently removed with fluoride. One of the analogs prepared in this manner, **5a**, was only 110-fold selective and actually showed poorer in vivo activity. Since the results for sulfonamides were not encouraging, we renewed our focus on the sulfones.

Other modifications we tried in the sulfone series included methylation of of the imidazole N-H and replacement of the imidazole-(2)-trifluoromethyl moiety with various alkyl, aryl, and alkenyl groups, including furyl and isopropyl.[9] Some trifluoromethyl substitutions demonstrated good enzyme activity, but all 2-variants tested showed significantly reduced in vivo efficacy. It is not required for the substituent R- to be phenyl; compound **4s** in Table 1 exemplifies an analog with enzyme and in vivo activity where R- is a heterocycle.

**Table 1**

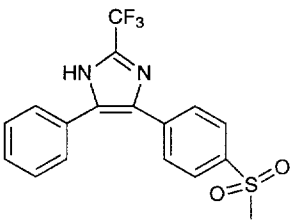


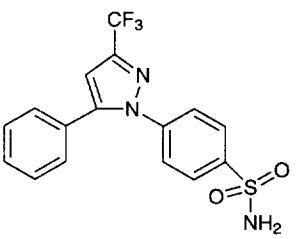

| | R | H-COX-2[a] (μ Mol) | H-COX-1 (μ Mol) | Air Pouch[b] (% inh.@ 2 MPK) |
|---|---|---|---|---|
| **4a** | phenyl | 0.69 | 1580 | 95 |
| **4b** | 2-F-phenyl | 3.0 | >100 | |
| **4c** | 3-F-phenyl | 0.24 | >100 | 92 |
| **4d** | 4-F-phenyl | 0.19 | >100 | 99 |
| **5a** | 4-F-phenyl (sulfonamide) | 0.10 | 11 | 33 |
| **4e** | 2-Cl-phenyl | 1.3 | >100 | 86 |
| **4f** | 3-Cl-phenyl | 0.080 | 540 | 98 |
| **4g** | 4-Cl-phenyl | 0.37 | 10 | 86 |
| **4h** | 2-Me-phenyl | 1.8 | >100 | |
| **4i** | 3-Me-phenyl | 0.61 | >100 | 29 |
| **5b** | 3-Me-phenyl (sulfonamide) | 0.15 | 6.2 | |
| **4j** | 4-Me-phenyl | 0.65 | 33 | |
| **4k** | 3-MeO-phenyl | 2.4 | >100 | |
| **4l** | 4-MeO-phenyl | 2.9 | 5.6 | |
| **4m** | 3,4-di-Cl-phenyl | 0.04 | 10 | 84 |
| **4n** | 2,4-di-F-phenyl | 0.55 | >1000 | 100 |
| **4o** | 3,4-di-F-phenyl | 0.16 | 760 | 68 |
| **4p** | 3-Cl-4-Me-phenyl | 0.23 | 56 | 0 |
| **4q** | 3-F-2-Me-phenyl | 1.7 | 1000 | 94 |
| **4r** | cyclohexyl | 4.0 | >100 | |
| **4s** | 2-thienyl | 1.4 | >1000 | 79 |
| **4t** | 3-thienyl | 2.0 | >100 | 0 |
| **4u** | 3-pyridyl | 2.4 | >100 | 29 |

[a]Human recombinant COX enzymes. [b]Mouse air pouch assay

In conclusion, potent diarylimidazole sulfones which compare pretty favorably with Celecoxib were synthesized, with **4f** showing the best profile overall. A typical inhibitor, **4a**, was carried forward through the rat adjuvant arthritis model. It is somewhat less active than Celecoxib in vitro (690 vs. 28 nM), but shows excellent activity in efficacy models.

**Table 2**




| | 4a | Celecoxib |
|---|---|---|
| COX-2 (μMol) | 0.69 | 0.028 |
| COX-1 (μMol) | 1600 | 15 |
| Air Pouch $ED_{50}$ (MPK) | 0.38 | 0.33 |
| Adj. Arth. $ED_{50}$ (MPK) | 0.16 | 0.37 |

**Representative Procedure for Synthesis of Stilbene Sulfones (6a)**

Benzyl triphenylphosphonium iodide (9.61 g, 20 mMol) was suspended in abs EtOH and cooled to 0%C. *n*-Buli (13.1 mL, 21 mMol) was added dropwise. 4-(Methylmercapto)-benzaldehyde (2.67 mL, 20 mMol) was added and the mixture was allowed to stir for 2.5 h at rt, then diluted with water (40 mL) and extracted with methylene chloride (200 mL). The organic layer was dried using $MgSO_4$, filtered through a silica plug (which removed most of the triphenylphosphine oxide), and concentrated to a yellow semi-solid. The solid was diluted with MeOH (50 mL), cooled to 0%C, and treated with Oxone™ (50 mMol) in water (100 mL). After 15 min, the cooling bath was removed and the mixture was stirred at rt for 1.5 h. The suspension was extracted with methylene chloride (200 mL, then 2 × 50 mL). The combined organic layers were dried over $MgSO_4$ filtered through silica, concentrated , and chromatographed (2/1, hexane/ethyl acetate) to afford the desired **6a** (3.95 g, 75%) as a mixture of *cis–trans* isomers.[12]

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