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SYNTHESIS OF 1-*P*-SULFAMYLPHENYL-3 TRIFLUOROMETHYLPYRAZOLES CLASS OF CYCLOOXYGENASE-2 INHIBITORS

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Abstract: Condensation of *p*-sulfamylphenylhydrazine with diketones 1 afforded pyrazoles 2. Reaction of 2 with isocyanate and isothiocyanate derivatives gave the corresponding ureas 3 and thioureas 4 respectively. Cyclization of the thioureido group of compounds 4 by treating with ethyl bromoacetate, ethyl β-bromopropionate and α-bromoacetophenone afforded the corresponding thiazolidinone, thiazinone and thiazoline derivatives 5 , 6 and 7 respectively .

Introduction:

A number of selective inhibitors of cyclooxygenase-2 (COX-2) were shown to possess anti-inflammatory activity with little or no gastric side effects[1,2]. To date, two distinct structural classes of molecules have been reported as selective inhibitors of COX-2, NS-398[3] and L-745, 337[4] are members of methanes sulfonamide class of inhibitors, and DUP 647[5], SC-57666,[6-8] (SC-58125)[9] **I** are few of the many examples of the tricyclic inhibitors class[10-13] (Figure 1).

Recently,[14] it was found that within the 1,5-diarylpyrazole class of COX-2 inhibitors, the *p*-sulfamylphenyl group was essential for good COX-2 inhibitors potency and in vivo efficacy. Also, although there was substantial flexibility in functionality allowed at the 3-position of the pyrazole, trifluoromethyl and difluoromethyl were optimal in terms of potency and selectivity. In addition, substituents on the phenyl moiety at 5-position of the pyrazole ring had profound effects on both in vitro potency and selectivity. Morover, CELEBRX **II** is a nonsteroided anti-inflammatory drug that exhibits antiflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of CELEBREX is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2) and at therapeutic concentrations in humans.

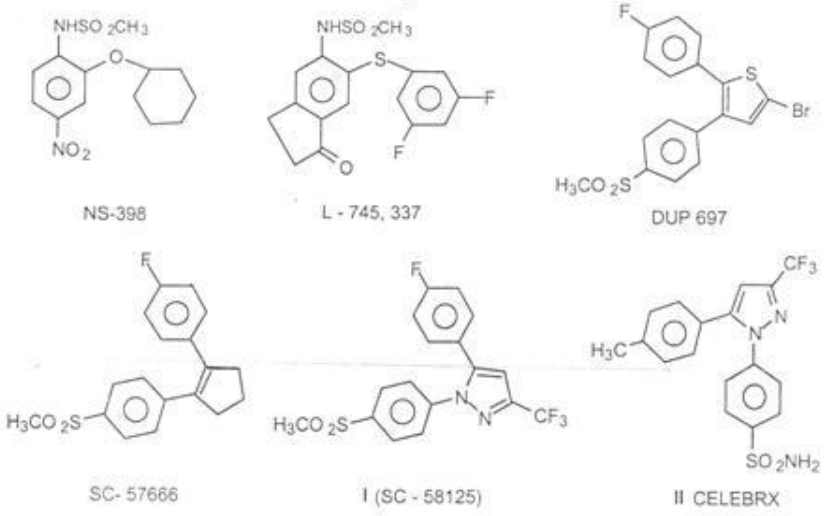
In continuation of our previous work[15-20] in the synthesis of trisubstituted pyrazoles containing trifluoromethyl and/or sulfonamide moieties, many new 1,5-diarylpyrazoles of selective COX-2 inhibitors related to the previously reported **I** and **II** were synthesised as a class of COX-2 inhibitors.

Results and Discussion:

Condensation of the key intermediate, *p*-sulfamylphenylhydrazine hydrochloride with fluorodiketones 1 afforded 5-substituted-3-trifluoromethyl-1-(*p*-sulfamylphenyl)pyrazoles (2; Table 1). The IR spectra of this pyrazoline displayed two absoption bands at 3225 cm^{-1} and 3347 cm^{-1} indicative of the NH_2 group, in addition to two strong bands at 1335-1345 and 1152-1150 cm^{-1} for the SO_2N group. Their ^1H NMR spectra exhibited the aromatic and the NH_2 protons as multiplets at δ 6.52 - 8.14 (Tabel 2).

Condensation of pyrazole derivatives 2 with the appropriate isocyanate and isothiocyanate in dry acetone yielded the corresponding benzenesulfonylurea 3 and thiourea 4 derivatives respectively (Table 1). The IR spectra of these compounds exhibited two bands at 1330-1350 cm^{-1} and 1150-1165 cm^{-1} due to SO_2N group as well as a urea carbonyl band at 1650-1656 cm^{-1} in the case of compounds 3 and a thiourea carbonyl absorption at 1136-1140 cm^{-1} in the case of compounds 4. The structure of the above compounds 3 and 4 were further supported by their elemental analyses as well as ^1H NMR spectra (Table 2).

Figure 1



It has has been reported that condensation of N, N-disubstituted thiourea with chloroacetic acid, its chloride or bromide esters afforded 2-imino-4-oxothiazolidines, and the reaction proceeds through the intermidiate formation of the cyclic pseudothiohydantoic acid[22-24]. In the present study, cyclization of the thiourea derivatives 4, with ethyl bromoacetate, ethyl β-bromopropionate and α-bromoacetophenone afforded the corresponding 4-oxothiazolidine 5, 4-oxo-5, 6-dihydrothiazine 6 and thiazoline 7 derivatives respectively. IR spectra of 5 and 6 showed a cyclic carbonyl absorption at 1721-1739 cm^{-1} and two lines at 1336-1347 cm^{-1} and 1151-1163 cm^{-1} for the SO_2N group. The structures of the above compounds 5-7 were further supported by their ^1H NMR data (Table 2). The sequence of reactions are outlined in Scheme 1.

Experimental:

Melting point were determined on a Kofler hot stage apparatus and were uncorrected. ^1H NMR spectra were recorded on a Varian EM 390-90 MHz spectrometer using TMS as internal standard. IR spectra were recorded on Unicam SP 1025 infrared spectrometer.

3-Trifluoromethyl-5-substituted-1-(*p*-sulfamylphenyl)pyrazole (2; Table 1):

A solution of the appropriate diketone (1; 0.01 mol) in ethanol (50 ml) was refluxed with *p*-sulfamylphenylhydrazine hydrochloride (0.01 mol) for 4 hr, cooled and diluted with water. The precipitated crude product was filtered and recrystallized from ethanol as needles.

***p*-(3-Trifluoromethyl-5-substituted-pyrazole-1-yl)benzenesulfonylureas (3; Table 1):**

A mixure of 2 (0.01 mol) and anhydrous potassium carbonate (0.02 mol) in dry acetone (25 ml) was stirred and refluxed for 1hr. At this temperature, a solution of the appropriate isocyanate (0.015 mol) in dry acetone (5 ml) was added dropwise. After the mixture was stirred and refluxed overnight, acetone was removed under reduced pressure, and the solid residue was dissolved in water. The crude product was isolated by acidification with 2N HCl and purified by recrystallization from ethanol as needles.

***p*-(3-Trifluoro-5-substituted-pyrazol-1-yl)benzenesulfonylthioureas (4; Table 1):**

A mixure of 2 (0.01 mol) and anhydrous potassium carbonate (0.02 mol) in dry acetone (25 ml) was stirred and treated with the appropriate isothiocyanate (0.012 mol). After the mixture was stirred and refluxed for 10 hr, acetone was removed under reduced pressure, and the solid mass dissolved in water and acidified with 2N HCl. The crude

Scheme 1

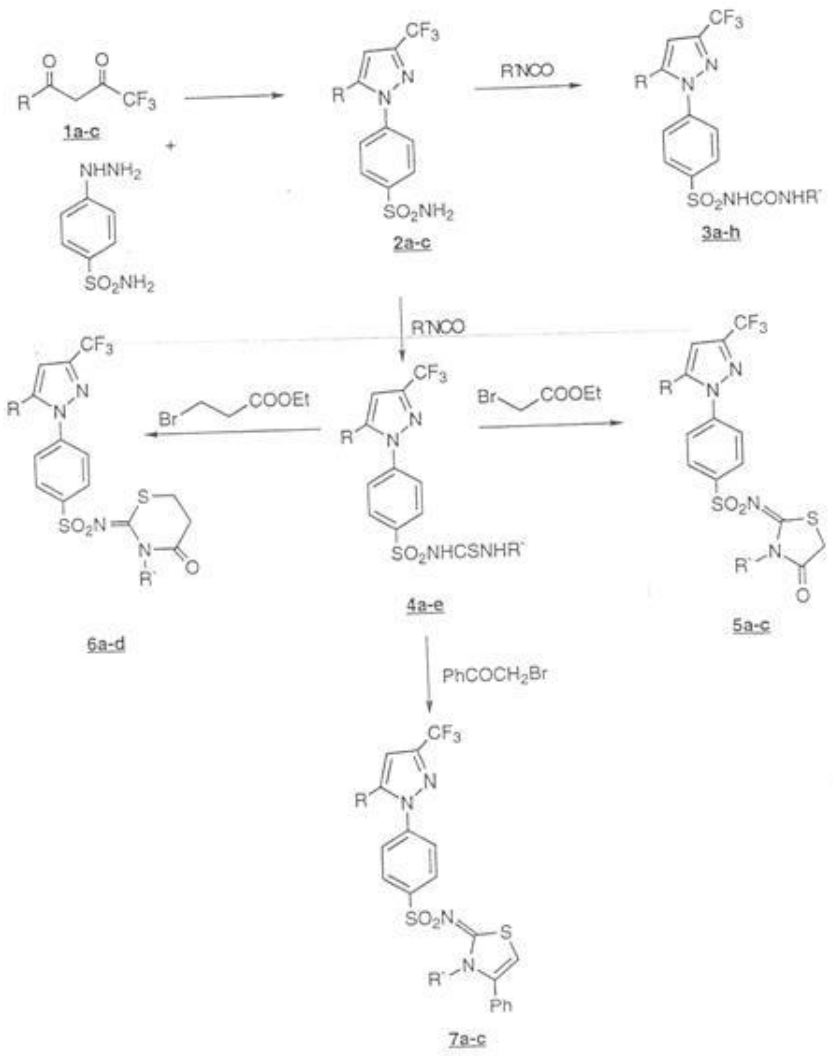


Table 1. Characterization Data of Pyrazole Derivatives (2-7)

Compound No	R	R'	Yield %	M.P. °C	Mol. Formula	Found %				Calc %			
						C	H	N	S	C	H	N	S
2a	CH_3		82	142	$C_{11}H_{10}F_3N_3O_2S$	43.25	3.33	13.80	10.60	43.30	3.28	13.77	10.49
2b	CF_3		73	168(166)[a]	$C_{11}H_7F_6N_3O_2S$	36.69	1.77	11.82	8.85	36.80	1.94	11.69	8.91
2c	2-Thienyl		78	202	$C_{14}H_{10}F_3N_3O_2S_2$	45.18	2.72	11.28	17.30	45.06	2.69	11.26	17.15
3a	CH_3	Cyclohexyl	72	165	$C_{18}H_{21}F_3N_4O_3S$	50.31	4.99	13.22	7.34	50.26	4.88	13.02	7.44
3b	CH_3	Ph	76	144	$C_{18}H_{15}F_3N_4O_3S$	51.00	3.44	13.08	7.56	50.96	3.54	13.20	7.54
3c	CF_3	Cyclohexyl	70	153(152)[a]	$C_{18}H_{18}F_6N_4O_3S$	44.80	3.80	11.69	6.81	44.65	3.72	11.57	6.61
3d	CF_3	Ph	75	142(143)[a]	$C_{18}H_{12}F_6N_4O_3S$	45.32	2.65	11.82	6.72	45.21	2.51	11.71	6.69
3e	CF_3	Naphthyl	78	172	$C_{22}H_{14}F_6N_4O_3S$	50.12	2.80	10.66	6.17	50.03	2.65	10.60	6.06
3f	2-Thienyl	Cyclohexyl	74	168	$C_{21}H_{21}F_3N_4O_3S_2$	50.81	4.40	11.32	12.90	50.63	4.22	11.24	12.85
3g	2-Thienyl	Ph	76	144	$C_{21}H_{15}F_3N_4O_3S_2$	51.28	3.12	11.50	12.99	51.24	3.05	11.38	13.00
3h	2-Thienyl	Naphthyl	74	148	$C_{25}H_{17}F_3N_4O_3S_2$	55.24	3.05	10.44	11.88	55.33	3.14	10.33	11.80
4a	CH_3	Ph	78	132	$C_{18}H_{15}F_3N_4O_2S_2$	49.22	3.42	12.80	14.60	49.12	3.41	12.72	14.54
4b	CH_3	Benzyl	68	145	$C_{19}H_{17}F_3N_4O_2S_2$	50.35	3.80	12.43	14.11	50.25	3.74	12.33	14.09
4c	CF_3	Ph	70	159(160)[a]	$C_{18}H_{12}F_6N_4O_2S_2$	43.80	2.52	11.25	13.05	43.75	2.43	11.33	12.95
4d	CF_3	Benzyl	72	119(117)[a]	$C_{19}H_{14}F_6N_4O_2S_2$	45.00	2.81	11.10	12.62	44.91	2.75	11.02	12.60
4e	2-Thienyl	Benzyl	74	118	$C_{22}H_{17}F_3N_4O_2S_3$	50.65	3.30	10.82	18.42	50.60	3.26	10.72	18.38
5a	CH_3	Benzyl	72	204	$C_{21}H_{17}F_3N_4O_3S_2$	51.30	3.33	11.25	13.00	51.04	3.44	11.33	12.95
5b	CF_3	Benzyl	69	172	$C_{21}H_{14}F_6N_4O_3S_2$	46.02	2.60	10.25	11.80	46.01	2.55	10.21	11.67
5c	2-Thienyl	Benzyl	72	196	$C_{24}H_{17}F_3N_4O_3S_3$	51.30	3.22	9.78	17.08	51.27	3.02	9.96	17.07
6a	CF_3	Ph	68	158	$C_{21}H_{14}F_6N_4O_3S_2$	46.02	2.65	10.25	11.77	46.01	2.55	10.21	11.67
6b	CF_3	Benzyl	65	148	$C_{22}H_{16}F_6N_4O_3S_2$	47.20	2.75	10.11	11.42	47.00	2.84	9.96	11.38
6c	2-Thienyl	Ph	75	186	$C_{24}H_{15}F_3N_4O_3S_3$	51.30	3.22	10.12	17.00	51.27	3.02	9.96	17.07
6d	2-Thienyl	Benzyl	72	192	$C_{25}H_{17}F_3N_4O_3S_3$	52.21	3.42	9.56	16.58	52.11	3.30	9.72	16.66
7a	CH_3	Benzyl	70	132	$C_{27}H_{21}F_3N_4O_2S_2$	58.66	3.85	10.12	11.67	58.51	3.79	10.10	11.55
7b	CF_3	Benzyl	68	138	$C_{27}H_{18}F_6N_4O_2S_2$	53.15	3.05	9.12	10.60	53.32	2.96	9.21	10.52
7c	2-Thienyl	Benzyl	72	206	$C_{30}H_{21}F_3N_4O_2S_3$	58.01	3.38	8.89	15.40	57.90	3.37	9.00	15.43

Table 2. Spectral Data of Pyrazole Derivatives (2-7)

Compound No	R	R'	^{1}H NMR[a] Ar H & NH (m)	^{1}H NMR[a] Others	IR (KBr, cm^{-1}) SO_2N	IR (KBr, cm^{-1}) CO or CS	IR (KBr, cm^{-1}) NH_2 or NH
2a	CH_3		6.52-8.07 (7H)	3.32(s, 3H, CH_3)	1345, 1158		3235, 3338
2b	CF_3		6.96-8.14 (7H)		1335, 1152		3228, 3342
2c	2-Thienyl		6.63-8.01 (10H)		1337, 1155		3225, 3347
3b	CH_3	Ph	7.00-8.10 (11H)	3.40 (s, 3H, CH_3); 8.56 (s, 1H, NH)	1350, 1150	1650	3330
3f	2-Thienyl	Cyclohexyl	6.88-8.15 (10H)	0.90-1.92 (m, 11H, cyclohexyl H)	1338, 1165	1653	3330
3g	2-Thienyl	Ph	6.98-8.25 (13H)	8.60 (s, 1H, NH); 8.75 (s, 1H, NH)	1339, 1161	1650	3325
3h	2-Thienyl	Naphthyl	7.02-8.20 (16H)	8.78 (s, 1H, NH)	1330, 1160	1656	3283
4a	CH_3	Ph	7.12-8.15 (11H)	3.31(s, 3H, CH_3); 8.80 (s, 1H, NH)	1339, 1154	1140	3177, 3385
4e	2-Thienyl	Benzyl	7.00-8.15 (14H)	4.72 (d, J = 6Hz, 2H, CH_2); 8.95 (t,J = 6Hz, 1H, NH)	1350, 1159	1136	3061, 3330
5a	CH_3	Benzyl	7.05-8.11 (10H)	3.30 (s, 3H, CH_3); 3.80 (s, 2H, CH_2); 4.30 (s, 2H, CH_2)	1347, 1151	1739	
5c	2-Thienyl	Benzyl	7.05-8.02 (13H)	3.75 (s, 2H, CH_2); 4.30 (s, 2H, CH_2)	1338, 1153	1738	
6a	CF_3	Ph	7.10-8.12 (10H)	3.60-4.11 (m, 4H, $2CH_2$)	1336, 1162	1725	
6c	2-Thienyl	Ph	6.98-7.95 (13H)	3.50-4.08 (m, 4H, $2CH_2$)	1337, 1156	1721	
7a	CH_3	Benzyl	7.12-8.25 (16H)	3.29 (s, 3H, CH_3); 4.39 (s, 2H, CH_2)	1332, 1162		
7c	2-Thienyl	Benzyl	7.00-8.10 (19H)	4.40 (s, 2H, CH_2)	1339, 1156		

a Solutions in a mixture of $CDCl_3$ and DMSO-d_6 δ in ppm

product was purified by recrystallization from ethanol as needles.

3-Substituted-2[*p*-(3-trifluoro-5-substituted-pyrazol-1-yl)benzenesulfonylimino]-4-oxothiazolidines (5; Table 1):

A mixture of 4 (0.01 mol), ethyl bromoacetate (0.01 mol) and sodium acetate (0.02 mol) in absolute ethanol (30 ml) was refluxed for 2hr. The reaction mixture was then filtered while hot, concentrated and allowed to cool. The product obtained was recrystallized from ethanol as needles.

3-Substituted-2-[*p*(3-trifluoro-5-substituted-pyrazol-1-yl)benzenesulfonylimino]-4-oxo-5,6-dihydro-1,3-thiazines (6; Table 1):

A solution of 4 (0.01 mol) in absolute ethanol (20 mol) was refluxed with ethyl β-bromopropionate (0.01 mol) and sodium acetate (0.02 mol) for 2hr. The reaction mixture was then cooled and poured into water; the precipitated thiazine was recrystallized from ethanol as needles.

3-Substituted-2-[*p*-(3-trifluoro-5-thienylpyrazol-1-yl)benzenesulfonylimino]-1,3-thiazolines (7; Table 1):

A solution of the corresponding thiourea derivative 4 (0.01 mol) in absolute ethanol was refluxed with α-bromoacetophenone (0.01 mol) and sodium acetate (0.02 mol) for 2h. The reaction mixture was then cooled and poured into water; the precipitated thiazoline was recrystallized from ethanol as needles.

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