Synthesis of New 1-[4-Methane(amino)sulfonylphenyl)]-5-[4-(aminophenyl)]-3-trifluoromethyl-1*H*-pyrazoles

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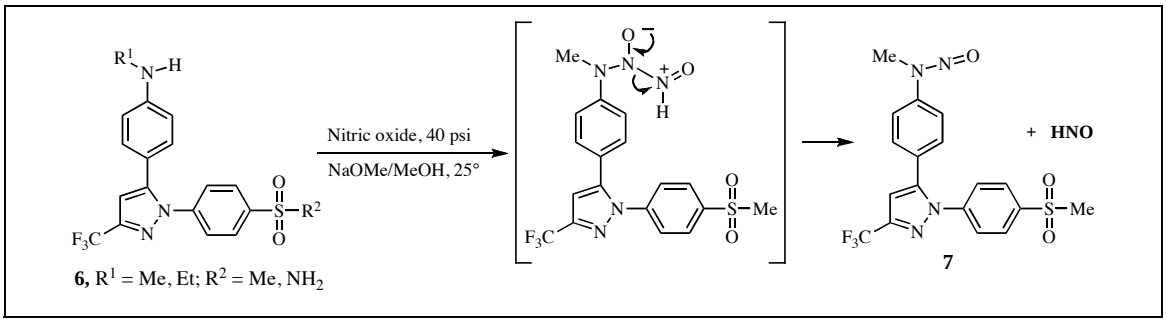

A regiospecific cyclization-dehydration reaction of a 1-[4-(*N*-alkyl-*N*-(*tert*-butyloxycarbonyl)amino)-phenyl]-4,4,4-trifluorobutane-1,3-done with a 4-aminosulfonyl-, or 4-methylsulfonyl-, phenylhydrazine hydrochloride in refluxing ethanol proceeded with simultaneous loss of the *N*-*tert*-butyloxycarbonyl protecting group to afford a group of 1-(4-methanesulfonylphenyl or 4-aminosulfonylphenyl)-5-[4-(*N*-alkylaminophenyl)]-3-(trifluoromethyl)-1*H*-pyrazoles (**6**). Subsequent reaction of the pyrazole **6** ($R^1 = R^2 =$ Me) with nitric oxide (40 psi) proceeded *via* a *N*-methylamino-*N*-diazen-1-ium-1,2-diolate intermediate that undergoes protonation of the more basic diazen-1-ium-1,2-diolate N^2-nitrogen and then loss of a nitroxyl (HNO) species to furnish the *N*-nitroso product **7**.

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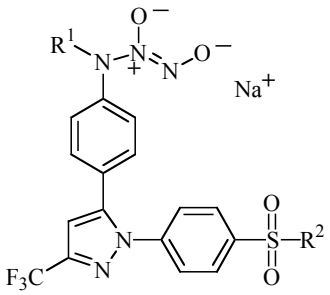
INTRODUCTION

The original concept that an anti-inflammatory drug which selectively inhibits the inducible cyclooxygenase-2 (COX-2) isozyme in the periphery would be devoid of adverse ulcerogenic effects was confirmed with the development of celecoxib [1], rofecoxib [2] and valdecoxib [3]. It soon became evident that highly selective COX-2 inhibitors alter the balance in the COX pathway causing a decrease in the level of the favorable vasodilatory and anti-aggregatory prostacyclin (PGI_2) together with a simultaneous increase in the level of the unfavorable prothrombotic thromboxane A_2 (TxA_2). These contraindicated biochemical changes culminated in higher incidences of elevated blood pressure and myocardial infarction which prompted the voluntary withdrawal of rofecoxib and valdecoxib [4]. Nitric oxide (NO) is an effective vasodilation agent that also inhibits platelet aggregation and adhesion [5]. Accordingly, attachment of a NO-donor moiety to highly selective COX-2 inhibitors offers a potential drug design concept to circumvent the adverse cardiovascular events associated with their chronic clinical use. We now describe an investigation directed toward the synthesis of model hybrid NO donor selective COX-2 inhibitory anti-inflammatory agents that would be devoid of adverse cardiovascular effects (see structure **1** in Figure 1).



1, R^1 = Alkyl; R^2 = Me, NH_2

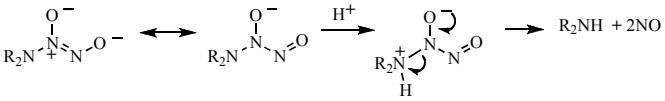
Figure 1. Structure of putative hybrid nitric oxide donor *N*-diazen-1-ium-1,2-diolate derivatives of selective COX-2 inhibitory 1-(4-methane-(amino)sulfonylphenyl)-5-[4-(*N*-alkylaminophenyl)]-3-trifluoromethyl-1*H*-pyrazoles.

RESULTS AND DISCUSSION

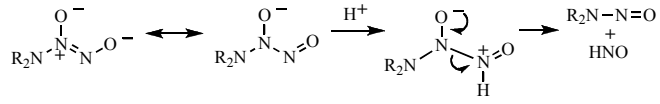
In earlier studies, we reported *N*-diazen-1-ium-1,2-diolate derivatives of secondary dialkylamines covalently attached to the non-steroidal anti-inflammatory drugs (NSAIDs) aspirin (acetylsalicylic acid), ibuprofen [2-(4-isobutylphenyl)propionic acid] and indomethacin [1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid]. Biological evaluation indicated that these hybrid NO-donor / NSAID prodrugs i) released NO efficiently, ii) unlike the parent NSAIDs were devoid of gastrointestinal ulcerogenicity, and iii) exhibited *in vivo* antiinflammatory activities comparable to the parent NSAID [6-8].

The synthetic strategy employed to prepare putative model compounds of general structure **1** (see Figure 1) is illustrated in Scheme 1. Thus, reaction of the 4-alkylaminoacetophenones (**2a** and **2b**) with di-*tert*-butyl dicarbonate gave the respective 1-[4-(*N*-alkyl-*N*-(*tert*-butyloxycarbonyl)amino)phenyl]ethanone **3a** (R^1 = Me, 84%) and **3b** (R^1 = Et, 73%). The subsequent base-catalyzed Claisen condensation of **3a** and **3b** with ethyl trifluoroacetate furnished the corresponding 1-[4-(*N*-alkyl-*N*-(*tert*-butyloxycarbonyl)amino)phenyl]-4,4,4-trifluorobutane-1,3-diones **4a** (R^1 = Me, 93%) and **4b** (R^1 = Et, 87%). The subsequent cyclization-dehydration reaction of the 1,3-diones **4a** and **4b** with either (4-sulfamoylphenyl)hydrazine hydrochloride (**5a**), or (4-methylsulfonylphenyl)hydrazine hydrochloride (**5b**), proceeded with a simultaneous loss of the *N*-*tert*-butyloxycarbonyl protecting group to afford the respective 1,5-diaryl-3-trifluoromethylpyrazole product **6a-d** in good yield (81-98%). It is well documented that this latter reaction occurs in a regiospecific manor to yield the 1,5-diarylpyrazole product when a phenylhydrazine hydrochloride is employed and the reaction is carried out in ethanol at reflux temperature [1]. Reaction of 1-(4-methanesulfonylphenyl)-5-[4-(*N*-methylaminophenyl)]-3-trifluoromethyl-1*H*-pyrazole (**6b**) with nitric oxide gas (40 psi) at 25° in the presence of NaOMe yielded a product which exhibited a molecular ion in the mass spectrum (m/z 446.93, M + Na) and microanalytical data that was consistent with the *N*-nitroso product 1-(4-methanesulfonylphenyl)-5-[4-(*N*-methyl-*N*-nitrosoaminophenyl)]-3-trifluoromethyl-1*H*-pyrazole (**7**) in 47% yield.

The decomposition pathway of the *N*-amino-*N*-diazen-1-ium-1,2-diolate moiety (see Figure 1) is dependent upon the site of protonation. In this regard, protonation at the amine nitrogen and then decomposition would produce the amine and 2 molecules of NO as illustrated below.

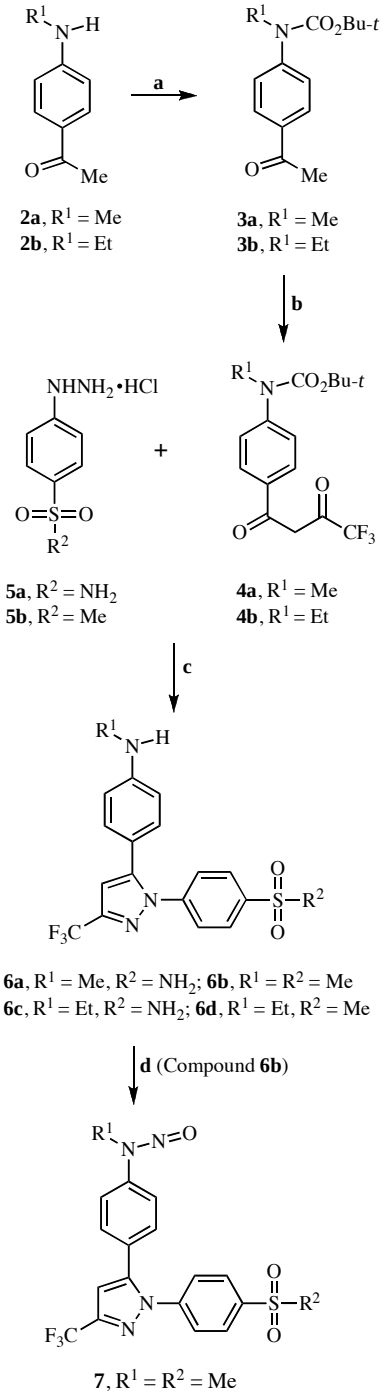


Alternatively, protonation of the diazen-1-ium-1,2-diolate N^2-nitrogen and then decomposition would furnish a nitrosamine (such as product **7** in Scheme 1) and a nitroxyl species (HNO) as indicated below.



The formation of the *N*-nitroso product **7** indicates that the intermediate *N*-amino-*N*-diazen-1-ium-1,2-diolate product (see structure **1** in Figure 1) must undergo protonation of the more basic diazen-1-ium-1,2-diolate N^2-nitrogen that is unstable undergoing subsequent elimination of a HNO species [9].

Scheme 1



Reagents and conditions: a) di-*tert*-butyl dicarbonate, 4-dimethylaminopyridine (DMAP), THF, reflux, 16 hours; b) NaOMe in MeOH (25% w/v), methyl *tert*-butyl ether (MTBE), CF_3CO_2Et, 25°, 16 hours; c) EtOH, reflux, 20 hours, d) NaOMe in MeOH (25% w/v), diethyl ether, nitric oxide (40 psi), 25°, 48 hours.

The biological activity of the N-nitroso product **7** was not investigated in view of the tumorigenic activity frequently associated with the use of *N*-nitroso agents.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Unless otherwise noted, infrared (IR) spectra were recorded as films on NaCl plates using a Nicolet 550 Series II Magna FT-IR spectrometer. ^{1}H NMR spectra were measured on a Bruker AM-300 spectrometer in $CDCl_3$ with TMS as the internal standard. Mass spectra (MS) were recorded on a Water's Micromass ZQ 4000 mass spectrometer using the ESI ionization mode. Microanalyses were performed for C and H (MicroAnalytical Service Laboratory, Department of Chemistry, University of Alberta) and were within ± 0.4% of theoretical values unless otherwise stated. Silica gel column chromatography was performed using Merck silica gel 60 ASTM (70-230 mesh). 1-(4-Methylaminophenyl)ethanone (**2a**) [10], (4-aminosulfonylphenyl)hydrazine hydrochloride (**5a**) [11] and (4-methylsulfonylphenyl)hydrazine hydrochloride (**5b**) [12] were prepared according to literature procedures. All other reagents, purchased from the Aldrich Chemical Company (Milwaukee, WI), were used without further purification.

1-(4-Ethylaminophenyl)ethanone (2b). A solution of ethylamine (70% w/v in H_2O, 23.3 mL, 362 mmoles) was added to a solution of 4'-fluoroacetophenone (5.0 g, 36.2 mmoles) in DMSO (10 mL), the reaction flask was fitted with a reflux condenser, and the mixture was heated at 90° for 20 hours. The reaction mixture was cooled to 25°, H_2O (100 mL) was added, the solid was filtered, dried, and then purified by silica gel column chromatography (gradient elution: 10–60% EtOAc–hexanes) to furnish **2b** (2.1g, 36%) as a yellow solid: mp 101-102° (lit [13] mp 103°); IR (film) 3325 (NH), 2935 (C-H aromatic), 2904 (C-H aliphatic), 1652 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, *J* = 7.3 Hz, 3H, CH_2CH_3), 2.51 (s, 3H, $COCH_3$), 3.24 (q, *J* = 7.3 Hz, 2H, CH_2CH_3), 4.15 (br s, 1H, N*H*, D_2O exchangeable), 6.56 (dd, *J* = 7.0, 1.8 Hz, 2H, phenyl H-3, H-5), 7.84 (dd, *J* = 7.0, 1.8 Hz, 2H, phenyl H-2, H-6).

1-[4-(*N*-Methyl-*N*-(*tert*-butyloxycarbonyl)amino)phenyl]-ethanone (3a). A solution of **2a** (1.86 g, 12.5 mmoles), di-*tert*-butyl dicarbonate (4.1 g, 18.8 mmoles) and DMAP (0.14 g, 1.3 mmoles) in THF (50 mL) was heated at reflux temperature for 16 hours. The solution was cooled to 20° and the solvent was removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and a saturated aqueous $NaHCO_3$ solution (50 mL), and the aqueous fraction was extracted with EtOAc (2 × 25 mL). The combined organic fractions were washed with water (2 × 25 mL) and then brine (25 mL), the organic fractions were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-hexane (1:3, v/v) as eluent to give **3a** (2.6 g, 84%) as a pale yellow oil: IR (film) 2978 (C-H aromatic), 2930 (C-H aliphatic), 1704 (CO_2), 1681 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.49 [s, 9H, $C(CH_3)_3$], 2.59 (s, 3H, $COCH_3$), 3.31 (s, 3H, NCH_3), 7.37 (d, *J* = 8.8 Hz, 2H, phenyl H-3, H-5), 7.94 (d, *J* = 8.8 Hz, 2H, phenyl H-2, H-6).

1-[4-(*N*-Ethyl-*N*-(*tert*-butyloxycarbonyl)amino)phenyl]ethanone (3b). The title compound was synthesized starting from 1-(4-ethylaminophenyl)ethanone (**2b**), using the same procedure described for the preparation of **3a**, as a pale yellow oil in 73% yield: IR (film) 2977 (C-H aromatic), 2935 (C-H aliphatic), 1701 (CO_2), 1684 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 1.44 [s, 9H, $C(CH_3)_3$], 2.60 (s, 3H, $COCH_3$), 3,74 (q, *J* = 6.9 Hz, 2H, CH_2CH_3), 7.33 (d, *J* = 8.6 Hz, 2H, phenyl H-3, H-5), 7.94 (d, *J* = 8.6 Hz, 2H, phenyl H-2, H-6).

1-[4-(*N*-Methyl-*N*-(*tert*-butyloxycarbonyl)amino)phenyl]-4,4,4-trifluorobutane-1,3-dione (4a). A solution of NaOMe in MeOH (25% w/v, 4 mL, 17.7 mmoles) was added to a solution of ethyl trifluoroacetate (2.35 g, 16.6 mmoles) in 7.5 mL of methyl *tert*-butyl ether (MTBE) over a 2 minute period. A solution of (**3a**) (3.74 g, 15 mmoles) in MTBE (4 mL) was then added dropwise over 5 minutes, the reaction was stirred for 18 hours at 25°, and 3 *N* HCl (7 mL) was added. The organic layer was collected, washed with brine (7.5 mL), dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo* to give the dione **4a** (4.8g, 93%) as a brown oil: IR (film) 2979 (C-H aromatic), 2934 (C-H aliphatic), 1707 (CO_2), 1682 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.51 [s, 9H, $C(CH_3)_3$], 3.34 (s, 3H, NCH_3), 6.55 (s, 1H, H-2), 7.44 (d, *J* = 8.7 Hz, 2H, phenyl H-3, H-5), 7.93 (d, *J* = 8.7 Hz, 2H, phenyl H-2, H-6).

1-[4-(*N*-Ethyl-*N*-(*tert*-butyloxycarbonyl)amino)phenyl]-4,4,4-trifluorobutane-1,3-dione (4b). The title compound **4b** was prepared starting from **3b**, using a procedure similar to that described to prepare **4a**, as a brown oil in 87% yield: IR (film) 2978 (C-H aromatic), 2935 (C-H aliphatic), 1701 (CO_2), 1684 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.51 [s, 9H, $C(CH_3)_3$], 3.78 (q, *J* = 7.2 Hz, 2H, CH_2CH_3), 6.56 (s, 1H, H-2), 7.42 (d, *J* = 8.7 Hz, 2H, phenyl H-3, H-5), 7.93 (d, *J* = 8.7 Hz, 2H, phenyl H-2, H-6).

General method for preparation of pyrazoles (6a-d). 4-Aminosulfonylphenylhydrazine hydrochloride (**5a**, 0.982 g, 4.4 mmoles), or 4-methylsulfonylphenylhydrazine hydrochloride (**5b**, 0.979 g, 4.4 mmoles) was added to a stirred solution of the dione **4a** or **4b** (4.0 mmoles) in EtOH (50 mL) and the reaction mixture was heated at reflux with stirring for 20 hours. After cooling to 25°, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with water and brine, dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo* to give the respective product **6a-d** for which the physical and spectral data are listed below.

4-[5-(4-*N*-Methylaminophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (6a). 98% yield; pale yellow powder; mp 148-150°; IR (film) 3438 (NH), 3319, 3174 (NH_2), 2961 (C-H aromatic), 2928 (C-H aliphatic), 1333, 1163 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 3H, NCH_3), 3.00 (br s, 1H, N*H*, D_2O exchangeable), 6.51 (d, *J* = 8.5 Hz, 2H, methylaminophenyl H-3, H-5), 6.59 (s, 1H, pyrazole H-4), 6.84 (br s, 2H, NH_2, D_2O exchangeable), 6.94 (d, *J* = 8.5 Hz, 2H, sulfonamidophenyl H-2, H-6), 7.40 (d, *J* = 8.5 Hz, 2H, methylaminophenyl H-2, H-6), 7.86 (d, *J* = 8.5 Hz, 2H, sulfonamidophenyl H-3, H-5), MS 397.04 (M + 1). *Anal*. Calcd. for $C_{17}H_{15}F_3N_4O_2S$: C, 51.51; H, 3.81. Found: C, 51.55; H, 3.95.

1-(4-Methanesulfonylphenyl)-5-[4-(*N*-methylaminophenyl)]-3-(trifluoromethyl)-1*H*-pyrazole (6b). 93% yield; yellow crystals; mp 65-67°, IR (film) 3413 (NH), 3024 (C-H aromatic), 2927 (C-H aliphatic), 1318, 1151 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.88 (s, 3H, NCH_3), 3.09 (s, 3H, SO_2CH_3), 4.50 (br s, 1H, N*H*, D_2O exchangeable), 6.61 (d, *J* = 8.6 Hz, 2H, methylaminophenyl H-3, H-5), 6.69 (s, 1H, pyrazole H-4), 7.04 (dd, *J* = 6.8, 1.8 Hz, 2H, methanesulfonylphenyl H-2, H-6), 7.58 (d, *J* = 8.6 Hz, 2H, methylaminophenyl H-2, H-6), 7.95 (dd, *J* = 6.8, 1.8 Hz, 2H, methanesulfonylphenyl H-3, H-5); MS 396.08 (M + 1). *Anal.* Calcd. for $C_{18}H_{16}F_3N_3O_2S.1/5H_2O$: C, 54.19; H, 4.11. Found: C, 54.56; H, 4.50.

4-[5-(4-*N*-Ethylaminophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (6c). 86% yield; white crystals; mp 64-66°, IR (film) 3395 (NH), 3357, 3263 (NH_2), 2972 (C-H aromatic), 2932 (C-H aliphatic), 1332, 1153 (SO_2) cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.29 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.50 (br s, 1H, N*H*, D_2O exchangeable), 3.19 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 4.94 (br s, 2H, NH_2, D_2O exchangeable), 6.60 (d, *J* = 7.2 Hz, 2H, ethylaminophenyl H-3, H-5), 6.68 (s, 1H, pyrazole H-4), 7.03 (d, *J* = 8.6 Hz, 2H, sulfonamidophenyl H-2, H-6), 7.53 (d, *J* = 7.2 Hz, 2H, ethylaminophenyl H-2, H-6), 7.92 (d, *J* = 8.6 Hz, 2H, sulfonamidophenyl H-3, H-5); MS 411.05 (M + 1). *Anal.* Calcd. for $C_{18}H_{17}F_3N_4O_2S.2/5H_2O$: C, 51.77; H, 4.20. Found: C, 52.07; H, 4.23.

1-(4-Methanesulfonylphenyl)-5-[4-(*N*-ethylaminophenyl)]-3-(trifluoromethyl)-1*H*-pyrazole (6d). 81% yield; white crystals; mp 54-56°, IR (film) 3395 (NH), 2971 (C-H aromatic), 2876 (C-H aliphatic), 1321, 1154 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.61 (br s, 1H, N*H*, D_2O exchangeable), 3.07 (s, 3H, SO_2CH_3), 3.19 (q, *J* = 7.2 Hz, 2H, CH_2CH_3), 6.59 (d, *J* = 7.9 Hz, 2H, ethylaminophenyl H-3, H-5), 6.68 (s, 1H, pyrazole H-4), 7.02 (d, *J* = 8.5 Hz, 2H, methanesulfonylphenyl H-2, H-6), 7.59 (d, *J* = 7.9 Hz, 2H, ethylaminophenyl H-2, H-6), 7.95 (d, *J* 8.5 Hz, 2H, methanesulfonylphenyl H-3, H-5), MS 410.09 (M + 1), *Anal.* Calcd for $C_{19}H_{18}F_3N_3O_2S$: C, 55.74; H, 4.43. Found: C, 56.12; H, 4.81.

1-(4-Methanesulfonylphenyl)-5-[4-(*N*-methyl-*N*-nitrosoaminophenyl)]-3-(trifluoromethyl)-1*H*-pyrazole (7). A solution of **6b** (0.791g, 2 mmoles) in a 1:1 mixture of acetonitrile/diethyl ether (25 mL) was mixed with a solution of NaOMe (0.2 mmoles, 0.43 mL of a 25% w/v solution in MeOH) with stirring at 25°. This mixture was purged with dry nitrogen gas for 5 min, and then the reaction was allowed to proceed under an atmosphere of nitric oxide (40 psi internal pressure) with stirring at 25° for 48 hours. The reaction mixture was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography using EtOAc /hexane (1:1, v/v) as eluent to give **7** (0.399g, 47%) as a pale yellow powder: mp 141-143°; IR (film) 3021 (C-H aromatic), 2930 (C-H aliphatic), 1317, 1153 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.09 (s, 3H, SO_2CH_3), 3.47 (s, 3H, NCH_3), 6.86 (s, 1H, pyrazole H-4), 7.37 (dd, *J* = 6.7, 1.8 Hz, 2H, methanesulfonylphenyl H-2, H-6), 7.61 (m, 4H, methylaminophenyl), 7.99 (dd, *J* = 6.7, 1.7 Hz, 2H, methanesulfonylphenyl H-3, H-5); MS 446.93 (M + Na). *Anal.* Calcd. for $C_{18}H_{15}F_3N_4O_3S$: C, 50.94; H, 3.56. Found: C, 51.34; H, 3.94.

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