A Convenient Synthesis of 5-Alkylthio-3,4-diarylisoxazoles by Palladium-Catalyzed Coupling Reactions.

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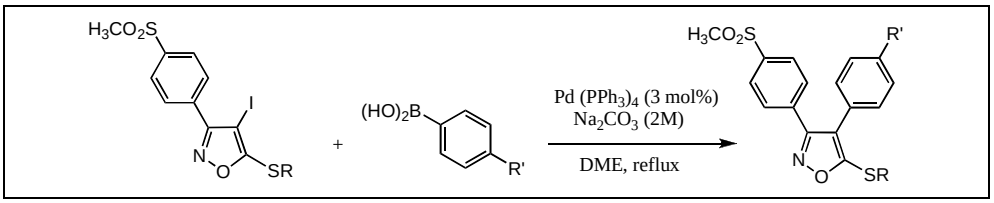

Palladium-catalyzed coupling reaction was found effective for rapid access to pharmacologically interesting 3,4-diarylisoxazoles derivatives as selective COX-2 inhibitors. Thus, the coupling reaction between 5-alkylthio-3-aryl-4-iodoisoxazoles and arylboronic acids afforded the target 5-alkylthio-3,4-diarylisoxazoles in good yields.

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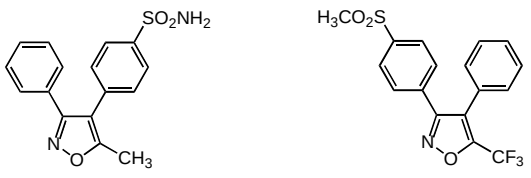
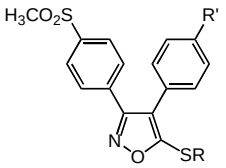
A 3,4-diarylisoxazole scaffold has frequently been incorporated into the pharmacophore design for a wide range of pharmaceutical agents [1]. Some examples include non-steroidal anti-inflammatory drugs (NSAIDs) [2], protein kinase inhibitors [3] and hypertensive agents [4]. The discovery of cyclooxygenase-2 (COX-2) enzyme in the beginning of the last decade has set off a race to develop selective COX-2 inhibitors [5]. Selective COX-2 inhibitors are potential anti-inflammatory drugs with reduced side effects as compared to NSAIDs which are non-selective COX-1/COX-2 inhibitors [6].

From the evaluation of numerous compounds, diaryl heterocycles and diaryl carbocyles with a 4-sulfonamide or 4-methylsulfonyl group in one of the phenyl rings have been identified as the pharmacophore for selective COX-2 inhibition [5]. Several diaryl isoxazole rings have shown extremely high COX-2 selectivity and potency, represented by 4-(5-methyl-3-phenyl-4-isoxazolyl) benzenesulfonamide, Valdecoxib, (Bextra ®) (1) [7] and 3-(4-methylsulfonylphenyl)-4-phenyl-5-trifluromethyl-isoxazole (2) [8] (Figure 1).



Valdecoxib (**1**) (**2**)



12, R: -CH_3 R': F
13-17, R: -CH_2CH_3 R':H, F, Br, CH_3, C_2H_5

Representative examples and designed 3,4-diarylisoxazoles as COX-2 selective inhibitors.

Figure 1

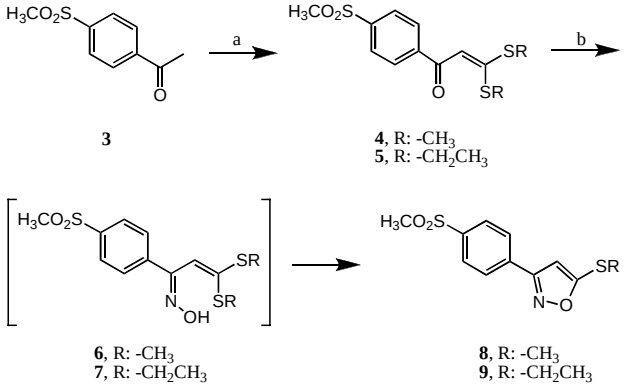
Whereas small lipophilic central ring substitutent (Me, CF_3) frequently enhances, or is often a requirement for COX-2 selectivity [9], modification of them to find a new ligand with improved properties is desirable.

Although several methods are available for the synthesis of substituted isoxazoles [10], no selective method to 5-alkylthio-3,4-diarylisoxazole is available in the literature. Krogsgaard Larsen *et al*. [11] have recently reported the synthesis of 4-arylisoxazololes by palladium-catalyzed cross-coupling reactions between O-protected 4-iodo-3-isoxazololes and arylboronic acids. We have therefore investigated the feasibility of the Suzuki cross-coupling reaction for arylation of the 4-position of 5-alkylthio-3-aryl-4-iodoisoxazoles, in order to prepare 5-alkylthio-3,4-diarylisoxazoles **12-17**. The synthetic reactions used for the synthesis of 5-alkylthio-4-aryl-3-(4-methylsulfonylphenyl)isoxazoles **12-17** are outlined in Schemes 1-3.

5-Alkylthio-4-(4-methylsulfonylphenyl)isoxazoles **8/9** are key intermediates for the production of the desired compounds **12-17**. The latter was prepared from α-oxoketene dithioacetals. The α-oxoketene dithioacetal **4/5**

was prepared from the known 4-methylsulfonylacetophenone **3** [12] according to the standard procedure [13,14] which involved treatment of **3** with NaH in benzene and subsequent addition of CS_2 and alkyl iodide (Scheme 1).

Scheme 1



Reagents and conditions: (a) NaH, benzene, 0 ºC, 2 hours, then CS_2, alkyl iodide, below 45 ºC, 24 hours; (b) $NH_2OH.HCl$, $Ba(OH)_2$, reflux, 4 hours.

The reaction of hydroxylamine hydrochloride with α-oxoketene dithioacetal afforded highly regioselective 5-alkylthioisoxazole. In this case ring closure performed by using hydroxylamine hydrochloride and barium hydroxide in boiling ethanol (pH = 5-9) via *in-situ* oxime **6/7** formation [15].

A clear distinction of regioselectivity of above reaction could be made by means of mass spectral fragmentation. The 3-(4-methylsulfonylphenyl)-5-alkylthioisoxazole showed characteristic peaks due to loss of –SR and –COSR fragment (M-47 and M-75 in the case of 5-methylthio isomer) suggesting that the alkylthio group is adjacent to the ring O-atom [15,16].

Iodination of C_4 position of isoxazoles is accomplished through the addition of iodine monochloride in aqueous acetic acid solution [17]. The polar medium induces heterolytic dissociation of ICl to produce I^+ species [18].

The activity of I^+ species is so high that it could be used for successful iodination of **8/9** at 20 °C, higher iodination temperature of these substrates lead to mixture of higher oxidized form of alkylthio group.

Each iodinated isoxazole prepared was characterized by ir, ^{1}H nmr and ms. The location of iodine was confirmed by both the absence of the strong isoxazole C-H stretch at *ca*. 3145-3149 cm^{-1} in the ir and the singlet for the C_4 proton in the ^{1}H nmr.

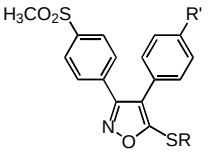
Compounds **10/11** are proper intermediates for organometallic cross-coupling reaction. Since boronic acids can tolerate a wide range of functional groups such as alkylthio, aromatic cross-coupling can be obtained in the presence of palladium catalyst with iodo derivatives [19, 20].

Many parameters have been studied such as base, the solvent and the ionic additives for the improvement of Suzuki coupling reaction. It is important to note that influence of these parameters depend on the nature of the substrate [21].

The Suzuki cross-coupling reaction between **10/11** and commercially available arylboronic acids was performed in a mixture of dimethoxyethane (DME) and aqueous solution of Na_2CO_3 as base and $Pd(PPh_3)_4$ as catalyst (Table1) [11].

Table 1

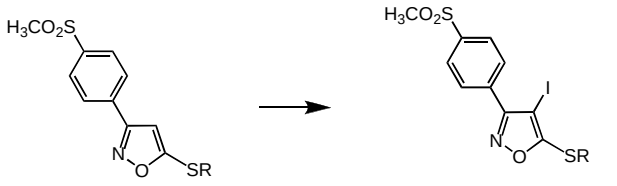
Suzuki cross-coupling of 5-alkythio-4-iodo-3-(4-methylsulfonylphenyl)isoxazole and arylboronic acids and their anti-inflammatory activity.



Compound	R	R´	Yield (%)	Mp (°C)	AI activity[a] % inhibition at 3 h	AI activity[a] % inhibition at 5 h
12	CH_3	F	94	135-137	84.5 ± 1.1	63.3 ± 3.3
13	CH_2CH_3	H	88	178-180	84.2 ± 6.05	76.6 ± 12.3
14	CH_2CH_3	F	92	120-121	83.3 ± 1.3	82.5 ± 1.83
15	CH_2CH_3	Br	81	152-154	n.t.[b]	n.t.
16	CH_2CH_3	CH_3	80	147-149	74.6 ± 5.7	70.0 ± 6.4
17	CH_2CH_3	CH_2CH_3	85	126-128	75.7 ± 3.7	63.0 ± 6.24
celecoxib					70.53 ± 4.7	50.0 ± 2.5

[a] Inhibitory activity on carrageenan-induced rat paw edema. The results are expressed as mean ± SEM (n = 4-6) following a 50 mg/kg oral dose of the test compound. [b] not tested.

Scheme 2

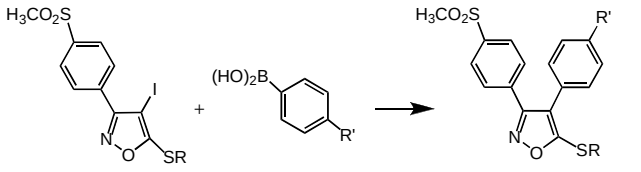


8, R: -CH_3
9, R: -CH_2CH_3

10, R: -CH_3
11, R: -CH_2CH_3

Reagents and condition: ICl, HOAc, H_2O, 20 ºC, 2 hours.

Scheme 3



10, R: -CH_3
11, R: -CH_2CH_3

12, R: -CH_3
R': F
13-17, R: -CH_2CH_3
R':H, F, Br, CH_3, C_2H_5

Reagents and condition: $Pd(PPh_3)_4$ (3 mol%), DME, reflux, 12 hours, aqueous Na_2CO_3 (2 M).

The reaction proceeded efficiently leading to formation of desired 5-alkylthio-4-aryl-3-(4-methylsulfonylphenyl)isoxazoles in good yields (Table1). These results have paved the way for the synthesis of analogues of the 5-alkylthio-3,4-diarylisoxazoles.

In vivo pharmacological evaluation of compounds **12-14**, **16** and **17** was carried out to assess their potential anti-inflammatory activity. Qualitative structure-activity relationship data, acquired using the anti-inflammatory rat paw edema assay [22], showed this group of C-5 alkylthio substituted 3,4-diarylisoxazoles exhibits anti-inflammatory activity with excellent activity range. In this regards, these compounds reduced inflammation by 75-85% and 63-82% at 3 and 5 h post drug administration, respectively, relative to the reference drug celecoxib (70 and 50% reduction in inflammation at 3 and 5 h drug administration, respectively), administered at the same dose (see Table 1).

EXPERIMENTAL

Melting points were determined with a Reichert-Jung hot-stage microscope and are uncorrected. ^{1}H nmr (400 MHz) spectra were recorded on a Varian Utility plus 400 spectrometer using deuteriochloroform or DMSO-d_6 as solvent. Chemical shifts (δ) are reported in ppm relative to TMS as internal standard. Infrared spectra were acquired on a Nicolet Magna 550-FT spectrometer. Mass spectra were obtained with a Finnigan Mat TSQ-70 spectrometer. Elemental microanalyses were within ± 0.4% of the theoretical values for C, H and N.

1-(4-Methylsulfonylphenyl)-3,3-bis-methylthio-propenone (4). To an ice chilled solution of 4-methylsulfonylacetophenone **3** [12] (19.8 g, 0.1 mole) in dry benzene (150 ml) was added sodium hydride (8.0 g of a 60% in mineral oil, 0.2 mole). Carbon disulfide (12.0 g, 0.15 mole) and methyl iodide (42.6 g, 0.3 mole) were added cautiously to the cold solution. *N*,*N*-Dimethylacetamide (5 ml) was added dropwise while the mixture was kept below 45º. After stirring for 24 hours at room temperature, a small amount of crushed ice was added to the heterogenous solution to consume any unreacted NaH. The solvent was removed under reduced pressure, and the residue was partitioned between water and dichloromethane. The organic layer was washed with water, dried (Na_2SO_4), filtered and evaporated to afford an oily residue which was crystallized from ethanol to give **4** (24.2 g, 80%) as a yellow crystal, mp 174-176º; ir (potassium bromide): 1147, 1306 (SO_2CH_3), 1685 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.57 (s, 3H), 2.60 (s, 3H), 3.08 (s, 3H), 6.71 (s, 1H), 8.23 (d, J = 8.8 Hz, 2H), 8.07 (d, J = 8.8 Hz, 2H); ms: m/z 302 (M^+, 32), 287 (92), 241 (9), 198 (32), 183 (100), 121 (74). *Anal.* Calcd. for $C_{12}H_{14}O_3S_3$: C, 47.66; H, 4.67. Found: C, 47.51; H, 4.80.

1-(4-Methylsulfonylphenyl)-3,3-bis-ethylthiopropenone (5). Compound **5** (26.4 g, 80%) was prepared following the procedure described for **4** as an orange crystal, mp 147-148°; ir (potassium bromide): 1151, 1307 (SO_2CH_3), 1610 (CO) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.41 (t, J = 7.2 Hz, 3H), 1.46 (t, J = 7.2 Hz, 3H), 3.08 (s, 3H), 3.10 (q, J = 7.2 Hz, 2H), 3.12 (q, J = 7.2 Hz, 2H), 6.75 (s, 1H), 8.02 (d, J = 8.4 Hz, 2H), 8.06 (d, J = 8.4, 2H); ms: m/z 330 (M^+, 18), 301 (100), 273 (4), 241 (15), 183 (34), 121 (7). *Anal.* Calcd. for $C_{14}H_{18}O_3S_3$: C, 50.88; H, 5.49. Found: C, 50.69; H, 5.63.

3-(4-Methylsulfonylphenyl)-5-methylthioisoxazole (8). To a stirred suspension of $Ba(OH)_2.8H_2O$ (151.2 g, 0.48 mole) in EtOH (250 ml) was added hydroxylamine hydrochloride (22.4 g, 0.32 mole), followed by the addition of α-oxoketene dithioacetal (**4**). The mixture was refluxed with stirring for 4 hours and then the solvent was removed under reduced pressure. The residue was poured into ice/cold water (1500 ml) and this mixture was acidified with diluted AcOH (5%, 120 ml). The isoxazole was filtered and passed through a neutral alumina column using EtOAc as solvent. The residue crystallized from EtOAc/hexane gave **8** (11.2 g, 52%) as a yellow crystal, mp 142-143º; ir (potassium bromide): 1155, 1309 (SO_2CH_3), 1539 (C=N, isoxazole), 3149 (H_4) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.66 (s, 3H), 3.10 (s, 3H), 6.44 (s, 1H), 7.98 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.4 Hz, 2H). ms: m/z 269 (M^+, 22), 222 (100), 194 (4), 143 (16). *Anal.* Calcd. for $C_{11}H_{11}NO_3S_2$: C, 49.05; H, 4.12; N, 5.20. Found: C, 49.23; H, 4.01; N, 5.37.

5-Ethylthio-3-(4-methylsulfonylphenyl)isoxazole (9). Compound **9** (11.3 g, 50%) was prepared following the procedure described for **8** as a yellow crystal, mp 112-113º; ir (potassium bromide): 1148, 1299 (SO_2CH_3), 1537 (C=N, isoxazole), 3145 (H_4) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.44 (t, J = 7.2 Hz, 3H), 3.10 (s, 3H), 3.18 (q, J = 7.2 Hz, 2H), 6.52 (s, 1H), 7.98 (d, J = 6.8 Hz, 2H), 8.05 (d, J = 6.8 Hz, 2H); ms: m/z 283 (M^+, 75), 222 (100), 194 (5), 143 (52), 132 (24), 115 (11). *Anal.* Calcd. for $C_{12}H_{13}NO_3S_2$: C, 50.86; H, 4.62; N, 4.94. Found: C, 50.71; H, 4.78; N, 4.77.

4-Iodo-3-(4-methylsulfonylphenyl)-5-methylthioisoxazole (10). To a solution of **8** (38 mmoles) in AcOH (150 ml) and water (180 ml) was added iodine monochloride (9.29 g, 57.2 mmoles). The solution was stirred for 24 hours at 20º and then

was added to 75 ml solution of Na_2SO_3 (10%), the precipitate was filtered off and redissolved in acetone (120 ml). The solvent was removed under reduced pressure and the residue was crystallized from diethyl ether to give **10** (12.0 g, 80%) as a white crystal, mp 157-160º (decomp.); ir (potassium bromide): 1153, 1308 (SO_2CH_3), 1503 (C=N, isoxazole) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.74 (s, 3H), 3.12 (s, 3H), 8.02 (d, J = 8 Hz, 2H), 8.08 (d, J = 8 Hz, 2H); ms: m/z 395 (M^+, 34), 348 (100), 268 (10), 221 (85), 206 (37), 158 (33), 114 (20). *Anal*. Calcd. for $C_{11}H_{10}INO_3S_2$: C, 33.43; H, 2.55; N, 3.54. Found: C, 33.60; H, 2.37; N, 3.66.

5-Ethylthio-4-iodo-3-(4-methylsulfonylphenyl)isoxazole (11). Compound **11** (11.0 g, 71%) was prepared following the procedure described for **10** as a pale yellow crystal, mp 116-118º; ir (potassium bromide): 1145, 1305 (SO_2CH_3), 1506 (C=N, isoxazole) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.47 (t, J = 7.2 Hz, 3H), 3.12 (s, 3H), 3.24 (q, J = 7.2 Hz, 2H), 8.02 (d, J = 8.4 Hz, 2H), 8.08 (d, J = 8.4 Hz, 2H); ms: m/z 409 (M^+, 34), 348 (100), 282 (14), 254 (13), 221 (84), 206 (26), 158 (23). *Anal*. Calcd. for $C_{12}H_{12}INO_3S_2$: C, 35.22; H, 2.96; N, 3.42. Found: C, 35.10; H, 2.79; N, 3.61.

General procedure for Palladium-catalyzed Suzuki coupling of 5-alkythio-4-iodo-3-(4-methylsulfonylphenyl)-isoxazole (12-17). To a solution of 5-alkythio-4-iodo-3-(4-methylsulfonylphenyl)isoxazole (**10** and **11**, 0.1 mmole) in DME (5 ml) was added $Pd(PPh_3)_4$ (3.5 mg, 0.003 mmole). The resulting solution was allowed to stir for 5 minutes and then to this solution was added a 2 *M* aqueous solution of Na_2CO_3 (1 ml) and boronic acid (1.2 mmoles). The reaction was refluxed for 12 hours. The mixture was cooled to room temperature and was extracted with diethyl ether (5 ml). The organic phase was washed with brine (5 ml), NaOH (2 M, 2×5 ml), brine (5 ml) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the product was purified by flash chromatography on silica gel using appropriate solvent.

4-(4-Fluorophenyl)-3-(4-methylsulfonylphenyl)-5-methylthioisoxazole (12). From **10** (39.5 mg, 0.1 mmole) following the general procedure, flash chromatography AcOH-EtOAc-hexane (1:25:75) afforded **12** (34.2 g, 94%) as a white crystal, mp 135-137º; ir (potassium bromide): 1148, 1312 (SO_2CH_3), 1557 (C=N, isoxazole) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.66 (s, 3H), 3.08 (s, 3H), 7.10 (t, J = 8.8 Hz, 2H), 7.18 (dt, J = 2.4, 8.8 Hz, 2H), 7.64 (dd, J = 1.6, 6.4 Hz, 2H), 7.94(dd, J = 1.6, 6.4 Hz, 2H); ms: m/z 363 (M^+, 69), 316 (100), 288 (64), 225 (36), 208 (52), 199 (75), 139 (38), 107 (73), 75 (74). *Anal*. Calcd. for $C_{17}H_{14}FNO_3S_2$: C, 56.18; H, 3.88; N, 3.85. Found: C, 56.38; H, 4.02; N, 3.69.

5-Ethylthio-3-(4-methylsulfonylphenyl)-4-phenylisoxazole (13). From **11** (40.5 mg, 0.1 mmole) following the general procedure, flash chromatography AcOH-EtOAc-hexane (2:20:80) afforded **13** (31.6 mg, 88%) as a white crystal, mp 178-180º; ir (potassium bromide): 1143, 1312 (SO_2CH_3), 1542 (C=N, isoxazole) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.40 (t, J = 7.6 Hz, 3H), 3.07 (s, 3H), 3.15 (q, J = 7.6 Hz, 2H), 7.18-7.21 (m, 2H), 7.38-7.40 (m, 3H), 7.66 (d, J = 8.4 Hz, 2H), 7.92 (d, J = 8.4 Hz, 2H). ms: m/z 359 (M^+, 29), 298 (100), 270 (34), 207 (11), 199 (37), 190 (12), 121 (16), 89 (45). *Anal*. Calcd. for $C_{18}H_{17}NO_3S_2$: C, 60.14; H, 4.77; N, 3.90. Found: C, 60.01; H, 4.89; N, 3.71.

5-Ethylthio-4-(flurophenyl)-3-(4-methylsulfonylphenyl)isoxazole (14). From **11** (40.5 g, 1 mmole) following the general procedure, flash chromatography AcOH-EtOAc-hexane (2:20:80) afforded **14** (33.0 mg, 92%) as a white crystal, mp 120-121º; ir (potassium bromide): 1153, 1312 (SO_2CH_3), 1557 (C=N, isoxazole) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.40 (t, J = 7.2 Hz, 3H), 3.08 (s, 3H), 3.15 (q, J = 7.2 Hz, 2H), 7.07-7.12 (m, 2H, H-Ar), 7.16-7.19 (m, 2H, H-Ar), 7.65 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 8.4 Hz, 2H); ms: m/z 377 (M^+, 57), 316 (100), 288 (38), 208 (18), 199 (41), 139 (17). *Anal*. Calcd. for $C_{18}H_{16}FNO_3S_2$: C, 57.28; H, 4.27; N, 3.71. Found: C, 57.42; H, 4.10; N, 3.55.

4-(Bromophenyl)-5-ethylthio-3-(4-methylsulfonylphenyl)-isoxazole (15). From **11** (40.5 mg, 0.1 mmole) following the general procedure (in this case reflux continued for 36 hours), flash chromatography AcOH-EtOAc-hexane (1:50:50) afforded **15** (35.5 mg, 81%) as a pale yellow crystal, mp 152-154º; ir (potassium bromide): 1153, 1317 (SO_2CH_3), 1557 (C=N, isoxazole) cm^{-1}; ^1H nmr (deuterio- chloroform): δ 1.40 (t, J = 7.2 Hz, 3H), 3.08 (s, 3H), 3.25 (q, J = 7.2 Hz, 2H), 7.07 (dd, J = 8.0 Hz, 2H), 7.58 (t, J = 8.4 Hz, 4H), 7.95 (d, J = 8.0 Hz, 2H); ms: m/z 439 (M^+, 57), 437 (63), 378 (79), 376 (77), 350 (30), 348 (28), 300 (14), 201 (18), 199 (100), 190(17). *Anal*. Calcd. for $C_{18}H_{16}BrNO_3S_2$: C, 49.32; H, 3.68; N, 3.20. Found: C, 49.50; H, 3.51; N, 3.33.

5-Ethylthio-3-(4-methylsulfonylphenyl)-4-*p*-tolyl isoxazole (16). From **11** (40.5 mg, 0.1 mmole) following the general procedure, flash chromatography AcOH-EtOAc-hexane (2:20:80) afforded **16** (30.0 mg, 80%) as a white crystal, mp 147-149º, ir (potassium bromide): 1148, 1317 (SO_2CH_3), 1547 (C=N, isoxazole) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.39 (t, J = 7.6 Hz, 3H), 2.39 (s, 3H), 3.07 (s, 3H), 3.13 (q, J = 7.6 Hz, 2H), 7.07 (d, J = 8 Hz, 2H), 7.20 (d, J = 8 Hz, 2H), 7.67 (d, J = 8.8 Hz, 2H), 7.92 (d, J = 8.8 Hz, 2H). ms: m/z 373 (M^+, 44), 312 (96), 284 (55), 199 (100),135 (20). *Anal*. Calcd. for $C_{19}H_{19}NO_3S_2$: C, 61.10; H, 5.13; N, 3.75. Found: C, 61.22; 5.22; N, 3.55.

5-Ethylthio-4-(4-ethylphenyl)-3-(4-methylsulfonylphenyl)-isoxazole (17). From **11** (40.5 g, 0.1 mmole) following the general procedure, flash chromatography AcOH-EtOAc-hexane (2:20:80) afforded **17** (33 mg, 85%) as a white crystal, mp 126-128º; ir (potassium bromide): 1153, 1317 (SO_2CH_3), 1552 (C=N, isoxazole) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.27 (t, J = 7.6 Hz, 3H), 1.39 (t, J = 7.2 Hz, 3H), 2.69 (q, J = 7.6 Hz, 2H), 3.07 (s, 3H), 3.14 (q, J = 7.2 Hz, 2H), 7.10 (d, J = 8 Hz, 2H), 7.22 (d, J = 8 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.92 (d, J = 8.4 Hz, 2H); ms: m/z 387 (M^+, 29), 326 (61), 298 (35), 199 (100), 149 (19), 117 (29). *Anal*. Calcd. for $C_{20}H_{21}NO_3S_2$: C, 61.99; H, 5.46; N, 3.61. Found: C, 62.18; H, 5.30; N, 3.79.

Anti-inflammatory Assay. The test compounds were evaluated using *in vivo* rat carrageenan-induced foot paw edema model reported previously [22].

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